NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID968]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID968]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission summary** from BlueBird Bio

2. **Clarification questions and company responses:**
   a. Clarification response
   b. Additional clarification response
   c. Appendix F (paper on company's vignette study)

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. UK Thalassaemia Society
   b. Royal College of Pathologists and British Society for Haematology
   c. NHS England and Improvement

4. **Expert personal perspectives** from:
   a. Kate Ryan, Consultant Haematologist – clinical expert, nominated by BlueBird Bio
   b. Emma Drasar, Consultant Haematologist – clinical expert, nominated by UK Thalassaemia Society
   c. Roanna Maharaj, Public Health, Projects, and Patient Advocacy Lead – patient expert, nominated by UK Thalassaemia Society

5. **Evidence Review Group report** prepared by **Centre for Reviews and Dissemination and Centre for Health Economics – York**

6. **Evidence Review Group report – factual accuracy check**

7. **Technical report**

Post-technical engagement documents

8. **Technical engagement response from company:**
   a. Response form
   b. Model-related appendices
   c. Clinical evidence-related appendix

d. Response to query on patient numbers

9. Technical engagement responses from consultees and commentators:
a. Cell and Gene Therapy Catapult

10. Evidence Review Group critique of company response to technical engagement prepared by **Centre for Reviews and Dissemination and Centre for Health Economics – York**

11. Kwiatkowski paper presented at ASH conference with latest data cut (mentioned in slides)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

Document A

Company evidence submission summary for committee

bluebird bio confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

October 2019

File name	Version	Contains confidential information	Date
ID968 Zynteglo NICE STA Document A [Redacted] vpost ERG 4Feb2020	**Vpost ERG**	**Yes**	**4 February 2020**

Instructions for companies

This is the template you should use to summarise your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision-making.

This submission summary must not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted. Please submit a draft summary with your main evidence submission. The NICE technical team may request changes later.

When cross referring to evidence in the main submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

Submission summary

A.1 Health condition

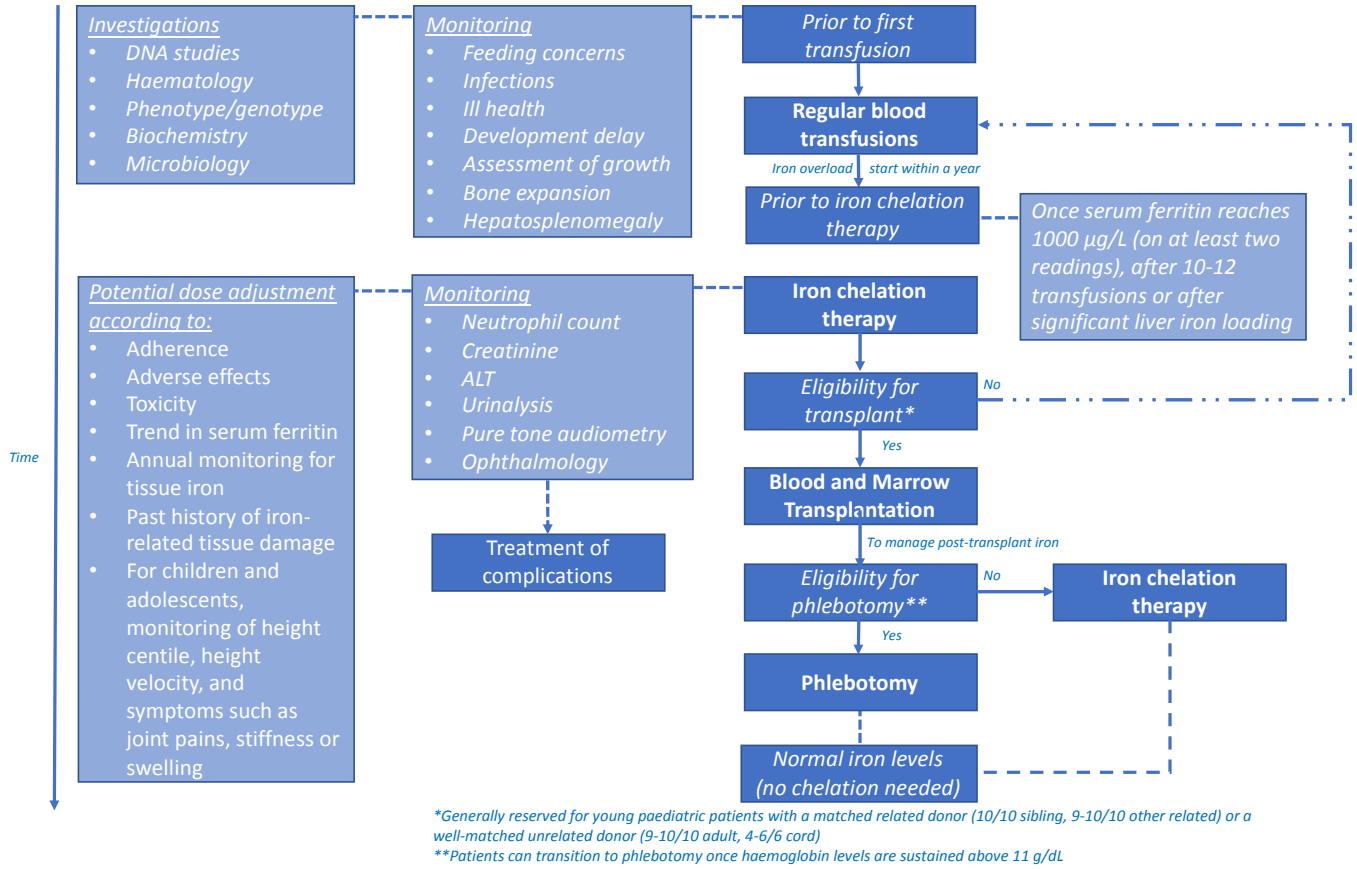
β-thalassaemia is a genetic blood disease leading to absent or reduced production of the β-globin chains of haemoglobin A [1]. The most severe forms of β-thalassaemia, transfusion-dependent β-thalassaemia (TDT), require packed red cell blood (pRBC) transfusions every 2-4 weeks for survival [2]. The accumulation of excess iron from transfusions leads to iron overload [3, 4] which is the major cause of morbidity and mortality in patients with TDT [3, 5]. Despite iron chelation therapy, iron accumulates in various tissues including the heart, liver, and endocrine system, causing life-threatening organ dysfunction [3, 6]. This is evidenced by a recent chart review study conducted by bluebird bio in nine UK centres, which demonstrates substantial iron overload and reduced quality of life in TDT patients in the UK [7].

The most common cause of death in UK TDT patients is iron overload in the heart (54%) [8], while in the liver, iron overload leads to fibrosis and increases the risk of chronic liver disease and cirrhosis [2, 3]. Iron overload in the endocrine system leads to hypogonadotrophic hypogonadism (70-80% of TDT patients) [9], diabetes (31.3% of TDT patients) [10] and growth delay in children (30% of TDT patients have short stature) [11]. A recent analysis of the English Hospital Episode Statistics database showed the 10 year in-hospital mortality rate for TDT patients was [redacted] than the age/sex matched general population ([redacted] versus 1.2%, p<0.001), with a median age at death of [redacted] years [12].

A.2 Clinical pathway of care

Zynteglo is a genetically modified autologous $CD34^+$ cell enriched population that contains haematopoietic stem cells (HSC) transduced with lentiviral vector (LVV) encoding the $\beta^{A\text{-}T87Q}$-globin gene. The relevant comparator to Zynteglo is regular blood transfusions and iron chelation therapies. Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is not a comparator for Zynteglo as stated in the NICE scope, but elements of the allo-HSCT process are comparable to the treatment process with Zynteglo, which means that existing services within the NHS are accustomed to mobilisation, apheresis and conditioning of the patient. While allo-HSCT is presented as a potentially transformative treatment, it is not recommended for adults due to the risk of treatment-related mortality. Only 25-30% of paediatric TDT patients have a suitable stem cell donor [13] (Document B, section B.1.3.1 pg. 18 and B.1.3.6 pg. 42). Therefore, the majority of patients with TDT depend on a lifelong regimen of frequent blood transfusions usually initiated in the first two years of life [3], coupled with chelation therapy and iron monitoring to manage the resulting iron overload introduced by transfusions [3] (Figure 1). Transfusions temporarily relieve symptoms of anaemia but do not address the underlying globin chain imbalance or restore normal erythropoiesis. The requirement for lifelong transfusions, iron monitoring and chelation therapy inevitably place a significant burden on the health system, patients and carers, such that new treatment options that can address the underlying cause of the condition are needed (Document B, section B.1.3.5 pg. 36).

Figure 1 Current standard of care adapted from the UKTS guidelines



Source: [2]

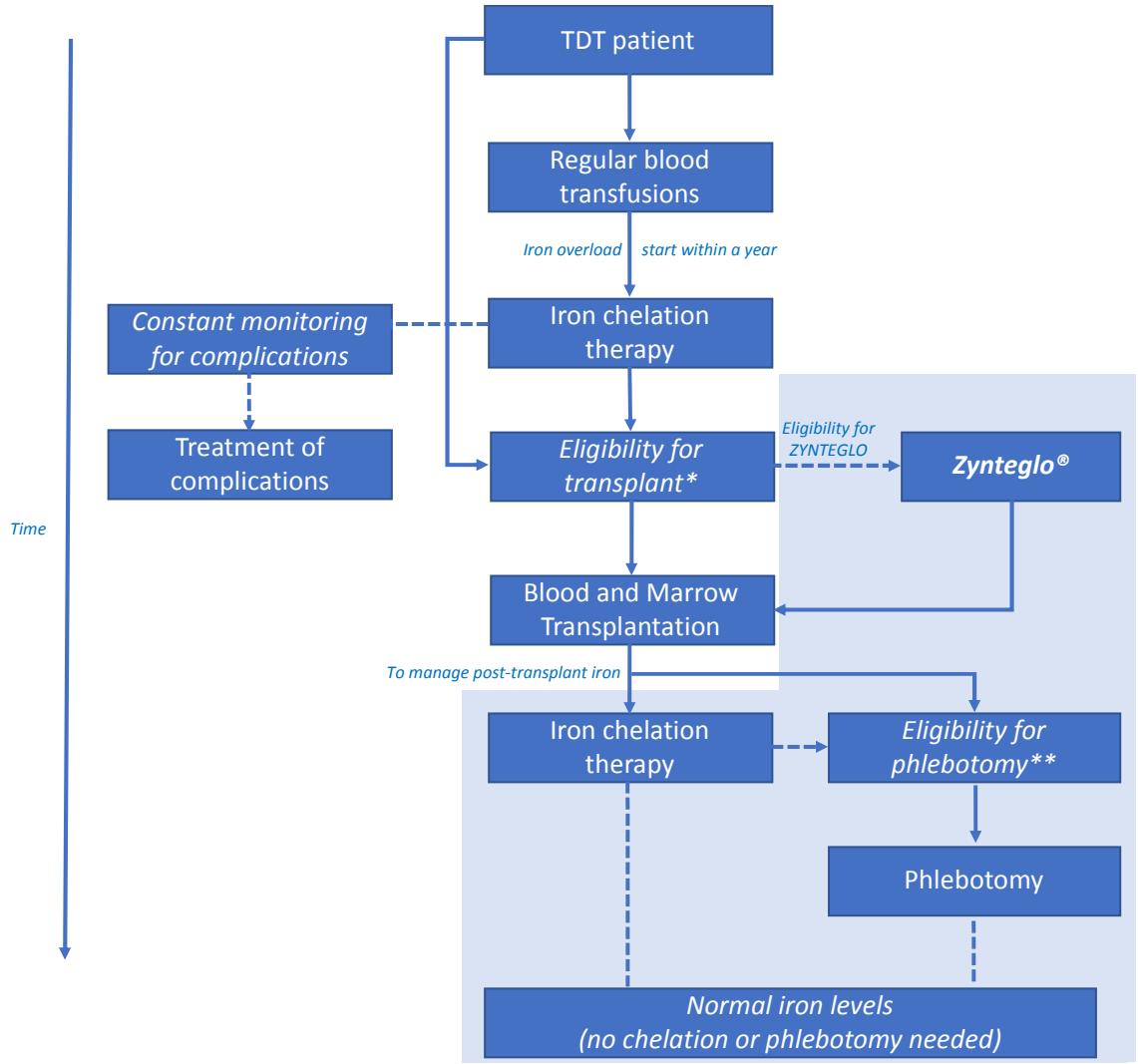
Through a one-time administration of gene-modified autologous haematopoietic stem cells, Zynteglo offers a transformative approach that uniquely addresses the underlying genetic cause of TDT in patients that cannot undergo allo-HSCT.

Following successful engraftment and achievement of transfusion-independence (TI), the effects of Zynteglo are expected to be life-long, negating the need for chronic symptom management over a patient's lifetime as required by conventional therapies. To achieve persistent durability of efficacy in the case of *ex-vivo*, lentiviral vector-based gene therapies such as Zynteglo, treatment must result in the establishment of a population of undifferentiated, long-term haematopoietic stem cells in the bone marrow which carry the gene of interest, integrated into their genome. Based on the mechanism of action of Zynteglo, which involves the insertion of functional copies of a modified β-globin gene (β-$^{A\text{-}T87Q}$) into long-term repopulating haematopoietic stem cells, it is expected that the effects of treatment will indeed be life-long.

The introduction of Zynteglo in the pathway of care will therefore lead to significant resource savings for the NHS over the patient's lifetime through reductions in the need for donor blood and transfusion services, fewer hospital visits and mitigation of complications related to iron overload (Document B, section B.1.3.7 pg. 43). This is expected to result in long-term quality of life benefits for patients and parents/carers, allowing them to lead as normal a life as possible (Document B, section B.1.3.5 pg. 36). Treatment choices in the overall pathway of

care will remain consistent, with the addition of the potentially transformative option of Zynteglo (Figure 2).

Figure 2 Treatment pathway for TDT patients including Zynteglo



**Generally reserved for young paediatric patients with a matched related donor (10/10 sibling, 9-10/10 other related) or a well-matched unrelated donor (9-10/10 adult, 4-6/6 cord)*
***Patients can transition to phlebotomy once haemoglobin levels are sustained above 11 g/dL*
Note: Following treatment with Zynteglo, the patient may need to utilize chelators or phlebotomy to manage post-transplant iron.

A.3 The technology

Table 1 Technology being appraised – Document B, B.1.2 pg. 12

UK approved name and brand name	Pseudo international non-proprietary name (INN): A genetically modified autologous $CD34^+$ cell enriched population that contains haematopoietic stem cells (HSC) transduced with lentiviral vector (LVV) encoding the $\beta^{A\text{-}T87Q}$-globin gene. Brand name: Zynteglo™ (also known as LentiGlobin in TDT)
Mechanism of action	β-thalassaemia is caused by the absence or reduced production of the β-globin chains of haemoglobin A (HbA), resulting in an excess of uncomplexed α-globin chains that precipitate in erythroblasts leading to premature death of the cells, ineffective erythropoiesis, and haemolysis [1].

	Zynteglo is an autologous CD34+ cell enriched population that contains haematopoietic stem cells (HSCs) transduced with LVV encoding the βA-T87Q-globin gene. The autologous CD34+ cells collected via mobilisation and apheresis are transduced with the BB305 LVV and are intended for infusion into the same patient following myeloablative conditioning. BB305 LVV is a replication-defective, self-inactivating LVV, based on HIV-1, that carries a modified functional copy of the β-globin (HBB) gene. Zynteglo adds functional copies of a modified β-globin gene into the patients' HSCs through transduction of autologous CD34+ cells with BB305 LVV, thereby addressing the underlying genetic cause of the disease. After Zynteglo infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce red blood cells (RBCs) containing biologically active βA-T87Q-globin (a modified β-globin gene) that will combine with α-globin to produce functional haemoglobin containing βA-T87Q-globin (HbAT87Q). βA-T87Q-globin can be quantified relative to other globin species in peripheral blood using high performance liquid chromatography. βA-T87Q-globin expression is designed to correct the β/α-globin imbalance in erythroid cells of patients with TDT and has the potential to increase total Hb to normal levels and eliminate dependence on chronic RBC transfusions. Following successful engraftment and achievement of transfusion independence, the effects of the product are expected to be life-long.
Marketing authorisation/CE mark status	Zynteglo received a conditional marketing authorisation from the European Medicines Agency (EMA) on the 29th May 2019. bluebird bio will provide the EMA with results of ongoing studies to further assess the effectiveness and safety of the medicine at each annual renewal (starting 29th May 2020).
Indications and any restriction(s) as described in the summary of product characteristics	The full licensed indication is for the treatment of patients 12 years and older with TDT who do not have a β^0/β^0 genotype, for whom HSC transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.
Method of administration and dosage	Zynteglo is to be administered intravenously in a qualified treatment centre (qualified treatment centres will be designated by NHS England) via a nominated and trained healthcare professional. Zynteglo must be administered in a qualified treatment centre by a physician(s) with experience in HSC transplantation and in the treatment of patients with TDT. Zynteglo should only be administered after consultation with the patient and family/carer as applicable, and their haematologist/ haemoglobinopathy specialist, with appropriate consent documented [14]. Zynteglo-treated patients are expected to enrol in a bluebird bio registry (more details below in 'Additional tests or investigations' section) and will be followed long term in order to better understand the long-term outcomes associated with Zynteglo. The minimum recommended dose of Zynteglo is 5.0×10^6 CD34+ cells/kg. Zynteglo is intended for autologous use and should only be administered once. The Zynteglo treatment process begins with the harvesting of the patient's own HSCs through a standard peripheral stem cell collection procedure, known as apheresis, following the administration of mobilising agents. The collected stem cells are then purified and functional copies of the gene are inserted using a viral vector delivery system outside the body (*ex vivo*). The patient then undergoes myeloablative conditioning using chemotherapy to make space in the bone marrow, and the modified stem cells are given back to the patient through peripheral infusion. This procedure is also known as an autologous haematopoietic stem cell transplant (auto-HSCT). In summary, the complete treatment process, from mobilisation to the end of inpatient stay, lasts 13-19 weeks (further details in Document B, Table 2, pg. 12):

	• Pre-treatment (hypertransfusion regimen) (from 30 to 90 days to maintain Hb ≥11 g/dL, prior to myeloablative conditioning) • Step 1: Mobilisation and apheresis (depending on the requirement of a 2nd cycle, there is a two-week gap before the 2nd cycle commences (approx. 7 to 28 days if 2nd cycle is required) • Step 2: Stem cell processing (56 days) • Step 3: Patient conditioning: (approximately 7 days) • Step 4: Zynteglo infusion via auto-HSCT (maximum of four hours) • Step 5: Inpatient stay until the patient is deemed medically stable for discharge (from 21 to 42 days, including a median of 19.5 days [13, 38 days] for neutrophil engraftment [15])
Additional tests or investigations	There will be no substantial increase in the usage of tests, interventions, facilities or technologies needed (Document B, B.1.3.7, page 43). Apart from the required training provided by bluebird bio to healthcare professionals for the administration of Zynteglo, all aspects can be adopted within current skills, and the service can be delivered without significant changes in the system [16]. These skills and services will include: • Cell collection (from highly specialised professionals as stated above), already in place via NHS Blood and Transplant Service (NHSBT) or other relevant local services • Non-malignant HSC transplantation in the licensed age range, already conducted and set up in a number of hospitals within the UK for other indications • Medical management of haemoglobinopathies to ensure readiness for transplantation such as maintaining haemoglobin levels at pre-specified levels and iron detoxification (not necessarily required at site) • Ability to access patients through their referral networks and potential link to the national haemoglobinopathy panel which is in planning; as well as to implement necessary bluebird bio's operating processes and systems. For monitoring purposes of safety and efficacy, specific tests will be performed such as simple blood tests [collection of samples for HbA^{T87Q} and vector copy number) and also insertion site analysis (ISA) testing. These will be shipped to a bluebird bio contracted lab and will be undertaken at the company's expense. Treatment with Zynteglo involves structured and regular collaboration between qualified treatment centres and the manufacturing site to meet regulatory obligations and ensure patient safety.
List price and average cost of a course of treatment	Zynteglo 1.2-20x10^6 dispersion for a one-time infusion: £1,450,000 per treatment excluding VAT
Patient access scheme (if applicable)	Two patient access schemes have been submitted to the Patient Access Scheme Liaison Unit (PASLU), both of which are subject to approval. The first is a simple patient access scheme (PAS) including a discounted price per patient of [redacted]. Additionally, a complex PAS, consisting of an outcomes-based payment over time scheme, complements the simple PAS and helps address any NHS concerns about affordability, or the efficacy and health economic uncertainties of Zynteglo. The complex PAS consists of periodic payments that are conditional on the patient remaining free of requiring transfusions for thalassaemia. Specifically, the NHS would pay an initial [redacted] of the cost of Zynteglo [redacted] upon receipt of the product, and subsequent payments of [redacted], contingent on the patient's freedom from transfusions. Full details of the operation of the complex PAS are provided in the PASLU submission. Both the simple and complex PAS will be in place concurrently,

	[redacted] In anticipation of the schemes being agreed upon for consideration by the NICE committee, all budget impact analyses have been presented with both patient access schemes included i.e. the discounted price along with outcomes-based payment over time

A.4 Decision problem and NICE reference case

The submission covers the technology's full marketing authorisation for this indication. The company submission is consistent with the final NICE scope and the NICE reference case.

Table 2 The decision problem – Document B, B.1.1 pg. 15

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 12 years and over with transfusion-dependent beta-thalassaemia with a non-β0/β0 genotype, who are eligible for haematopoietic stem cell transplantation but do not have access to a matched related donor	As per scope	Not applicable
Intervention	Zynteglo gene therapy (autologous CD34+ cells encoding βA-T87Q-globin gene)	As per scope	Not applicable
Comparator(s)	Established clinical management of transfusion-dependent beta-thalassaemia, including blood transfusions and chelating agents	As per scope	Not applicable
Outcomes	The outcome measures to be considered include: • overall survival • symptoms of anaemia • need for transfusion • iron overload complications (e.g. cardiac,	As per scope	Not applicable

	liver and endocrine complications) • growth and development (for non-adults) • adverse effects of treatment • health-related quality of life.		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year	As per scope	Not applicable
Subgroups to be considered	People aged 12 years and over with transfusion-dependent beta-thalassaemia with a non-β0/β0 genotype, who are eligible for haematopoietic stem cell transplantation but do not have access to a matched related donor	As per scope	Not applicable
Perspective for outcomes	All direct health effects, whether for patients or, when relevant, carers.	The model captures outcomes for just patients, and not their caregivers.	The impact on caregivers has been quantified in the bluebird bio UK chart review. The mean EQ-5D of caregivers in the chart review was 0.89, compared to 0.9345 in the general population. Since the sample of caregivers included in the UK chart review was limited and there are likely to be strong associations between patient age and the care burden, caregiver disutilities have not been included in the ICER, resulting in the ICER potentially being overestimated.
Perspective for costs	NHS and personal social services (PSS)	The perspective on costs is that of the NHS in England and Wales; PSS and	It was not possible to quantify costs from the perspective of PSS which are required for the reference case. More than two-thirds of families with children with TDT received disability living allowance and nearly half received care allowance [17]. Furthermore, family members acting as

		non-health costs are not accounted for.	carers may reduce their working hours or change their job; and patients of working age may have reduced working hours or be unable to work due to their regular transfusions or complications. The base case results are therefore likely to be overestimating the ICER.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	As per the NICE reference case, a life-long time horizon has been utilised.	Not applicable
Synthesis of evidence on health effects	Based on systematic review	Evidence for the intervention health effects were obtained from international single arm clinical trials. Adequate evidence of the comparator health effects used to populate the model were not found in the published literature, so were obtained from a UK chart review.	There have been no additional relevant studies of Zynteglo conducted outside of bluebird bio, and therefore a systematic review of clinical efficacy studies for Zynteglo is not required. As per section 2.1. of the NICE 'User guide for company evidence submission template', a SLR of comparator technologies is only required 'when an indirect or mixed treatment comparison is carried out'. Since Zynteglo has only been evaluated in single-arm studies, an indirect or mixed treatment comparison is not possible. In addition, transfusions and chelation therapy would not be an appropriate comparator for the primary and key secondary study endpoints of transfusion-independence and transfusion-reduction because patients with TDT receiving supportive care do not spontaneously achieve transfusion independence or have significant reductions in their transfusion requirements (Document B, Section B.2.9). However, bluebird bio has historically conducted a SLR including treatment patterns and outcomes available for reference [18].
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	As per the reference case, health effects are expressed in QALYs. Age-related utilities in the general population, which are used as the baseline quality of life, were based on the EQ-5D-3L. As per the reference case, the EQ-5D-3L was used to measure quality of life in patients receiving transfusions and iron chelation therapy in the UK chart review.	Due to the limitations of collecting Zynteglo quality of life data from the clinical studies, a vignette study was conducted in the UK general population to inform assumptions around the quality of life impact of TDT and Zynteglo. Vignette-based methodology can be used to estimate the utility impact associated with a treatment process, which in the case of TDT, includes the ongoing cycle of transfusion and chelation, as well as differences between conventional and investigational stem cell transplant procedures. Generic preference-based instruments such as the EQ-5D are not designed to be sensitive to treatment process variables. In contrast, vignette-based methods are useful for this purpose because health states can be designed to focus

		The utility for transfusion-independence and the utility during the transplant-year were obtained from a vignette study. Utilities for the vignette health states were then elicited in a time trade-off (TTO) task with a 10-year time horizon for the five chronic health states and a 1-year time horizon for the three path states (which described a series of typical health-related events during the year in which the patient would undergo either an autologous HSCT (i.e. Zynteglo) or an allo-HSCT).	on treatment process attributes. Therefore, almost all studies estimating treatment process utilities use the vignette-based approach.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The EQ-5D-3L data collected from the UK chart review was measured directly in patients. The vignette study was a hypothetical study conducted with the general population in the UK.	See row above.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	In line with the reference case.	The EQ-5D-3L data collected from the UK chart review and the age-related EQ-5D-3L data was valued using the UK value set, which is based on general population preferences. The vignette study was conducted with the general population in the UK.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in end-of-life or highly specialised technologies,	One-third of the expected patient population are paediatric patients that stand to benefit most from Zynteglo, and thus require specific consideration. bluebird bio believe that QALY modifiers should apply on the basis of severity, unmet need, the transformative nature of the treatment	The All-Party Parliamentary Group on Access to Medicines recently recommended that NICE methods include QALY modifiers for severity and unmet need. This is consistent with the process already in place within the highly-specialised technology process, where a linear QALY weighting between 1 and 3 is applied, dependent on the magnitude of undiscounted incremental QALY gains. Products which offer 10 or fewer incremental undiscounted QALYs have a QALY weighting of 1; 30 QALYs or more equates to QALY weighting of 3.

	where QALY weightings are applied	and the magnitude of benefit that it is expected to provide. The model indicates that patients treated with Zynteglo are expected to gain 16 additional years of life, and 23.6 undiscounted QALYs.	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	As per the reference case, except one cost which could not be obtained for the UK. A French study was used for hospitalisation for harvest and harvest procedure, which was only £1,505 of the pre-infusion costs. bluebird bio have been working with NHS England to seek confirmation of the costs associated with the preparation, administration and monitoring of Zynteglo treatment.	All costs obtained through micro-costing using the NHS tariff, NHS Blood and Transplant Price Lists, and published studies (inflated to 2018, where appropriate). The distribution of iron chelation use in UK patients is obtained from the UK chart review, including the proportion of patients that are receiving combination therapies.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The same annual rate for both costs and health effects has been used, however a 1.5% rate has been used.	The use of lower discount rates (1.5% rather than 3.5%) is aligned with the most recent UK HM Treasury Green Book [19]. The All-Party Parliamentary Group on Access to Medicines recently recommended that NICE adopts the HM Treasury Green Book rate of 1.5%. Zynteglo meets the 2013 NICE Guide to the Methods of Technology Appraisal criteria for non-reference case discounting: • TDT patients in the UK face a quality of life equal to that of progressed non-small-cell lung cancer • By the nature of the gene therapy, there is no scientific rationale to suggest that the benefits of Zynteglo will not be sustained over a very long period • The consistent evidence base for Zynteglo demonstrates that it is highly likely that these outcomes will be achieved • The introduction of Zynteglo will not commit the NHS to significant irrecoverable costs, as the outcomes-based commercial arrangement will ensure that the majority of payment ([redacted]) is conditional on the patient remaining free of requiring transfusions for thalassaemia

A.5 Clinical effectiveness evidence

Table 3 Clinical effectiveness evidence

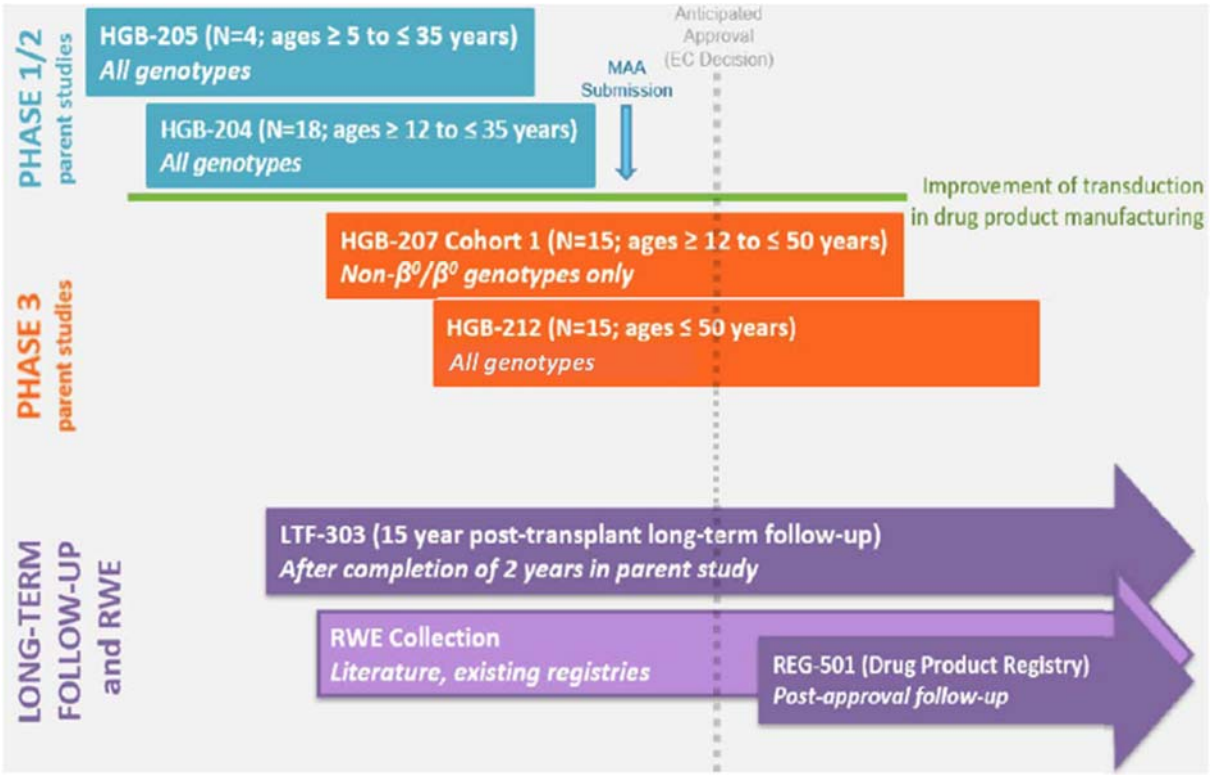
Study title	**HGB-205** **Completed February 2019**	**HGB-204 (Northstar)** **Completed February 2018**	**HGB-207 (Northstar-2)** **Ongoing**	**LTF-303** **Ongoing**
Study design	Phase 1/2 open-label, non-randomised, single site, single dose, uncontrolled	Phase 1/2 open-label, non-randomised, multi site, single dose, uncontrolled	Phase 3 open-label, non-randomised, multi site, single dose, uncontrolled	Long-term follow-up Study for patients enrolled in Studies HGB-205, HGB-204, HGB 207, and HGB-212
Population	Subjects with TDT who had received at least 100 mL/kg/year of pRBCs or ≥8 transfusions of pRBCs per year in each of the 2 years preceding enrolment. n=7 (**4 non-β^0/β^0 genotype TDT patients** and 3 severe SCD)	Subjects with severe SCD, or TDT who received at least 100 mL/kg/year of pRBCs in each of the 2 years preceding enrolment. n=18 (**10 non-β^0/β^0 genotype** and 8 β^0/β^0 genotype)	Subjects with TDT who do not have a β^0 mutation at both alleles of the HBB gene (i.e., non-β^0/β^0): Cohort 1 subjects ≥12 and ≤50 years of age, and Cohort 2 subjects <12 years of age. **n=15 (all belong to non-β^0/β^0 genotype)**	Patients with TDT or severe SCD treated in bluebird-sponsored clinical trials of Zynteglo.
Intervention(s)	Zynteglo Dose: ≥3.0 × 10^6 CD34+ cells/kg	Zynteglo Dose: ≥ 3.0 × 10^6 CD34+ cells/kg	Zynteglo Dose: ≥5.0 × 10^6 CD34+ cells/kg	No investigational treatment was administered in this Study
Comparator(s)	N/A	N/A	N/A	N/A

Outcomes specified in the decision problem	• Overall survival • Symptoms of anaemia • **Need for transfusion** • Iron overload complications: cardiac and liver • Adverse effects of treatment • Health-related quality of life	• Overall survival • Symptoms of anaemia • **Need for transfusion** • Iron overload complications: cardiac and liver • Adverse effects of treatment • Health-related quality of life	• Overall survival • Symptoms of anaemia • **Need for transfusion** • Iron overload complications: cardiac, liver and endocrine • Growth and development (for children and adolescents) • Adverse effects of treatment • Health-related quality of life	• Overall survival • Symptoms of anaemia • **Need for transfusion** • Iron overload complications: cardiac and, liver and endocrine • Growth and development (for children and adolescents) • Adverse effects of treatment • Health-related quality of life
Reference to section in submission	B.2.2. (pg. 53)	B.2.2. (pg. 53)	B.2.2. (pg. 54)	B.2.2. (pg. 55)

Transfusion independence (TI) defined as weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months at any time during the Study, after Zynteglo transfusion
TI evaluable defined as subjects who have completed their parent study, or achieved TI, or won't achieve TI in their parent study due to insufficient follow-up time remaining in parent study

The safety and efficacy of Zynteglo in TDT patients with a non-β^0/β^0 genotype has been assessed in two phase 1/2 Studies (HGB-205 and HGB-204) in patients with any TDT genotype and an ongoing phase 3 Study (HGB-207) in patients specifically with non-β^0/β^0 genotypes (Figure 3). An additional phase 3 Study (HGB-212) containing non-β^0/β^0 patients will also be used to support the safety and efficacy data of Zynteglo in the process of the NICE appraisal, however as yet relevant patients from this study are not yet TI evaluable. Patients from these 24-month Studies enter a long-term follow-up Study (LTF-303) for ongoing data collection up to fifteen years in total. Patients who receive Zynteglo in the commercial setting will be encouraged to enrol in a registry, which has been determined by the EMA to be part of a post-marketing commitment, with a 15-year follow-up period (REG-501).

Figure 3 Zynteglo Lifespan Approach to Clinical Evidence Generation



Note: The numbers of subjects given reflects the number planned for each group specified

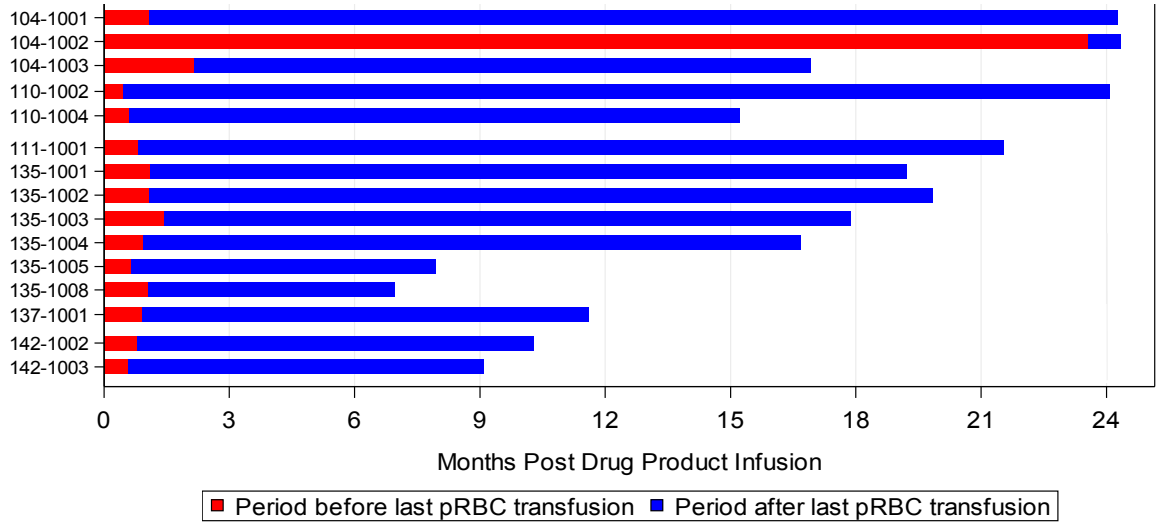
A.6 Key results of the clinical effectiveness evidence

A.6.1. Proportion of patients achieving 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 Zynteglo infusion. From a total of 24 TI evaluable patients, 20 patients (83.3%) have achieved TI. For patients treated with Zynteglo in Studies HGB-204 and HGB-205, 11 out of 14 non-β^0/β^0 subjects (78.6%) met the definition of TI at any time. The subjects who did not achieve TI in Phase 1/2 Studies were either producing relatively low amounts of HbA^{T87Q} and/or low amounts of endogenous HbA.

In Study HGB-207, all but one of the 15 patients with at least three months' follow-up have become transfusion-free [20] (Figure 4), with 9/10 patients achieving TI. The patient that did not achieve TI had [redacted] (Document B, section B.2.6.1.1, pg. 88).

Figure 4 Time since last transfusion in patients in HGB-207



Note: The figure includes patients >12 years who discontinued transfusions with ≥ 3 months follow-up

A.6.2. Time from Zynteglo administration to last transfusion and to reach TI (secondary endpoint)

To date, all non-β^0/β^0 treated patients (100%) with sufficient follow-up time (minimum 6 months after Zynteglo infusion) have responded to Zynteglo, either discontinuing transfusions or achieving notable reductions in transfusion requirements [20, 21].

Following the administration of Zynteglo, patients are expected to continue receiving transfusions for a relatively short period of time. For non-β^0/β^0 subjects across studies who achieved TI at any time (N=20), the median (min, max) duration of time from drug product infusion to last pRBC transfusion was relatively short, at [redacted] months. Median (min, max) time to reach TI was [redacted] months (Document B, section B.2.6.1.2, pg. 90).

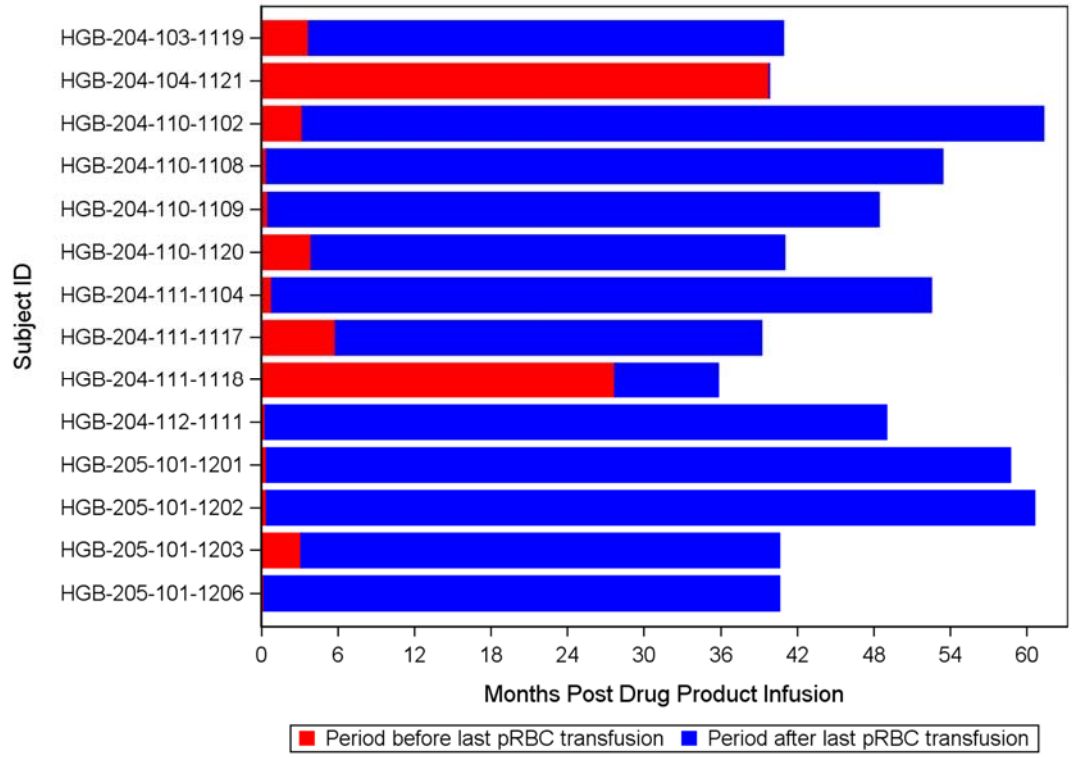
The long-term follow-up Study confirms that the majority of non-β^0/β^0 patients treated with Zynteglo become TI (according to the protocol definition in the phase 3 Studies), and those becoming TI maintained this status for the duration of follow-up to date.

A.6.3. Duration of TI (secondary endpoint)

The most recent TI data indicate that once TI is achieved, subjects maintain a state free from chronic pRBC transfusions through latest follow-up. Duration of TI was calculated for patients in Studies HGB-204 and HGB-205 who achieved TI at any time.

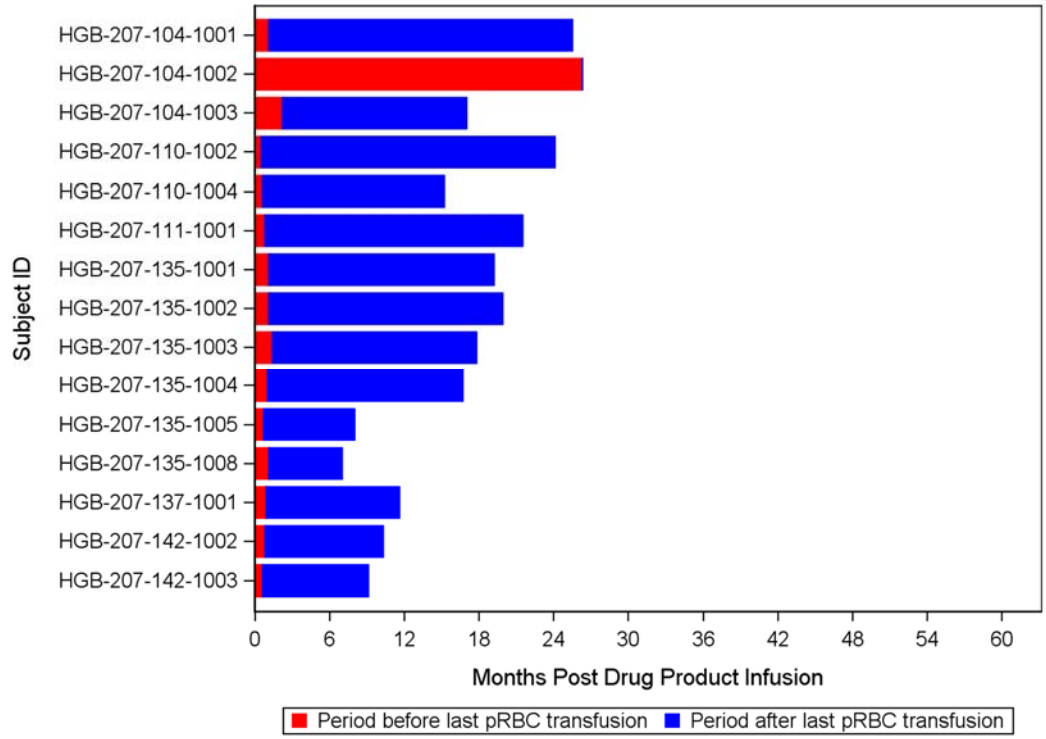
All non-β^0/β^0 subjects who achieved TI at any time (N=20) have maintained their TI status through all Hb assessments. The duration of TI was censored at the last Hb assessment and no events for loss of TI have yet been recorded. For these 20 non-β^0/β^0 subjects, median (min, max) observed duration of TI to date was 31.20 (12.1, 57.6) months, as all patients that have achieved TI remain free from transfusions at last follow up (Document B, section B.2.6.1.3, pg. 92).

Figure 5. Duration of transfusion and transfusion-free periods in LTF-303 (HGB-204 and HGB-205)



Source: June 2019 datacut, ISE Figures, pg. 1-2
Includes data through last available visit in Study LTF-303 as applicable [20]

Figure 6. Duration of transfusion and transfusion-free periods in LTF-303 (HGB-207)



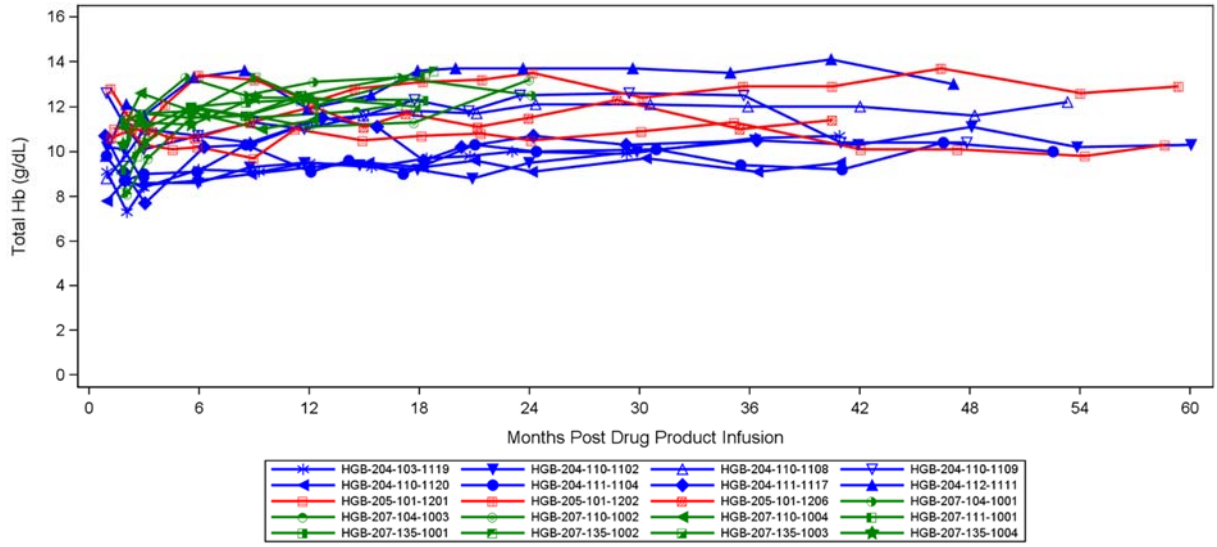
Source: June 2019 datacut, ISE Figures, pg. 1-2
Includes data through last available visit in Study LTF-303 as applicable [20]

A.6.4. Durable production of Haemoglobin (Hb) (secondary endpoint)

In Studies HGB-204, -205 and -207, for the subjects who achieved TI at any time (N=20), median (min, max) weighted average Hb during TI was 11.67 (9.3, 13.3) g/dL. For these subjects, their weighted average Hb during TI was generally equal or greater than their baseline pre-treatment weighted average nadir Hb, when they were dependent on transfusions, ranging from [redacted] g/dL (Document B, section B.2.6.2.1 pg. 93).

Regarding the total Hb over time, for the nine subjects from Study HGB-207 who achieved TI, median (min, max) total Hb in the absence of transfusions at Month 6 was 11.90 (11.5, 13.3) g/dL. The total Hb remains stable over time for patients that have achieved TI up to Month 60 (Figure 7). From the subjects in Study HGB-207 who are not yet evaluable for TI, if they maintain high levels of total Hb in the absence of transfusions, the majority are predicted to achieve TI.

Figure 7 Total Haemoglobin over time in non-β0/β0 in TI subjects



Data as of 31 July 2019.
Source: June 2019 data cut, ISE Figures, pg.110
Note: Subjects achieved TI are presented with solid lines, subjects who are TI evaluable but did not achieve TI are presented with dotted lines, subjects who are not TI evaluable yet due to short follow-up are presented with dash lines.

To achieve persistent durability of efficacy in the case of ex vivo, LVV-based gene therapies such as Zynteglo, treatment must result in the establishment of a population of undifferentiated, long-term HSCs in the bone marrow which carry the gene of interest, integrated into their genome.

Based on the mechanism of action of Zynteglo, which involves the insertion of functional copies of β-A-T87Q into long-term repopulating HSCs, durable clinical efficacy has been demonstrated out to 61.3 months, underscoring stable integration of the vector in the HSCs, and consequently, stable expression of the transgene in erythroid cells. Therefore, it is expected that the effects of the treatment will be life-long, and clinical data for patients that have successfully engrafted and achieved transfusion-independence across clinical studies support this view.

A.6.5. Transfusion reduction (secondary endpoint)

All patients from Studies HGB-204, HGB-205 and HGB-207 who did not achieve TI (N=4), maintained similar levels of transfusion reduction to last follow-up in Study LTF-303, with an overall percent change of annualised number of transfusions from baseline at a median of [redacted]% (from [redacted] per year) (Document B, section B.2.6.3.1 pg. 100). For the three non-β^0/β^0 subjects from Studies HGB-204 and HGB-205 who did not achieve TI at any time, their change in annualised transfusion frequency was [redacted] fewer transfusions per year for the two subjects from Study HGB-204, and [redacted] fewer transfusions per year for the subject from Study HGB-205. In patients from HGB-207 who did not achieve TI or are not yet evaluable for TI, there was a [redacted] % reduction from [redacted] transfusions to [redacted]

up to the last follow-up visit [20]. The single patient who was evaluable and did not achieve TI, achieved an annualised reduction of [redacted] % in transfusion frequency [20].

The changes in pRBC transfusion volume as compared to baseline pre-treatment transfusion requirements for non-TI subjects showed an overall percent change from baseline annualised volume at [redacted]% (Document B, section B.2.6.3.2 pg. 101).

A.6.6. Reduction in iron stores post-treatment

Patients who become TI no longer experience additional iron loading. From the long-term-follow up Study LTF-303, some patients who have completed their parent Studies (those treated in Studies HGB-204 and HGB-205) and have achieved TI, have a decrease in burden according to liver iron content (LIC), cardiac T2* and serum ferritin.

In the 11 non-β^0/β^0 patients in the HGB -204 and -205 Studies who achieved TI to date, [redacted] had an LIC value at 48 months post-treatment [20, 22] lower than their pre-treatment baseline measurement (Document B, section B.2.6.4.1 pg. 103). Cardiac T2* data, showed that all patients continue to have normal cardiac T2* values through their last follow-up, with [redacted] subjects demonstrating a cardiac T2* value that was higher than their pre-treatment baseline demonstrating a reduction in cardiac iron (Document B, section B.2.6.4.2 pg. 104). Finally, serum ferritin data showed [redacted] have a serum ferritin value at their last follow-up lower than baseline (Document B, section B.2.6.4.3 pg. 106). According to latest follow-up, the iron burden data for the nine subjects in Study HGB-207 who have achieved TI is not yet mature enough to show a definitive trend, with only approximately 12 months of follow-up (two patients up to 24 months).

Following Zynteglo treatment, of the 33 subjects (from HGB-204, HGB-205 and HGB-207) who have completed at least their Month 6 Visit, there were eight subjects who underwent phlebotomy post-Zynteglo infusion, while twelve subjects stopped iron chelation therapy post-Zynteglo infusion and did not undergo phlebotomy (Document B, section B.2.6.4.4 pg. 108).

A.6.7. Health related quality of life

HRQoL assessments were initiated in Studies HGB-204 and HGB-205 at different times (as these studies weren't initially intended to be registrational) and therefore several subjects did not have baseline QOL assessments, making it challenging to draw conclusions regarding the HRQoL data reported (Document B, section B.2.6.5 pg. 109).

Considering results from EQ-5D-3L and EQ-5D-Y, measured values reported an improvement in the HRQoL of non-β^0/β^0 TDT patients, with [redacted] having improved or similar scores for TTO and VAS, while [redacted] showed significant HRQoL improvement in the 'health state today' measurements ([redacted] in EQ-5D-3L and from [redacted] in EQ-5D-Y)..

PedsQL questionnaires also showed that [redacted] had improved results. [redacted], did not have consistent results with EQ-5D-Y. PedsQL

questionnaires were also completed by the parents of the TDT patients, with results showing that their HRQoL from baseline up to month [redacted], [redacted] parents, had an improvement in their total scale score.

For the SF-36v2, [redacted] showed a decrease in either category or both of the physical and mental component summary.

The FACT-BMT showed similar or improving values from baseline to last follow-up for [redacted] for the FACT-BMT Trial Outcome Index, the FACT-G Total Score and the FACT-BMT Total Score.

A.6.8. Hospitalisation and health care resource utilisation

During Study HGB-204, hospitalisations were associated with mobilisation/apheresis, conditioning, and recovery after Zynteglo BB305 Drug Product infusion. There was no meaningful change in hospitalisation visits when comparing frequency of visits before treatment and post-discharge following engraftment for all subjects. During the extension Study LTF-303, there have been [redacted] that had overnight hospitalisation; [redacted].

From Study HGB-205, hospitalisations post-discharge following Zynteglo took place on three occasions, one for a wisdom tooth extraction which required hospitalisation for 9 days, one for pneumonia which required hospitalisation for 7 days and a hospitalisation for major depressive disorder for 2 days.

Finally, in the 2 years prior to enrolment in the HGB-207 Study there was [redacted]. The [redacted] subjects who have at least 365 day post-Zynteglo infusion follow-up were not hospitalised in the 2 years prior to enrolment and were also not hospitalised during the period from 12 months post-Zynteglo infusion to last follow-up (Document B, section B.2.6.6 pg. 113).

A.6.9. Growth and development

For patients <18 years old, growth and puberty parameters such as hormonal testing, physical examination and tanner staging were evaluated. This included Tanner staging at Screening and every 6 months during puberty, as well as bone density, diabetes, endocrine, and neurocognitive development evaluations. In Study HGB-207, Tanner staging was performed for adolescent subjects with sufficient follow-up up to month 24. All were [redacted] (Document B, section B.2.6.7 pg. 113).

A.6.10. Adverse reactions

No safety issues have been attributed to the BB305 lentiviral vector (LVV) in the phase 1/2 Studies [21] or the phase 3 HGB-207 Study [20] (Document B, section B.2.10.1 pg. 115).

There has been no detection of replication-competent lentivirus, clonal dominance, or haematological malignancy in these trials, including within LTF-303. In up to 61.3 months follow-up there have been no instances of transplant-related mortality, graft rejection or GvHD reported [22, 23]. Furthermore, [redacted] which is a potential concern with gene therapies, [redacted] [22, 23].

As of the latest data provided available, [redacted] of non-β^0/β^0 patients aged ≥12 years (ITT population) experienced at least 1 AE, [redacted] experienced AEs related to drug product, and [redacted] experienced an AE ≥ Grade 3 related to drug product. [redacted] subjects [redacted] experienced at least 1 SAE with [redacted] reported as a drug product-related SAEs. No deaths were reported in the studies (Document B, section B.2.10.3 pg. 116).

A.7 Evidence synthesis

As detailed in Table 2, since Zynteglo has only been evaluated in single-arm studies, an indirect or mixed treatment comparison is not possible. In addition, transfusions and chelation therapy would not be an appropriate comparator for the primary and key secondary study endpoints of transfusion-independence and transfusion-reduction because patients with TDT receiving supportive care do not spontaneously achieve transfusion independence or have significant reductions in their transfusion requirements (Document B, Section B.2.9. pg. 114).

A.8 Key clinical issues

- The clinical studies conducted for Zynteglo are uncontrolled, with a limited patient sample size which was inevitable due to the rarity of the TDT condition and the nature of the intervention.
- Risks associated with Zynteglo treatment include the risks of myeloablative conditioning with busulfan required prior to drug product infusion, as well as any identified or theoretical risks of Zynteglo. To date, no safety issues have been attributed to the BB305 lentiviral vector, with a risk management plan in place to monitor and address safety issues. Ongoing data collection through clinical studies and the Zynteglo registry (REG-501) will inform long-term safety of the therapy (Document B, section B.2.13 pg. 146).
- Study LTF-303 and the bluebird bio sponsored Zynteglo registry (REG-501) are designed to provide long term data for Zynteglo treatment with durable clinical efficacy being already demonstrated out to 61.3 months. Long term data gathering is still underway for gene therapies and Zynteglo, to show clinical efficacy over time. Zynteglo was accepted into the Adaptive Pathways programme of the EMA in June 2014, in order to engage early with stakeholders and discuss the development and registration strategy of the product. bluebird bio's approach to clinical evidence generation for Zynteglo was based on the Adaptive Pathways principle that "the evaluation of all drugs is not binary but a continuum" and so data will continue to be generated on the

product through various modalities, including active surveillance and additional Studies after initial and “full” licensing (Document B, section B.2.1.1 pg. 146).

- There is currently a limited data set available to provide clear evidence of the HRQoL impact of Zynteglo therapy. Whilst most patients showed an improvement in their HRQoL with time, there are limitations in the data due to an [redacted] for Studies HGB-204 and HGB-205 and ceiling effects in Study HGB-207, where several patients rated their EQ-5D as 1 at baseline, equating to perfect health (Document B, section B.2.6.5 pg. 109 and section B.3.4.5 pg. 182).
- Although the probability of patients achieving TI is high, a small number (4 out of 24) have not attained TI but have had a meaningful reduction in transfusion frequency and volume.

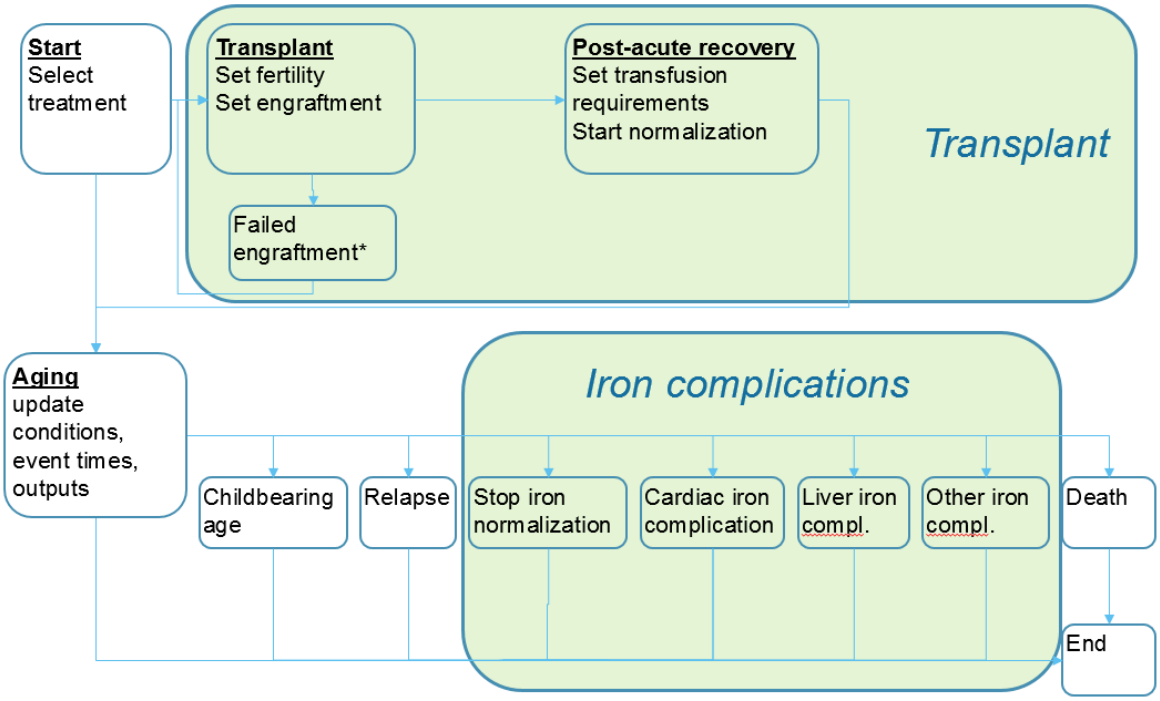
A.9 Overview of the economic analysis

The model compares transplantation with Zynteglo gene therapy to blood transfusions and iron chelation therapy, from the perspective of the NHS in England and Wales, over a lifelong time horizon.

Iron overload and related complications account for the majority of TDT morbidity and mortality. Historical data on overall rates of complications and mortality may not be predictive of future outcomes due to changes in the management of iron overload that have occurred in recent years. The modelling approach therefore maintains the focus on iron levels in the future as driver of cardiac, liver and endocrine outcomes. An individual patient modelling approach has been used to capture the effects of organ-specific iron overload, as it allows timing and order to vary between the various events that occur in TDT. An Excel-based discretely integrated condition event (DICE) simulation framework has been used to generate a discrete event simulation model, which uses a series of conditions (e.g. the development of iron overload) and events (e.g. blood transfusion).

As patients age, those who become transfusion-independent are assumed to have survival and utility closer to the UK general population than transfusion-dependent patients. Patients who are not transfusion-independent receive lifelong blood transfusions and iron chelation therapy (at baseline levels or reduced frequency). Patients then experience iron-related complications at rates consistent with the iron level in the appropriate tissue i.e. cardiac complications are based on cardiac iron levels, liver complications based on liver iron concentration (LIC), and endocrine complications based on serum ferritin. Mortality is assumed to be dependent on age, gender, whether or not the patient is transfusion-independent, and the presence of cardiac complications. A sequence of major events dictates how this progression will occur during transplant and acute recovery, post-acute recovery, and ongoing ageing (Figure 8). As myeloablative conditioning regimens given prior to Zynteglo may cause permanent sterility, modelled patients are also at risk of subfertility or infertility however this is commonly encountered with standard management due to iron overload affecting the endocrine and reproductive systems therefore only the expected incremental infertility is modelled.

Figure 8 Model diagram – B.3.2.5 (page 161)



A.10 Incorporating clinical evidence into the model

The baseline characteristics of the modelled population in terms of age and gender are based on the TI-evaluable patients from the clinical studies (HGB-204, 205 and 207) (n=24) to reflect a cohort of patients that wish to receive gene therapy. One third of these patients are paediatric patients, the oldest patient was [redacted] years and [redacted]% were female.

At baseline, transfusion-dependent patients have a specified level of iron as a function of serum ferritin, LIC and myocardial T2*. bluebird bio conducted a chart review of medical records in 9 UK centres (including 162 patients) to understand the current real-world routine management for patients with TDT in the UK and iron levels. Since patients with high cardiac iron loading would not be eligible for Zynteglo therapy, the distribution of Myocardial T2* was adjusted such that no patients had high iron. The model assumes that the TDT cohort receiving ongoing transfusions and iron chelation therapy will maintain a static distribution of iron levels in the population over time.

Table 4 Iron levels in transfusion-dependant patients, based on a UK chart review of 162 patients – B.3.3.1 (page 168)

Iron level	Serum Ferritin	LIC	Myocardial T2*
Low Iron	[redacted]	61%	88%
Moderate Iron	[redacted]	23%	12%
High Iron	[redacted]	16%	0%

The key clinical parameters for Zynteglo are the rates of transfusion-independence and transfusion-reduction. The proportion of patients becoming transfusion-independent (20/24, 83.3%) is based on all TI-evaluable patients from the HGB-204, 205 and 207 clinical studies. In the 4 patients that did not achieve transfusion-independence, there was a mean reduction in transfusion frequency of [redacted]% so these patients are assumed to have [redacted]% fewer transfusions and a reduction in iron chelation therapy dosing.

As detailed in A.7.4, based on the mechanism of action of Zynteglo, which involves the insertion of functional copies of a modified β-globin gene into long-term repopulating haematopoietic stem cells, it is expected that the effects of treatment will be life-long. Consequently, the rates of transfusion-independence and transfusion-reduction have been extrapolated to the life-long time horizon of the model.

The long-term change in iron levels following Zynteglo are not well established from the duration of follow-up data currently available. Therefore, data on iron levels in patients that have received allogeneic-HSCT are used as a proxy for the expected time to normalisation with Zynteglo. Transfusion-independent patients are assumed to have normalised iron levels 4 years after Zynteglo administration, whereas transfusion-reduced patients are assumed to have mostly low iron levels, or moderate iron levels.

To predict the complications of iron overload, the model uses literature-based rates and risk equations to estimate the rate of developing complications based on distribution of iron levels in the heart, liver, and endocrine system. The rate of developing cardiac complications is highest in patients with high iron (annual rate 0.065) but still occurs in patients with low iron (annual rate 0.011). Liver complications only develop in patients with high iron (0.083). In terms of endocrine complications, the rates of developing diabetes and hypogonadism are dependent on age, serum ferritin and myocardial T2* (Table 53, page 180).

A.11 Key model assumptions and inputs

Table 5 Key model assumptions and inputs

Model input and cross reference	Source/assumption	Justification
Baseline characteristics of patients Document B, section B.3.3.1 pg. 168	Age and gender of the patient population is based on patients enrolled in the clinical trials (HGB-204, 205 and 207) that were evaluable for TI. Weight is based on the bluebird bio UK chart review.	The age and gender reflect a cohort of patients that wish to receive gene therapy. This is consistent with the efficacy data which are also obtained from the same population. Since resource use and the distribution of iron-loading for chelation agents is obtained from the UK chart review, the same source is used for patient weight, rather than the clinical trials. The mean weight of patients in the UK chart review may in fact be an underestimate due to missing data being predominantly in adults rather than adolescents, so using the mean weight from the chart review may be considered conservative.
Mortality Document B, section B.3.3.5 pg. 176	Transfusion-independent: SMR 1.25 (assumed)	An assumed moderate impairment of survival is included for transfusion-independent patients to capture the potential mortality impact of

	Transfusion-dependant 3.9 (published literature) Transfusion-reduced 2.6 (assumed) Cardiac-related death probability 13% (published literature)	myeloablative conditioning. This is likely to be a conservative assumption as it applies for the patients' entire lifetime. The likelihood of this assumption being conservative is further highlighted when considering that the assumed value is consistent with SMR values reported for patients with Type 2 diabetes [24].
Utility decrements versus the general population Documents B, section B.3.4.5 pg 182	Transplant 0.31 (vignette study) Transfusion-independent: 0.02 (vignette study) Transfusion-dependant 0.27 (UK chart review EQ-5D) Transfusion-reduced 0.12 (assumed)	Utilities of 1.0 were observed before transplant which reflects ceiling effects and adaptation bias. Due to these limitations, quality of life data measured using the EQ-5D was prospectively collected directly from patients receiving transfusions and iron chelation during the UK chart review. A vignette study was conducted in the UK general population to inform assumptions around the quality of life impact of TDT and Zynteglo. A vignette method was appropriate for Zynteglo patients as it is not routine practice and therefore the utilities are hypothetical.
Costs associated Zynteglo administration and monitoring Document B, section B.3.5.1 pg. 187	Pre-infusion costs £27,057 and £27,130 for those below and above 18, respectively. Administration costs £34,539 and £18,529, respectively. Monitoring costs £1,138 for Year 1 and 2 and £937 for year 3 and 4.	All costs obtained through micro-costing the Zynteglo study protocols, using the NHS tariff, NHS Blood and Transplant Price Lists, NHS reference costs, the PSSRU Unit Costs of Health and Social Care and published studies (inflated to 2018, where appropriate). The only non-UK cost was for hospitalisation for harvest and harvest procedure, which was only £1,505 of the pre-infusion costs.
Annual acquisition and administration costs of blood transfusions and iron chelation therapies in transfusion-dependant patients Document B, section B.3.5.1 pg. 187	Transfusions: £2,326 and £4,527 for those below and above 18, respectively. Desferrioxamine acquisition costs £5,836 and £8,753 for those below and above 18, respectively; administration costs £9,220 Deferosirox acquisition £23,011 Deferiprone acquisition £5,829	All costs obtained through micro-costing using the NHS tariff, NHS Blood and Transplant Price Lists, and published studies (inflated to 2018, where appropriate). As a subcutaneous treatment, desferrioxamine is associated with administration costs whereas the other two iron chelation therapies and oral, with no administration costs. The distribution of iron chelation use in UK patients is obtained from the UK chart review, including the proportion of patients that are receiving combination therapies.

A.12 Base-case ICER (deterministic)

The base-case results for Zynteglo versus transfusions and iron chelation therapy are shown in Table 6, which includes the simple discount and the outcomes-based scheme. Note that the life years results presented are not discounted by costs and QALYs are discounted.

Table 6 Base-case results (deterministic) – B.3.7 (page 212)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Transfusions and iron chelation therapy	[redacted]	38.10	17.79				
Zynteglo	[redacted]	**54.27**	**31.42**	[redacted]	**16.17**	**13.62**	[redacted]
Abbreviations: Inc, incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

A.13 Probabilistic sensitivity analysis

The distributions used to measure uncertainty in each variable is detailed in Document B, Table 70 (pg. 202). The results of the PSA suggest that the total costs of transfusions and iron chelation therapy have decreased and the total QALYs have decreased in both the Zynteglo and the transfusions and iron chelation therapy arms. This results in greater incremental costs and lower incremental QALYs versus the base case analysis, resulting in a higher ICER. One potential reason for the discrepancy in deterministic and probabilities analysis is that the age distribution sampled in the PSA allowed ages of up to 50 years, whereas only patients up to the age of [redacted] are included in the efficacy population (patients evaluable for TI). This population was chosen for the base case to reflect a population wishing to receive a gene therapy.

Table 7 Base-case results (probabilistic) – B.3.8 (page 213)

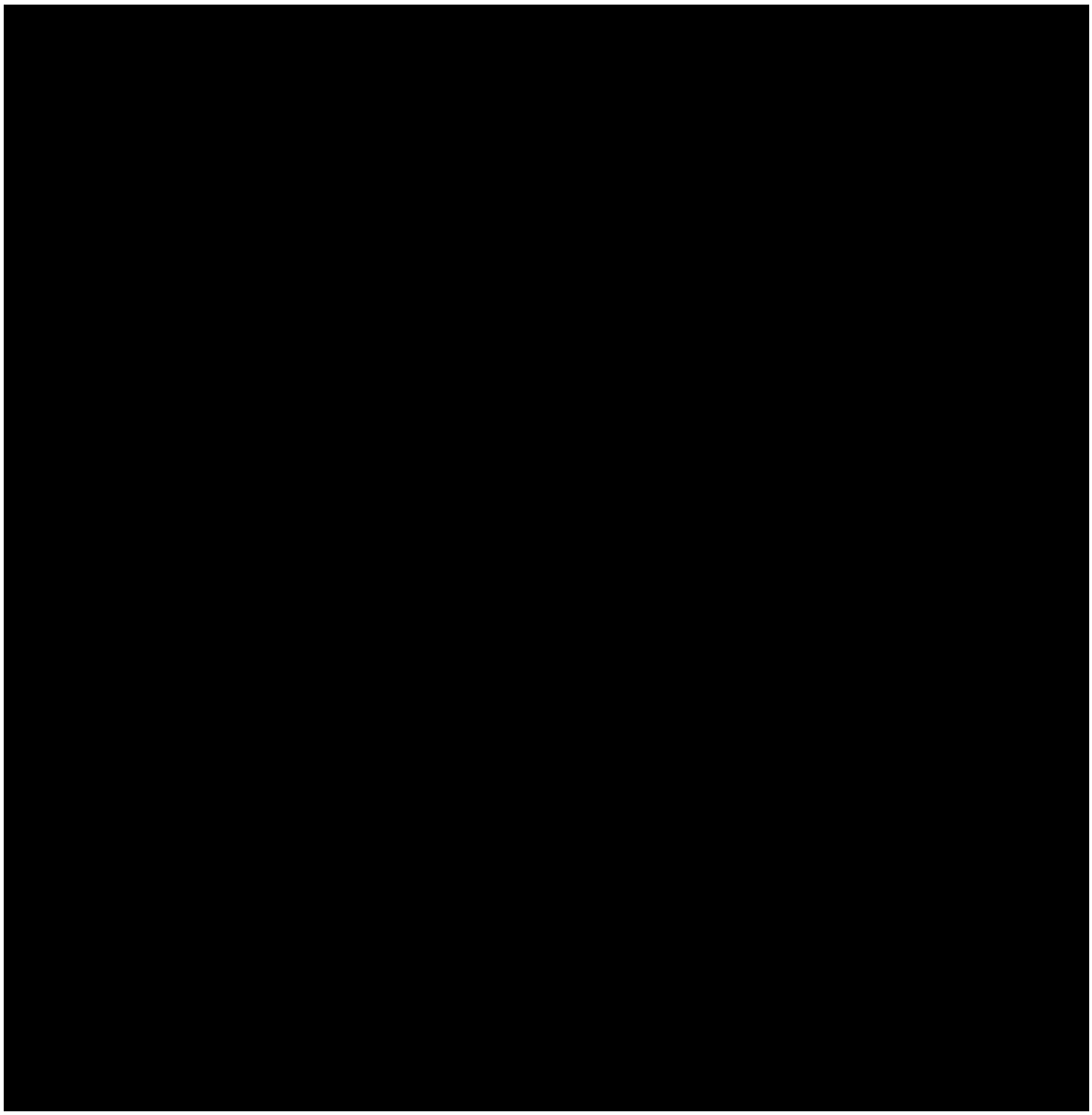
Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Transfusions and iron chelation therapy	[redacted]	17.04			
Zynteglo	[redacted]	**27.08**	[redacted]	**13.25**	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Figure 9 Scatterplot of probabilistic results – B.3.8 (page 214)

A.14 Key sensitivity and scenario analyses

The results of the deterministic sensitivity analysis indicate that the ICER is most sensitive to the cost of chelation therapies, the use of deferasirox versus deferiprone, the age distribution of the patient population, the disutility associated with transfusion-dependence, body weight and the cost of infertility. The results are insensitive to the distributions of iron loading, complication rates, Zynteglo administration and monitoring costs, other infertility variables, and standardised mortality ratios.

Figure 10 Tornado diagram – B.3.8 (page 215)



The results of the scenario analysis indicate that the results are sensitive to the age distribution and relatively insensitive to the mortality assumptions around transfusion-independence, which is consistent with the deterministic sensitivity analysis results.

Table 8 Key scenario analyses – B.3.8 (page 215)

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			
Use of HES for age distribution rather than clinical trial populations (Document B,	Broader age distribution with older patients included (e.g. % aged 12-17 and % aged 40-45 years), compared to trial populations (e.g. %	To consider the impact of introducing Zynteglo on the prevalent UK population rather than using international clinical trial populations. Note that this scenario is unlikely to accurately	[+24%]

B.3.3.1, page 168)	aged 12-17 years and oldest patient aged [redacted])	reflect a population that wish to receive a gene therapy.	
Mortality: no impairment of survival due to myeloablative conditioning (Document B, section B.3.3.5 pg. 176)	SMR for transfusion-independent patients of 1.00, rather than 1.25 in the base case	The assumed moderate impairment of survival is included to capture the potential mortality impact of myeloablative conditioning. This is likely to be a conservative assumption as it applies for the patients' entire lifetime.	[redacted] [-5%]
Utility values from vignette study (Document B, B.3.4.5, page 182)	First year of transplant: no change from base case Transfusion-independence: no change from base case Transfusion-dependant (oral chelation therapy): 0.23 versus 0.27 in base case Transfusion-dependant (subcutaneous chelation therapy): 0.33 versus 0.27 in base case Transfusion-reduction: 0.20 versus 0.12 in base case	To explore the impact of an alternative source of utilities, whereby the same source is used for all utilities, rather than the base case where both vignette decrements and the UK chart review are utilised.	[redacted] [+8%]

Results with [redacted] have been provided in Document B (section B.3.8 pg. 217).

A.15 Innovation

Ex-vivo gene therapy seeks to treat the underlying cause of a disease by transferring a target gene of interest into a patient's own cells, therefore this technology has the potential to offer patients a transformative treatment option without the safety risks associated with allogeneic HSCT. The UK government recognised the potential of gene and cell therapies early and invested significantly into the gene and cell therapy catapult, the new manufacturing opportunities in Stevenage and through innovate UK, directly into hospital providers to explore how these ground-breaking innovations could be incorporated into the NHS (Document B, section B.2.12 pg. 143).

Zynteglo is the first and only one-time gene therapy for TDT that gives patients the potential to reach transfusion independence. BB305 Lentiviral Vector (LVV) is a replication-defective, self-inactivating (SIN), third-generation, human immunodeficiency virus type 1 (HIV-1)-based LVV, which was specifically designed by bluebird bio to achieve sufficiently high levels of transgene-derived Hb that would eliminate or significantly reduce the need for transfusions.

Zynteglo offers eligible patients a one-time, ex-vivo, gene therapy treatment that addresses the underlying genetic cause of the condition. Since only 25-30% of paediatric patients will have access to a suitably matched donor and allo-HSCT in not performed in adults, Zynteglo therapy offers those patients unable to undergo allo-HSCT a new option that corrects the underlying genetic aberration in TDT patients. In light of this, treatment with Zynteglo is considered a disruptive innovation that can eliminate the need for life-long supportive care with regular transfusions and iron chelation therapy, for the majority of patients.

A.16 Budget impact

Table 9 Budget impact – Company budget impact analysis submission, Table 16 (page 32)

	Company estimate	Cross reference
Number of people in England who would have treatment	The base case analysis estimates [redacted] prevalent patients would be treated over several years, in addition to [redacted] incident patients per year. NHS England estimated uptake assumptions suggest this could be as high as [redacted] prevalent patients and [redacted] incident patients, which could be treated over a [redacted] year timeframe.	Document C, Section 3.2 and Section 5
Average treatment cost per person	[redacted] if patients becomes and remains transfusion-independent for [redacted] Based on the clinical trials, 83.3% of patients became transfusion-independent so the full cost of £[redacted] would be incurred for 83.3% of patients, whilst a cost of only £[redacted] would be incurred for the remaining 16.7% of patients. This equates to an average cost per patient of £[redacted] for Zynteglo (exclusive of pre-transplant costs and administration costs).	Document C, Section 1.1
Estimated annual budget impact on the NHS in England	With the submitted patient access schemes for Zynteglo (see Table 1), the budget impact is estimated to be £[redacted] in the first year rising to £[redacted] in year five.	Document C, Section 7.1

A.17 Interpretation and conclusions of the evidence

As detailed in section A.15, the UK government has recognised the potential of gene and cell therapies. Zynteglo has demonstrated consistent clinical efficacy in the population defined in the scope with pooled results across clinical studies showing a timely onset of effect and transfusion-independence achieved in the majority. Transfusion-independence represents a

clear and meaningful benefit to patients and prevents the significant life-shortening complications of TDT.

Compared to transfusions and iron chelation therapy, Zynteglo is expected to increase survival by 16.17 years and is associated with 23.55 undiscounted incremental QALYs and 13.62 discounted incremental QALYs. The ICER (including commercial arrangements) is £[redacted] per additional QALY gained. This ICER is driven by the utility gain and cost offsets from avoidance or reduction in lifelong transfusions and iron chelation therapies, as well as the avoidance of heart, liver and endocrine complications.

A key strength of the analysis was the collection of UK specific data to ensure generalisability of the results to England and Wales. The large chart review conducted by bluebird bio provides UK-specific, current treatment patterns and patient outcomes which are pivotal to the model structure. The vignette study, conducted to measure utilities which cannot be obtained accurately from the clinical trials (i.e. transplant year and transfusion-independence), was also conducted in the UK with respondents from the general population.

As stated in Table 2, it has not been possible to quantify the impact of the treatment on caregivers of children and adult patients with TDT. Furthermore, the modelled complications are limited to cardiac disease, liver disease, hypogonadism and diabetes so it is likely that not all health-related costs associated with chronic transfusions and the subsequent iron overload have been considered in the analysis. In addition to the underestimated health-state costs, it has not been possible to estimate the personal social service costs, such as disability living allowance, which a UK study indicated that two-thirds of families of children have received.

A.18 References

1. Galanello, R. and R. Origa, *Beta-thalassemia.* Orphanet Journal of Rare Diseases, 2010. **5**: p. 11-11.
2. UKTS, *Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK, 3rd Edition*. 2016.
3. Cappellini, M.D., et al., *Thalassemia International Federation: Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT), 3rd Edition*. 2014.
4. Olivieri, N.F., *The beta-thalassemias.* N Engl J Med, 1999. **341**(2): p. 99-109.
5. Borgna-Pignatti, C., et al., *Survival and Complications in Thalassemia.* Annals of the New York Academy of Sciences, 2005. **1054**(1): p. 40-47.
6. Angelucci, E., et al., *Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation.* Blood, 2002. **100**(1): p. 17-21.
7. Shah, F., et al. *Chart Review - Routine management, healthcare resource use and patient/caregiver-reported outcomes of patients with transfusion-dependent β-thalassaemia in the United Kingdom: a mixed methods observational study*. in *61st ASH annual meeting*. Draft poster. Orlando, FL, USA.
8. Modell, B., et al., *Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance.* Journal of cardiovascular

magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance, 2008. **10**(1): p. 42-42.
9. Srisukh, S., B. Ongphiphadhanakul, and P. Bunnag, *Hypogonadism in thalassemia major patients.* Journal of clinical & translational endocrinology, 2016. **5**: p. 42-45.
10. Jobanputra, M., C. Paramore, and S.G. Laird, *Comorbidites in transfusion-dependent beta(β)-thalassemia in England: a 10-year retrospective cohort analysis*, in *British Society for Haematology Annual Scientific Meeting*. 2018: Liverpool.
11. De Sanctis, V., A. Eleftheriou, and C. Malaventura, *Prevalence of endocrine complications and short stature in patients with thalassaemia major: a multicenter study by the Thalassaemia International Federation (TIF).* Pediatr Endocrinol Rev, 2004. **2 Suppl 2**: p. 249-55.
12. Jobanputra, M., et al., *Co-morbidities and mortality associated with Transfusion Dependent Beta-thalassaemia Patients in England: A 10-Year Retrospective Cohort Analysis - Draft manuscript.* Draft manuscript.
13. Angelucci, E., et al., *Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel.* Haematologica, 2014. **99**(5): p. 811-20.
14. Zynteglo SmPC, *bluebird bio, Zynteglo 1.2 20 × 106 cells/mL dispersion for infusion. Draft Summary of Product Characteristics.* 2019.
15. Zynteglo SmPC, *EMA SmPC Zynteglo.* 2019.
16. bluebird bio Inc, *Draft summary document for consideration in service specification design and procurement requirements for identifying appropriate Treatment Centres to deliver LentiGlobin for transfusion-dependent β-thalassaemia (TDT).* 2018.
17. Clarke, S.A., et al., *Health-related quality of life and financial impact of caring for a child with Thalassaemia Major in the UK.* Child Care Health Dev, 2010. **36**(1): p. 118-22.
18. bluebird bio Inc, *Systematic review of the burden of disease and treatment for transfusion dependent β-thalassemia.* 2018.
19. HM Treasury, *The Green Book. Central Government Guidance on Appraisal and Evaluation*. 2018.
20. bluebird bio Inc, *June 2019 integrated TLFs for HGB-204, HGB-205, HGB-207 and LTF-303*. 2019.
21. Thompson, A.A., et al., *Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia.* New England Journal of Medicine, 2018. **378**(16): p. 1479-1493.
22. Rasko JEJ and e. al. *Clinical outcomes of LentiGlobin gene therapy for transfusion-dependent β-thalassemia following completion of the Northstar HGB-204 study*. in *American Society of Hematology*. 2018. San Diego, CA.
23. Locatelli F and e. al. *LentiGlobin gene therapy for patients with transfusion-dependent β-thalassemia (TDT): results from the phase 3 Northstar-2 and Northstar-3 studies*. in *American Society of Hematology*. 2018. San Diego, CA.
24. Harding, J.L., et al., *Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997-2010.* Diabetes Care, 2014. **37**(9): p. 2579-86.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

Clarification questions

October 2019

File name	Version	Contains confidential information	Date
ID 968 Zynteglo clarification letter to PM [REDACTED] vpost ERG 4Feb2019	Vpost ERG	Yes	4 February 2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Zynteglo trial data

A1. Priority question: The CONSORT flow charts in Appendix D1.2 are unclear in terms of missing reasons for exclusion and which patient subgroups are included. Consequently, the numbers do not add up correctly. Please provide revised CONSORT flow charts specifically for the patients who fit the NICE scope – please ensure an intention-to-treat (ITT) approach is adopted. Please provide: number screened for eligibility, number ineligible/excluded, number who declined participation, number recruited into study, number of patients mobilised, and the number who received a Zynteglo infusion. Please provide clear reasons for withdrawals at each stage and ensure that the numbers add up.

Figure 1. Study disposition for HGB-204

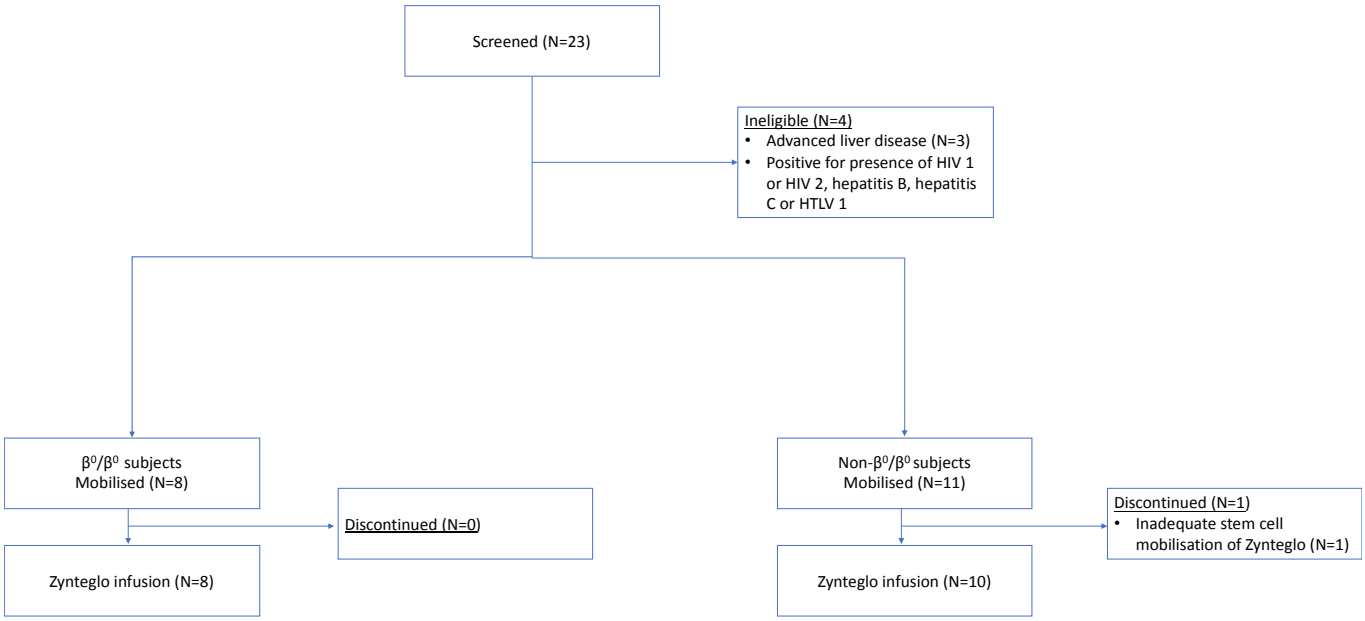


Figure 2. Study disposition for HGB-205

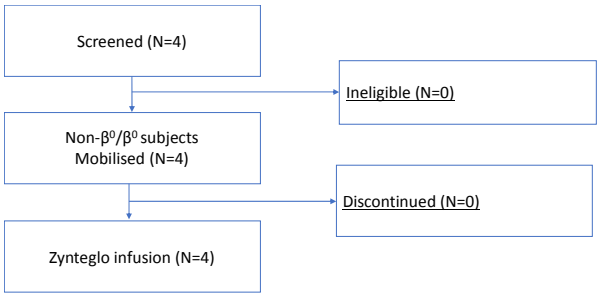
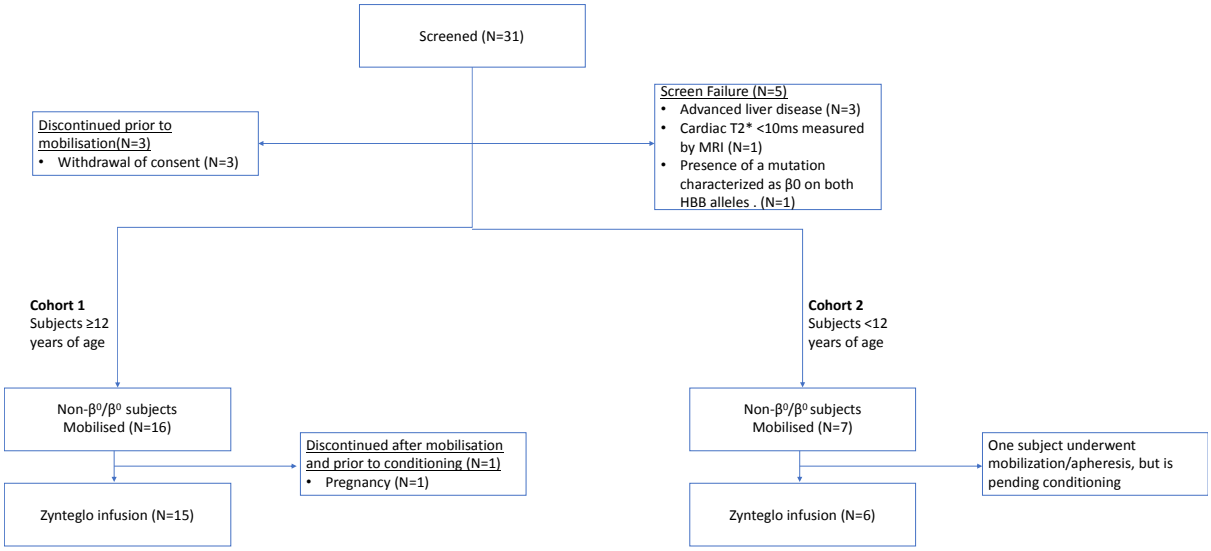
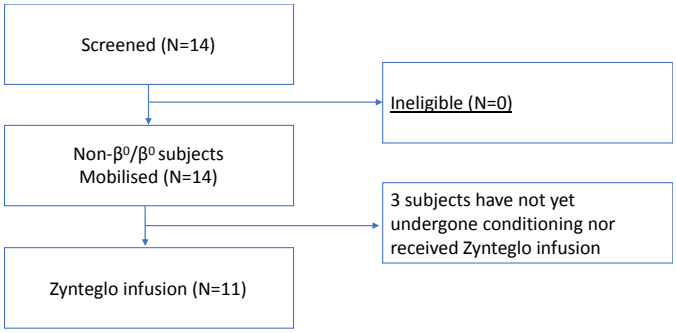


Figure 3. Study disposition for HGB-207



A2. Priority question: Please provide the most up-to-date CONSORT flow-chart for study HGB-212 for the subgroup of patients who fit the NICE scope.

Figure 4. Study disposition for HGB-212



A3. Priority question: Please provide further details for studies HGB-212 and LG001, specifically using the fields presented in Table 10 (in the Company Submission), and by adding rows for HGB-212 and LG001 to Table 8 (in the Company Submission). Please provide a clinical study report (CSR) and CONSORT diagrams for studies HGB-212 and LG001.

Study LG001 was a phase I study utilising a different vector for HSC transduction known as HPV569 and as a result, a different drug product to Zynteglo. The study was terminated as a new vector was developed however two patients were treated. In discussions with the EMA, LG001 was considered 'proof-of-concept' for Zynteglo, but ultimately utilised a different product. Therefore, as LG001 was a phase I study using a different vector and resultant drug product, evidence from the study is not being used in this submission and so a CSR and CONSORT diagram has not been provided.

The CONSORT diagram for study HGB-212 is provided in A2, while further details have been provided below.

Table 1. Overview of Clinical Studies Evaluating Zynteglo for non-β^0/β^0 genotype patients with TDT (Table 8 in main submission)

Study, status, manufacturing process*	**Study type, Zynteglo dose**	**Study population, planned n (actual n for completed studies)**	**Primary endpoint(s)**
HGB-212 (ongoing)	Phase 3 open-label, single-arm, multisite, single-dose study Dose: ≥ 5.0 × 10^6 CD34+ cells/kg	TDT (any genotype) Age ≤50 years n=14 (5 non-β^0/β^0 and 9 β^0/β^0 genotype TDT patients)	**Efficacy:** Proportion of patients achieving transfusion reduction (TR), defined as demonstration of a ≥60% reduction in the annualised volume of packed red blood cells (pRBCs) transfusion requirements (in mL/kg) in the post-treatment time period from 12 months post-drug product infusion through Month 24 (approximately a 12-month period), compared to the annualized mL/kg pRBC transfusion requirement during the 2 years prior to study enrollment.

Table 2. Clinical effectiveness evidence for Study HGB-212 (same as table 10 in main submission)

Study	HGB-212				
Study design	Open-label, single-arm, multisite, single-dose, Phase 3 study				
Population	Subjects with TDT who had received at least 100 mL/kg/year of pRBCs (all subjects) or be managed under standard thalassaemia guidelines with ≥8 transfusions of pRBCs per year in the 2 years preceding enrolment (subjects ≥12 years).				
Intervention(s)	Zynteglo gene therapy				
Comparator(s)	None; single-arm study				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	
	No			No	X
Rationale for use/non-use in the model	Data from this study have not yet been included in the submission as patients were not yet evaluable for transfusion-independence and so data was not yet mature to provide meaningful results.				
Reported outcomes specified in the decision problem	• Overall survival • Symptoms of anaemia • **Need for transfusion** • Iron overload complications: cardiac and liver • Adverse effects of treatment • Health-related quality of life				
All other reported outcomes	• Use of iron chelation • Phlebotomy • Dyserythropoiesis • **Hospitalisations** • Pharmacodynamic endpoints • **Success and kinetics of HSC engraftment** • Detection of vector-derived RCL in any subject • Presence of clonal dominance				

A4. Please clarify whether efficacy or safety data (or both) from studies HGB-212 and LG001 are being used in the submission.

As mentioned in the main submission (pg. 46), emerging data from the non-β^0/β^0 cohort of the HGB-212 study will be used to support this appraisal of Zynteglo, as patients become evaluable for transfusion-independence. Results from 3 TI evaluable patients from study HGB-212 will become available early December and will be presented during the appraisal. For the main submission in October, data was not yet mature to provide meaningful results.

Study LG001 was a phase I study utilising a different vector for HSC transduction known as HPV569, and therefore a different drug product from Zynteglo. As a result, evidence from the study is not being used in this submission.

A5. Priority question: Please provide genotype characteristics of all eligible ITT patients included in the Company Submission using the categories: β+/β+, β+/β0, βE/β0, βS/βS, βS/β0, βS/β+ e.g. how many patients were β+/β+ etc.

Please see below the genotype characteristics of all eligible non-β^0/β^0 subjects from the ITT population. Although study HGB-205 included Sickle Cell Disease (SCD) patients, this submission does not contain data from these patients (as these patients are not indicated per the Zynteglo SmPC). Therefore, genotypes such as βS/βS, βS/β0, βS/β+ are not included in this submission. The subject genotypes included in this submission are: 6 β+/β+ subjects (of which [redacted] IVS-I-110), 15 βE/β0 subjects and 10 β0/β+ subjects.

Table 3. Genotype characteristics of non-β^0/β^0 subjects of the ITT population included in the Zynteglo submission (Studies HGB-204, HGB-205, HGB-207)

Subject	Non-β^0/β^0 Genotype
[redacted]	β+/β+
	βE/β0
	β+/β+
	βE/β0
	β0/β+
	β0/βX*
[redacted]	βE/β0
	βE/β0
	βE/β0
	βE/β0
	βE/β0
	βE/β0
	βE/β0
	β+/β+
	βE/β0
	βE/β0
	βE/β0
	β0/β+
	β+/β+
	β0/β+
	βE/β0
	β0/β+
	β0/β+
	β0/β+
	β+/β+
	β0/β+
	β+/β+ [redacted]
	β+/β+ [redacted]
	βE/β0
	βE/β0
	β0/β+

* β0/βX: The unknown allele is a β+ mutation since this subject can produce some endogenous HbA

A6. Please state how many patients had an IVS-I-110 or IVS-I-5 mutation and provide results for these patients on transfusion independence and transfusion reduction. Please comment on whether the proportion of patients with IVS-I-110 or

IVS-I-5 mutations in the Zynteglo studies adequately reflects the proportion likely to be eligible in the NHS (under Zynteglo's current license).

In Study HGB-207, [redacted] patients (subject [redacted]) with the IVS-I-110 mutation were screened, however subject [redacted] did not receive Zynteglo as the study inclusion/exclusion criteria were not met. Study HGB-204 included [redacted] patient with the IVS-I-5 mutation (Subject [redacted]).

Subjects [redacted] were transfusion-free at last study visit although not yet TI evaluable (as determined by patients that have completed their parent study, or achieved TI, or won't achieve TI in their parent study due to insufficient follow-up time remaining in parent study).

From study HGB-204, subject [redacted] has achieved the definition of TI with duration of TI at last visit being [redacted] months.

Table 4. Transfusion requirements for non-β^0/β^0 subjects (IVS-I-110 or IVS-I-5)

Parameter	[redacted]	[redacted]	[redacted]
Baseline			
Annualised number of transfusions	[redacted]	[redacted]	[redacted]
6 months through last study visit			
Annualised number of transfusions	[redacted]	[redacted]	[redacted]
Change from Baseline annualised number of transfusions	[redacted]	[redacted]	[redacted]
Percent Change from Baseline annualised number of transfusions	[redacted]	[redacted]	[redacted]

With regard to the representativeness of the proportion of patients with IVS-I-110 and IVS-I-5 mutations included in the Zynteglo clinical studies and patients with these genotypes in the UK, specific genotype data from a bluebird bio sponsored study of genotyping adult patients with β-thalassaemia from the Manchester centre for Genomic Medicine demonstrate 4 of 14 patients with non β^0/β^0 genotypes with an underlying IVS-I-110 or IVS-I-5 mutation.

A7. Priority question: Please state the genotypes of all 4 patients who did not achieve transfusion independence.

Subject	**Non-β^0/β^0 Genotype**
[redacted]	[redacted]

A8. Priority question: Do any of the effectiveness results submitted in Document B include data from patients under 12 years old or with β^0/β^0 genotypes – if so, please resubmit the results excluding these patients.

The results in our submission do not include patients under 12 years old or with β^0/β^0 genotypes.

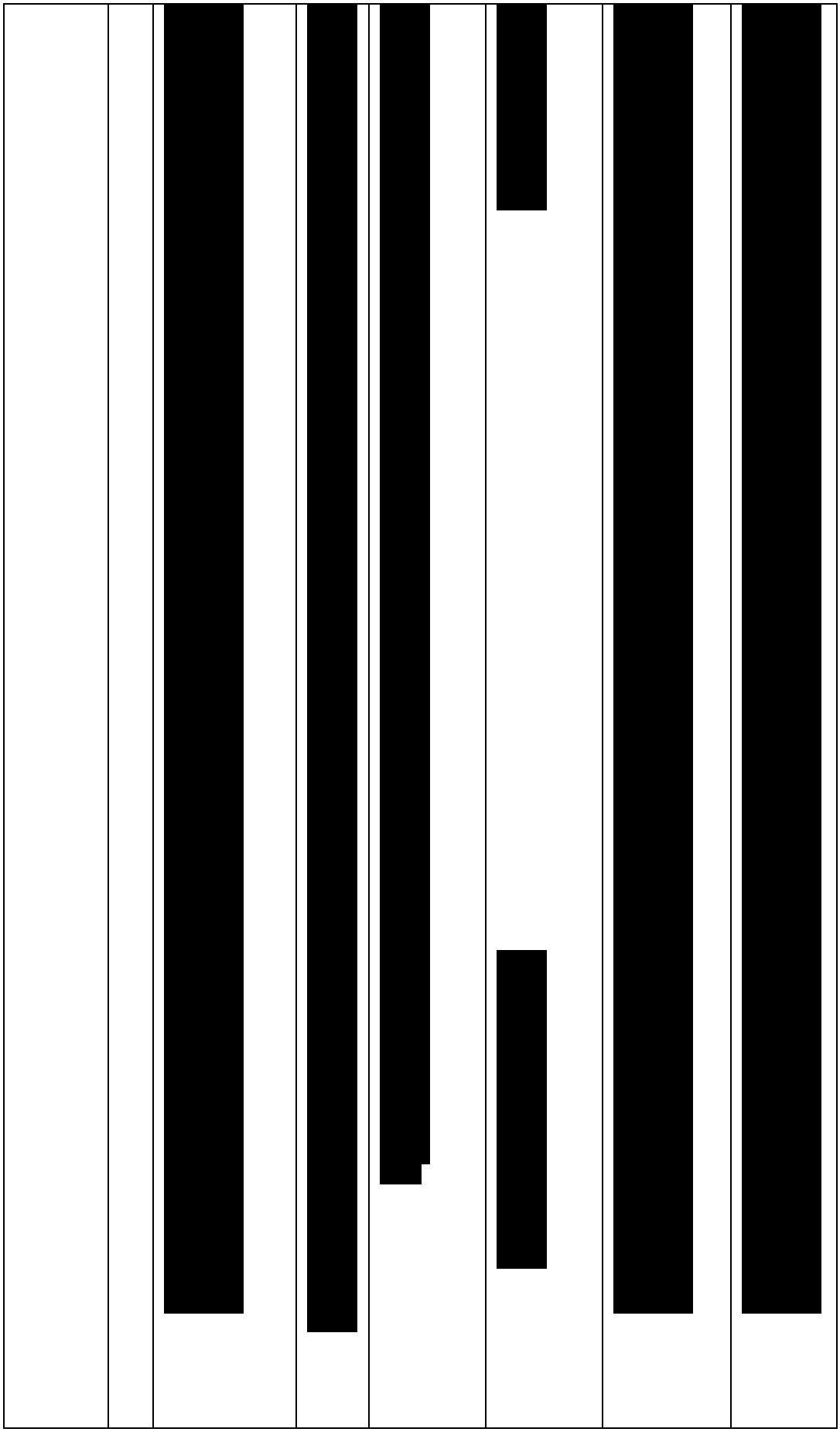
A9. Priority question: Please explain why [redacted] from HGB-205 [redacted] a transfusion despite having low levels of haemoglobin. Please explain why [redacted] was assumed to be transfusion-reduced, despite not receiving a transfusion (Company Submission, page 101).

The decision to transfuse a patient is at the investigator's discretion, in consultation with the patient, unless the haemoglobin level is <7g/dL or the patient has symptomatic anaemia, in which case RBC transfusion is recommended per protocol. Although the annualised number of transfusions for subject [redacted] have been reduced by [redacted], the subject cannot be considered TI as they have not achieved the pre-specified definition of TI stated in the clinical trials for Zynteglo i.e. a weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months at any time during the study, after Zynteglo transfusion. This subject's weighted average Hb in the absence of pRBC transfusions was not sufficient to achieve TI status as the weighted average Hb was [redacted] g/dL.

A10. Table 29 has the annualised number of transfusions for four patients (6 months through last study visit). Please provide the time points at which the transfusions occur for each patient.

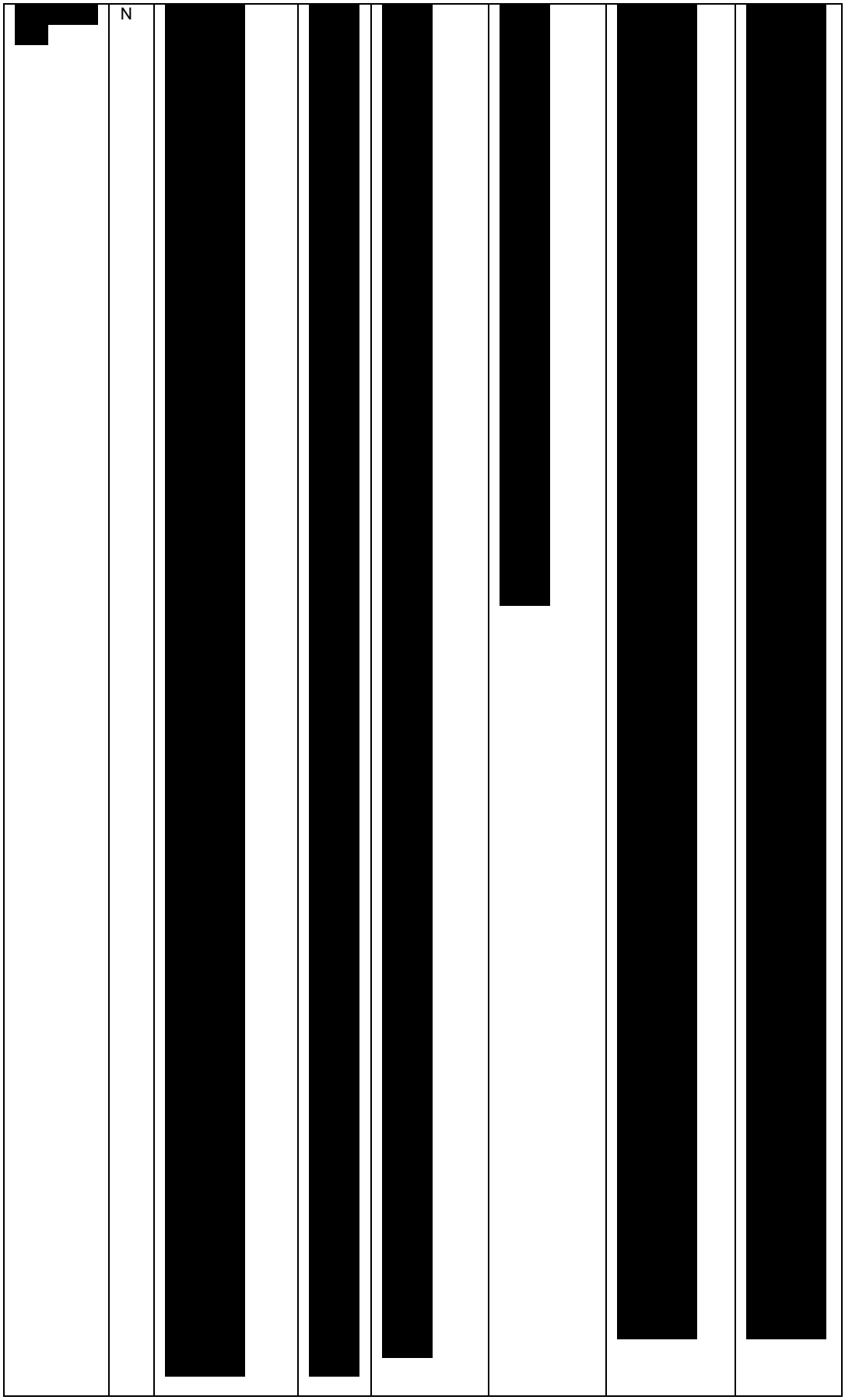
Table 5. pRBC (Packed Red Blood Cells) Transfusions

Subject	TI	Date of Transfusion	Rel Day	Amount Transfused (unit)	Average Volume per Unit (mL)	Patient Weight (kg)	Volume per Weight (mL/kg)
[redacted]	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



[redacted]	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	N	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]



A11. Please provide actual results (rather than just a narrative summary) on growth and development outcomes, detailed as endpoints on page 72 of the Company Submission.

Study HGB-207 includes the assessment of growth and puberty parameters (age appropriate), bone density, diabetes, endocrine evaluations, and neurocognitive development (paediatric subjects ≤ 18 years of age)**.**

Physical examination and Tanner staging results were summarised for subjects < 18 years of age at Screening and every 6 months post-drug product infusion during puberty (with individual patient data provided in a separate document under the file name: 'Individual patient growth data for HGB-207'). Results show that [redacted] subjects underwent Tanner staging at screening: [redacted] males ranging from 8 to 15 years of age, and [redacted] females ranging from 5 to 17 years of age. [redacted] subjects were considered pre-pubertal at the time of Zynteglo Infusion: [redacted] males ([redacted]) and [redacted] 5-year-old female. [redacted] subjects ([redacted]) were undergoing puberty, and the [redacted] was post-pubertal at the time of drug product infusion. The other [redacted] subjects who underwent Tanner staging did not have data for the screening visit.

For the [redacted] subjects with data after screening, [redacted] showed a progression of staging over time, with the exception of [redacted] who was already post-pubertal at the time of screening. Of note, Subject [redacted] (12-year-old male), was assessed as Stage II/I pubic hair/genitalia at screening, then assessed as Stage I/I pubic hair/genitalia at Month 6 but had [redacted] to Stage III/III pubic hair/genitalia by Month 18.

A12. Please provide an updated CSR for study HGB-204 with all tables and figures. The submitted CSR is referenced in the submission as a 'draft' and Figure 14 (page 126) does not show the relevant figures but states "Graphs being generated". In addition, Section 14 does not contain any of the tables or figures mentioned in the text.

This has been provided as separate documents 'hgb-204-body' and the supplementary errata 'HGB-204 - Clinical Study Report Errata - 24Sep2019'.

A13. Please provide a breakdown of which studies contributed patients to the safety analyses, including the number of patients from each study and their diagnoses. The footnotes for Table 36 (Company Submission, Page 116) refer to study HGB-206.

Has this study also been included in the safety analyses? If so, please provide the data (requested above) for this study.

The patients that contributed to the efficacy data of the submission also contributed to the safety results. The baseline characteristics of these patients are provided in Table 18 of the main submission (also copied below). All subjects are TDT patients with a non-β^0/β^0 genotype.

The footnote for Table 36 of the main submission is incorrect; the details mentioned for Study HGB-206 (SCD patients), including the details on SCD related AEs from LTF-303 should be excluded. Table 36 only contains non-β^0/β^0 patient data from studies HGB-204, HGB-205 and HGB-207. HGB-206 is not part of the submission.

Table 6. Baseline Characteristics of HGB-204, HGB-205 and HGB-207 (non-β^0/β^0) (Table 18 of main submission)

Parameter	HGB-204* (N=10)	HGB-205 (N=4)	HGB-207 (N=21)
Sex			
Male	3 (30.0)	2 (50.0)	[redacted]
Female	7 (70.0)	2 (50.0)	[redacted]
Race			
Asian	8 (80.0)	2 (50.0)	[redacted]
White	2 (20.0)	2 (50.0)	[redacted]
Other	-	-	[redacted]
Age at Informed Consent or Assent (category)			
≥18 years	8 (80.0)	2 (50.0)	9 (42.9)
≥12 to <18 years	2 (20.0)	2 (50.0)	6 (28.6)
<12 years	0 (0.0)	0 (0.0)	6 (28.6)
Splenectomy			
Yes	3 (30.0)	3 (75.0)	[redacted]
No	7 (70.0)	1 (25.0)	[redacted]
Medical History in 2 Years Prior to Study Enrolment			
pRBC (mL/kg/year)	164.06 (140.0, 234.5)	174.95 (138.8, 197.3)	201.53 (142.1, 274.4)
pRBC (number transfusions/year)	13.45 (10.0, 16.5)	12.13 (10.5, 13.0)	17.79 (11.5, 37.0)
Weighted mean Hb nadir (g/dL)	8.73 (7.0, 9.8)	9.46 (8.1, 10.8)	9.44 (7.5, 11.0)
Age at:			
Consent/assent (years)	22.2 (16, 34)	17.5 (16, 19)	16.1 (8, 34)

Diagnosis (months)	88.9 (0, 315)	9.3 (1, 30)	[redacted]
1st pRBC transfusion (months)	38.5 (0, 132)	31.8 (1, 84)	[redacted]
Established regular pRBC transfusion regimen (months)	99.2 (8, 312)	52.8 (1, 168)	[redacted]
Start iron chelation (years)	9.7 (2, 26)	5 (1, 12)	[redacted]

Ref: June 2019 datacut ISE Tables pg. 16, 22, 34
*Study HGB-204 also contained patients with the β^0/β^0 genotype which are not included in this NICE submission as not related to the population proposed.

Zynteglo treatment

A14. Priority question: Please provide details about how treatment with Zynteglo will be implemented and delivered to NHS patients e.g. where does bluebird bio propose Zynteglo will be manufactured and delivered?

bluebird bio has been in contact with NHS England to provide a detailed answer to NICE regarding the implementation and delivery of Zynteglo to NHS patients.

As mentioned in the main submission (pg. 189), following the apheresis step in the Zynteglo treatment process, collected cells will be shipped to the bluebird bio contract manufacturing facility in Munich, Germany, for individual medicinal product manufacture. Following drug product manufacturing, which takes approximately six to eight weeks, the product is cryopreserved and sent to the qualified treatment centre, prior to the patient undergoing myeloablative conditioning and subsequently, infusion of the drug product.

The delivery of the service will be performed at qualified treatment centres that have been identified and commissioned by NHS England and have then been trained and onboarded by bluebird bio. We are working with NHS England to assist in their planning for service provision. We understand the intention is to match capacity with demand. The pathway for Zynteglo is similar to an allo-HSCT and therefore providers must have JACIE accreditation for HST, as well as for Immune Effector Cell Therapy. The link with haemoglobinopathy services is also key and we understand NHS England is in the process of implementing the outcomes of the Haemoglobinopathy Service Review. Further specifics are not currently available, but discussion is ongoing between the company and NHS England's commissioning team with the intent that the service would be ready to treat patients at the point reimbursement is confirmed.

A15. Should Zynteglo be administered only once? Did any trial patients receive a repeat infusion?

Zynteglo is a one-time therapy to be administered as a single-dose, according to the summary of product characteristics (see section 4.2 Posology and method of administration of SmPC:

'Zynteglo is intended for autologous use and should only be administered once'). None of the patients in the studies underwent a subsequent infusion and this is not licensed.

A16. Does the price of Zynteglo include mobilisation and apheresis, stem cell processing and patient conditioning and inpatient stay (steps 1, 2, 3 and 5 as stated on page 16 of the Company Submission)? If a patient does not make it as far as step 4 (Zynteglo infusion), who pays for steps 1 to 3?

The economic model does not specifically include a price for stem cell processing. This is not a resource use item that is considered specifically in the model or expected to be paid for by the NHS. Separate from the price input for Zynteglo in the model, there is a separate model input for the cost of the inpatient stay for myeloablative conditioning of the patient and to deliver the therapy as part of an autologous haematopoietic stem cell transplant. There are also separate inputs for mobilisation and apheresis.

A17. The Company Submission mentions that back-up cells will be collected for subject rescue in the event of an engraftment failure. Please describe what you consider to be the likely clinical short- and long-term consequences for patients who end up needing the back-up cells (presumably they will be worse off than before?). Have back-up cells been needed in any trial of Zynteglo (regardless of diagnosis)?

No cases of engraftment failure have been observed in any of the Zynteglo clinical programmes across TDT and sickle cell disease, such that back-up cells have not been required to date. Since Zynteglo utilises the patient's own cells i.e. is autologous, the risk of engraftment failure is very low. Should this occur, the patient will be at short term risk of infections, anaemia and bleeding whilst their haematopoietic system undergoes reconstitution following infusion of the back-up cells, necessitating careful supportive management during this period. Side effects from myeloablative conditioning both short and long-term, including infertility, may occur and the patient's phenotypic expression of transfusion-dependent thalassaemia would return.

Population

A18. Priority question: The NICE scope says that "*HSCT is only considered in the under 18s"* (which our clinical adviser agrees with), and Zynteglo's license says it is for "*treatment of patients 12 years and older with transfusion-dependent β-thalassaemia who do not have a β^0/β^0 genotype,* ***for whom HSCT is appropriate***……". Doesn't this imply that the eligible population in the NHS are patients aged ≥12 and <18 years?

The language in the Zynteglo indication regarding HSCT has been selected to ensure the patient is eligible i.e. fit enough to undergo HSCT, irrespective of age, owing to the need for

myeloablative conditioning. Therefore, the indicated population reflects those patients that can safely undergo HSCT and are aged 12 or above. An upper age limit is not described in the indication, or elsewhere in the summary of product characteristics.

A19. Priority question: Patients with cardiac, liver, and endocrine comorbidities such as diabetes and hypogonadotrophic hypogonadism were excluded from the modelled population. Would these patients be eligible to receive Zynteglo for treatment on the NHS?

Individuals with TDT would not specifically be excluded from eligibility for Zynteglo due to either diabetes or hypogonadotrophic hypogonadism. Zynteglo would not be considered appropriate for TDT patients if they had a cardiac T2* value of < 10msec based on MRI. In patients with high liver iron content, myeloablative conditioning may not be appropriate and in Zynteglo clinical studies, patients with MRI findings suggestive of active hepatitis, significant fibrosis, inconclusive evidence of cirrhosis, or liver iron concentration ≥15 mg/g required follow-up liver biopsy in subjects ≥ 18 years of age. In subjects <18 years of age, these MRI findings were 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 was considered exclusionary.

A20. Priority question: Please estimate the size of the transfusion-dependent beta-thalassaemia (TDT) population expected to be eligible for Zynteglo over the next five years, and detail the assumptions underlying this estimate.

The eligible population included in the budget impact analysis is in line with the expected indication. Zynteglo is indicated for the treatment of patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β^0/β^0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Data from the Hospital Episode Statistics (HES) database (December 2018), indicated that of the [redacted] patients with TDT, [redacted] patients were aged below 12 years (not licensed for Zynteglo).

As allo-HSCT is available and funded for paediatric patients with TDT in England, it is expected that up to [redacted] of the adolescent patients may have access to a matched related donor, which would disqualify them per the licensed indication, equating to [redacted] of the patients identified in the HES database. Allo-HSCT is not recommended for adults regardless of donor availability due to the risks outweighing potential therapeutic benefit.

Taking this into account leaves [redacted] TDT patients aged 12 and above who do not have access to a matched related donor.

Turning to the genotype restriction per the licensed indication, data from the Oxford Molecular Haematology Reference Laboratory and the Royal London Hospital, suggests approximately [redacted]% of patients are expected to harbour a non-β^0/β^0 genotype. Applying this to the [redacted] TDT

patients aged 12 and above who do not have access to a matched related donor results in [redacted] patients remaining.

The actual patient pool eligible for Zynteglo in clinical practice is likely to be further reduced based on a small proportion of patients not fit to undergo transplantation. Approximately 10% of patients are expected to be unfit to undergo myeloablative conditioning given the risk for short and long-term toxicity, increasing with the age of the patient. Therefore, it is expected that there will be approximately [redacted] patients eligible for Zynteglo.

It is assumed that there are [redacted] incident TDT patients per year based on national screening report data (NHS, 2018). Applying the percentages for non-β^0/β^0 genotype patients ([redacted]) and patients without access to a matched related donor ([redacted]) it is estimated that there would be [redacted] incident patients per year. These incident figures do not account for immigration cases and European patients traveling to England for treatment, as data sources to estimate these do not exist.

The estimated patient pool eligible for Zynteglo of [redacted] patients is likely to be further reduced in clinical practice based on a proportion of patients choosing not to receive treatment due to the need for myeloablative conditioning and/or the risks of gene therapy. These patients may decline treatment with Zynteglo, particularly in the context of widely available standard management in the form of blood transfusions and iron chelation therapy. Recent market research conducted with TDT patients in England, suggests [redacted]% of patients would accept a referral to a transplant physician and wish to move forward with Zynteglo (Figure 5). This leads to a potential patient pool per the licensed indication that would be fit enough and willing to undergo treatment with Zynteglo at approximately [redacted].

Using this same rate of patient preference ([redacted]%) for incident patients suggests there would be approximately [redacted] incident patients per year that may receive Zynteglo. It is assumed that all [redacted] patients would be treated in each year, except the first year where uptake is expected to be only [redacted] patient due to timing of guidance. Hence, the number of incident patients treated reflects only preference.

Figure 5. Patient preference for Zynteglo treatment

NHS England has also provided an estimate on the patient population likely to receive Zynteglo with the number of total patients being [redacted] (based on higher assumed preference rate).

A21. Priority question: How does the company anticipate the availability of Zynteglo to change the eligible population over time? If all eligible patients are treated and 100% of patients are diagnosed early, over time the age of eligible patients will tend towards 12 years, given the current licence.

The patient preference study (Figure 5) shows a [redacted]% anticipated acceptance of Zynteglo by patients. Only [redacted]% of respondents would immediately accept a referral to a transplant specialist to discuss Zynteglo, limiting the population from which transplant specialists can choose eligible patients. This is due to a number of reasons such as the patient not being interested in any procedure similar to a bone marrow transplant or because the patient is satisfied with current treatment for beta thalassaemia. bluebird bio anticipates that as patients and clinicians become more familiar with Zynteglo administration and the potential patient benefits that the proportion of patients seeking treatment will be higher than the [redacted]% indicated in the patient preference study.

If all eligible patients are diagnosed early and treated, there will be [redacted] patients eligible per year (answer to question A20) with the addition of immigration cases and European patients travelling to England for treatment under cross-border arrangements.

A22. On page 140 of the Company Submission, reference is made to [redacted] patients having serious hepatic adverse events. Please provide the baseline characteristics of the [redacted] patients.

Table 7. Baseline Characteristics of the patients from HGB-204 and HGB-207 (non-β^0/β^0) experiencing serious hepatic adverse events

Study		HGB-204	HGB-207		
		[redacted]	[redacted]	[redacted]	[redacted]
Event Grade		[redacted]	[redacted]	[redacted]	[redacted]
Age (years) and Gender		[redacted]	[redacted]	[redacted]	[redacted]
VOD prophylaxis		[redacted]	[redacted]	[redacted]	[redacted]
Screening	Imaging LIC (mg Fe/g dw)	[redacted]	[redacted]	[redacted]	[redacted]
	AST (U/L)	[redacted]	[redacted]	[redacted]	[redacted]
	ALT (U/L)	[redacted]	[redacted]	[redacted]	[redacted]
	Total bilirubin (umol/L)	[redacted]	[redacted]	[redacted]	[redacted]
Busulfan dosing schedule		[redacted]	[redacted]	[redacted]	[redacted]
Average busulfan AUC (uM*min)		[redacted]	[redacted]	[redacted]	[redacted]

Systematic reviews

A23. Priority question: Please provide a systematic review which transparently demonstrates that all the Zynteglo studies have been identified.

The systematic review will be provided as a separate document and should be viewed as AIC.

A24. Search strategies are referred to in several places within the submission report, but they have not been included within the report or the appendices. Two systematic reviews by Evidera (marked as confidential) appear within the reference pack:

> Systematic review of the burden of disease and treatment for transfusion dependent β-Thalassemia. EVA-20726, April 20, 2018, Version 3.0
>
> Systematic literature review to support LentiGlobin® in transfusion-dependent β-Thalassemia for NICE submission. Study Report. EVA-20726-04, 2 July 2019, version 1.0

Please confirm if the search strategies included in these two reports were used to identify evidence for the SLRs included within the submission report.

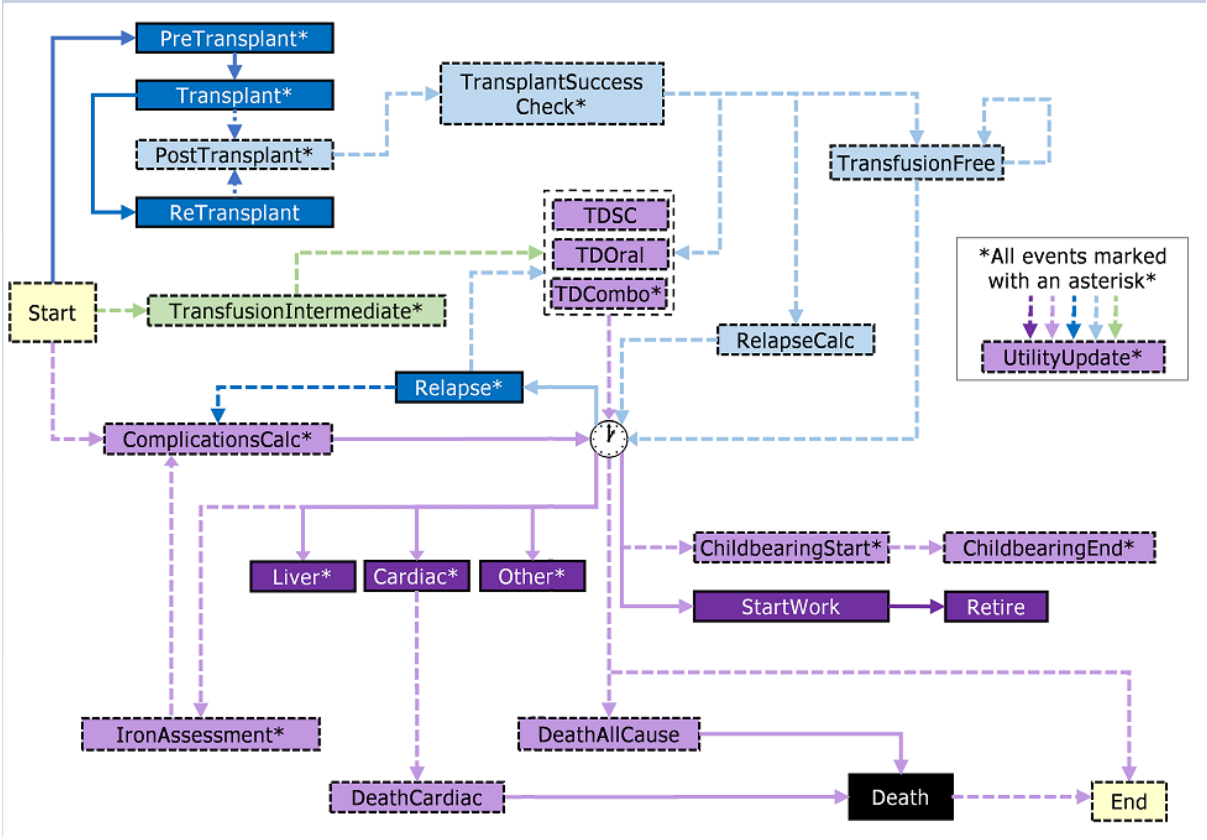
We can confirm the search strategies included in these two reports were used to identify evidence for the SLRs included within the submission report.

Section B: Clarification on cost-effectiveness data

Updated base case model

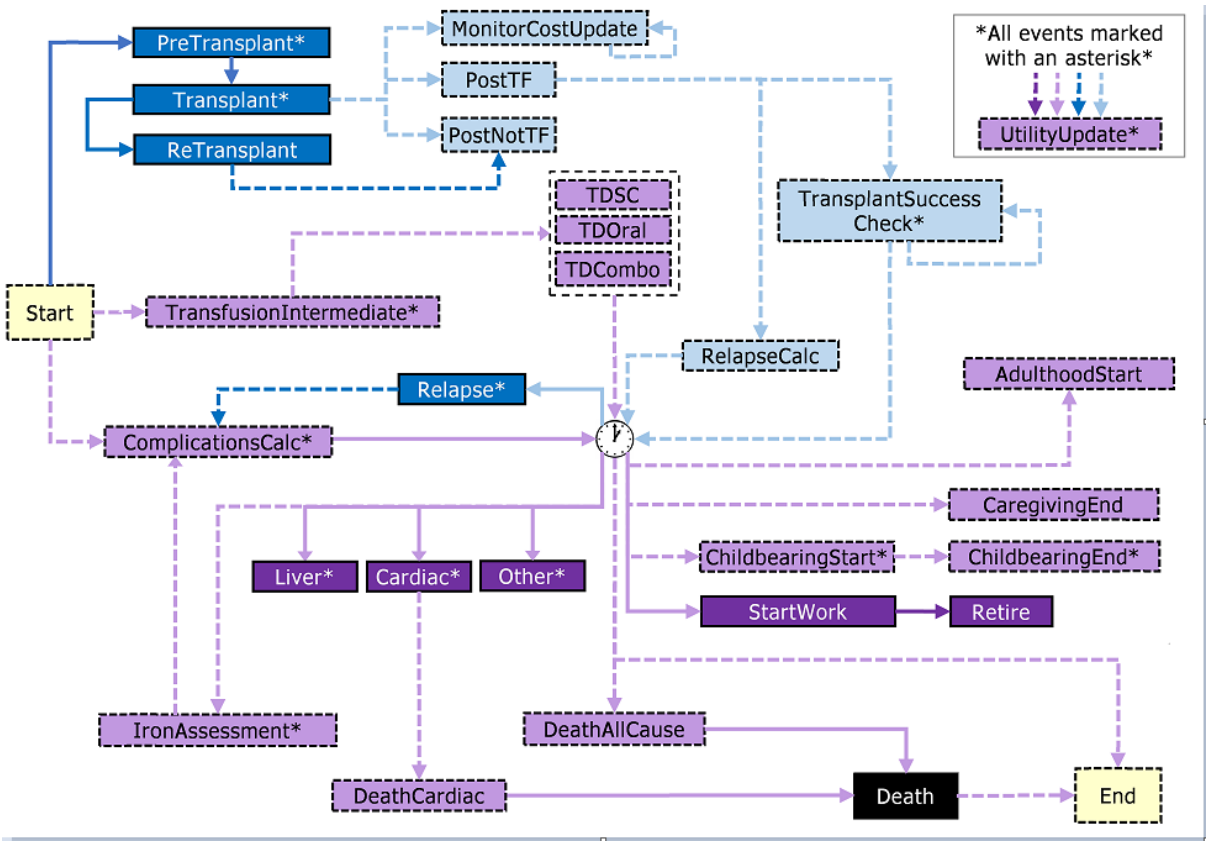
Please note that the model has been updated, taking into account ERG comments and streamlined in order to reduce run-time for any sensitivity analyses, by ensuring that instructions populating static conditions are not repeatedly executed. These changes have been documented in Appendix H and the individual response with reference to structural modifications to the model marked with * throughout. The original company submission and updated model schematics can be seen in Figure 6 and Figure 7 below.

Figure 6 Original company submission cost-effectiveness model schematic



Green text indicates pathways that apply to standard of care only; blue apply only to Zynteglo, purple apply to both. Direct arrows between events indicate mandatory sequences. The clock icon indicates that the next event depends on the time of possible events, with the shortest one taken. Solid arrows and borders indicate real-world events while dashed one indicate events included to facilitate the modelling. Further details have previously been outlined within the original submission.

Figure 7 Updated model schematic



The main changes relate to making the initial assignment of chelation consistent within both arms, in line with the ERG queries regarding utilities and costs of transfusions and chelation applied in the period after transplantation.

The updated base case results for Zynteglo versus transfusions and iron chelation therapy are shown in Table 8, [redacted]. Zynteglo is associated with 15.84 years increased survival, 13.14 discounted incremental QALYs. Zynteglo is associated with incremental costs of [redacted] per patient compared to chronic transfusions and iron chelation and the ICER is [redacted] per additional QALY gained.

Table 8 Base case results using simple PAS

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	37.79	17.2				
Zynteglo	[redacted]	53.63	30.34	[redacted]	15.84	13.14	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Following the same methodology as in the original company submission, deterministic and probabilistic sensitivity analyses were conducted for the base case. The results of the PSA are presented in Table 9, Figure 8 and Figure 9. The results are consistent with the deterministic base case, with QALY results remaining stable and cost results showing [redacted] for both Zynteglo and the comparator. This can be seen when looking at the spread of the individual iterations, with all paired comparisons showing large QALY gains and [redacted] in incremental cost.

Table 9 Probabilistic sensitivity analysis results using simple PAS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	17.33			
Zynteglo	[redacted]	30.44	[redacted]	13.11	[redacted]

Figure 8 Cost-effectiveness plane: updated model

Figure 9 Cost-effectiveness acceptability curve: updated model

The results of the DSA can be seen in Figure 10, the results are consistent with the original company submission DSA.

Figure 10 Tornado diagram illustrating deterministic sensitivity results

Three sets of scenario analyses were presented in the original company submission.

1) Hospital Episode Statistics (HES) data was used as a scenario analysis to approximate age distribution and gender, informed by data from England. The clinical studies were used to inform age distribution in the base case as they could be assumed to be a population wishing to undergo gene therapy, which HES doesn't offer.
2) For mortality following transfusion-independence, remove the assumed impairment of survival due to myeloablative conditioning (i.e. set the SMR from 1.25 to 1.00).
3) Utility values based on the vignette study only, which is a hypothetical study in which utilities are not obtained directly from patients. The following utilities are used:
    - First year of transplant: no change from base case
    - Transfusion-independence: no change from base case
    - Transfusion-dependent (oral chelation therapy): 0.23 versus 0.27 in base case
    - Transfusion-dependent (subcutaneous chelation therapy): 0.33 versus 0.27 in base case
    - Transfusion-reduction: 0.20 versus 0.13 in base case

The results using the updated model for these scenarios can be seen in Table 10 to Table 12. In line with the original company submission, these scenarios indicate that the results are sensitive to age distribution and relatively insensitive to the mortality assumptions around transfusion-independence, which continue to be consistent with the DSA results.

Table 10 Scenario 1: Demographic characteristics: HES data

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	32.69	15.22				
Zynteglo	[redacted]	46.67	27.23	[redacted]	13.98		[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 11 Scenario 2: Mortality: no impairment of survival due to myeloablative conditioning

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	37.79	17.2				
Zynteglo	[redacted]	55.67	31.05	[redacted]	17.88	13.85	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 12 Scenario 3: Utility values from vignette study

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	37.79	18.37				
Zynteglo	[redacted]	53.63	30.47	[redacted]	15.84	12.1	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Model

B1. PRIORITY QUESTION: Please provide full technical details of the DICE model, including a full list and justification of “conditions” and “events”.

Per the request, bluebird bio has provided the following documentation regarding the technical details for the DICE model for Zynteglo:

- Updated technical report with expanded model section (Appendix A)
- Detailed flow diagrams (above)
- Model Blueprint (Appendix B)
- User Guide (Appendix C)
- Updated Excel-based model with all components documented

B2. PRIORITY QUESTION: Please provide an explanation of how the model uses and generates results using profiles and replications, making reference to the following points:

a) How are profiles selected and cycled through? Is this sequential according to profile ID?

b) How are results based on the same profile averaged and weighted (by age group) within the same model iteration?

c) How does each model replication select the starting profile? 100 replications using 1 profile produces very different results to 1 replication of 100 profiles.

d) Are the results of each profile run visible (as in a probabilistic sensitivity analysis)? The results within the ‘Profile output’ tab do not seem to correspond to the previous model run.

e) Why does increasing the number of profiles run change the results so significantly?

a) The method of selection of profiles is specified in cell ProfSelChoice of the cost-effectiveness model. The model only includes sampling from filtered profiles using shares. To do this, a cumulative distribution of the shares is created, a random number is chosen, and the corresponding profile is selected. This process is repeated until the specified number of profiles (in cell NumProfiles) is reached. The Profile ID is only used to identify the selected profile and is not used in the sampling.

b) The results are averaged in an iteration across all profiles, rather than by matched profiles. The average is an unweighted mean.

c) The starting profile is selected randomly from the profiles with a non-zero share. If a single profile is selected in each of 100 iterations, there is no assurance that the 100 selections will correspond to the 100 selected in a single iteration because the random number sequences will differ.

d) The model includes the functionality to produce profile level output by using the option *PrintPrfLevelOutput*. However, this functionality has only been used for debugging purposes. Note that the Profile Output won't be updated or cleared out if the option to print profile output is set to 0 when the model is rerun. Also note that this option significantly increases model run time.

e) This indicates that the number of profiles needs to be greater to achieve stability of the results. However, since our base case reduces the profiles for better concordance between weight and age, the results remain stable. The PSA results remain consistent with the deterministic base case, suggesting a robust base case.

B3. In the submission, it is claimed that the key benefit of using a model using the DICE framework is that it avoids the need to model an unfeasibly large number of health states corresponding to range of possible iron levels in three organ systems, which may exist in a number of combinations and different timings (page 162 of the Company Submission).

a) Please explain how events interact with the baseline characteristics of age, gender and iron levels, and how they are modelled over time.

b) Please provide additional information on how the risk of complications of iron overload are implemented in the model. For example, is the annual rate of the risk of complications of iron overload applied to the patient's current health state, or does it take into account the time spent in that health state and in any previous health states? For example, if a patient was previously in the high iron health state but has successful chelation and reduced iron levels after a certain time point, is the risk based on their new health state or does it reflect the time spent in the higher iron level health state?

a) Age is used to select a time of death from baseline; determine the time of retirement, and childbearing years. All utility decrements related to the disease, treatment, and associated complications are applied to health utilities for a general UK population, which are age-dependent and change over time. Age is also used to determine if the patient is paediatric, impacting some cost inputs. Gender affects the parameters used in the survival functions, and infertility. Iron load is not dependent on age or gender. Mean weight is used to calculate the costs of chelators.

The age category is updated when a child becomes an adult. Iron load category is updated as described in response to Q B5d.

b) The risks of complications of iron overload are implemented in the Complications calculator event for those not suffering these complications at the *Start*. This event is called at the *Start*, in case of *Relapse*, at the time of *Iron Assessment*. The time to each complication event ('Cardiac', 'Liver', 'Other)' are selected from exponential distributions, with the corresponding hazards adjusted to the new iron load if it has changed. For 'Other', the shortest time of either diabetes or hypogonadism is selected.

   The hazards depend only on the iron load category, not on the history or duration of iron overload. A conditional failure-time approach is applied to adjust time-to-event calculations for each complication to reflect previous risks and the predicted probability of experiencing the complication at the current model time.

   No studies were identified in the SLR or search of real-world data sources which would provide evidence of the relationship between iron levels at Time X and subsequent clinical events (i.e. complications) at Time Y. It was determined that a long, prospective study with a large sample size would be needed to generate this evidence, which would not report in time to support the Zynteglo appraisal. Therefore, the model approach and design outlined above was considered the most appropriate.

B4. PRIORITY QUESTION. The submission states that “individual-patient characteristics are accounted for in the model” (Company Submission, page 163). From inspection of the model, it appears that age and gender are modelled for individual patient profiles, but baseline iron load and patient weight are modelled using the population average.

a) Please clarify how age and gender are linked to these other patient characteristics in the model.

b) Please include a scenario in the model which uses age- and gender-appropriate distributions of baseline iron load and patient weight, if it is not already incorporated in the model, i.e. for each age and gender profile, please produce an analysis of the chart review data that provides the mean patient weight and baseline iron levels, and incorporate that in the model.

a) Neither iron load nor patient weight were dependent on age and gender in the model included in the original submission. This has now been updated so that weight is specific to each profile. Mean weight for each profile is used to calculate the costs of chelators. There are insufficient data to make the baseline iron load distribution profile-specific (see response to B4 (b) below).

b) To make it possible to link the weight with age and gender, the profiles have been reduced to six: paediatric males and females, young adult males and females, older adult males and females. The model has been modified to handle these profiles.*

Profile Table (name: tblProfileFile)

ID	Gender	Age Category	BsAge	Time To Adult	Mortality Lambda	Mortality Gamma	Share
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Age category, Time to adulthood and the mortality parameters have been added to optimise execution time and Gender has been converted to the index used in the model (1=male, 2= female).

As requested, an analysis of body weight by age group and by gender has been conducted. Sample sizes were limited – the results are provided in Tables 1-3 in Appendix D.

As requested, an analysis of iron levels (liver, cardiac, serum ferritin) by age group and by gender has been conducted. Sample sizes were limited – the results are provided in Tables 4-14 in Appendix D. Based on the results, there are no clear trends for iron overload status by age. Therefore, it is still appropriate to handle iron overload distribution percentages at the population level, as currently modelled.

The results of a scenario utilising age category-specific body weight values for paediatrics and adults is presented in Table 13 below.

Table 13 Utilising age category-specific body weight values (pediatric and adult)

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	37.79	17.2				
Zynteglo	[redacted]	53.63	30.34	[redacted]	15.84	13.14	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

B5. Please clarify the following points regarding the timings of events in the model:

a) Please confirm the time point at which the costs and disutility for each type of iron complication are applied in the model, and the time point at which the elevated mortality risk for those with cardiac complications is applied.

b) Please allow for the time points in part (a) to be amendable inputs in the model.

c) Please clarify whether the standardised mortality ratio (SMR) for transfusion-independent patients is applied from baseline or from achieving independence (i.e. at one year).

d) For time to iron normalisation, there are data tables relating to two time points. Please provide further clarity on how these influence the model and describe how iron levels are distributed between the high/medium/low iron health states between these two time points. Is the four years to iron normalisation from Zynteglo treatment or from achieving independence from transfusions?

a) Utility is updated in the UtilityUpdate event. This event is called immediately after the following events: TransfusionDependentOral, TransfusionDependentSC, TransfusionDependentCombo, PreTransplant, Transplant, PostTransplantTF, PostTransplantNotTF, Childbearing Start, Childbearing End, Cardiac Complications, Liver Complications, Other Iron Complications, Death, Relapse, Iron Assessment, and when the age category for utility changes. The disutility due to transfusion status is updated whenever a change in transfusion status occurs. The disutility values associated with complications are constant (initialised in the Conditions table), but are only applied when the flag for the relevant complication is set to 1. A complication flag is set to 1 if and when the complication event occurs.

   After any change in parameters which relate to QALY accumulation (either the disutility values or flags), the UtilityUpdate event is called, the age-based utility is updated, and the current utility value is recalculated using either an additive or multiplicative equation (iron complications are highlighted in green):
   Additive: (AgeUtility(AgeUtilityIndex))(1) +*
   (uDecrementPreTransplant)(PreTransplantFlag) +*
   (uDecrementTransplant +
   uDecrementAcuteAE)(TransplantFlag) +*
   (uDecrementSecondTransplant)(ReTransplantFlag) +*
   (uDecrementPostTransplant)(PostTransplantFlag) +*
   (uDecrementInfertility)(Infertility*ChildbearingAge) +*
   (uDecrementCardiacComplications)(CardiacCompFlag) +*
   (uDecrementLiverComplications)(LiverCompFlag) +*
   (uDecrementOtherIronComplications)(OtherIronCompFlag) +*
   (uDecrementTransfFree)(TransfusionFreeFlag) +*
   (uDecrementTransfDep)((1-TransfusionFreeFlag)*(1-TrFailureReducedTransf)) +*

(uDecrementTransfRed)((1-TransfusionFreeFlag)*(TrFailureReducedTransf))*

*Multiplicative: AgeUtility(AgeUtilityIndex) *
*((1+uDecrementPreTransplant)^(PreTransplantFlag)) *
*((1+uDecrementTransplant+uDecrementAcuteAE)^(TransplantFlag)) *
*((1+uDecrementSecondTransplant)^(ReTransplantFlag)) *
*((1+uDecrementPostTransplant)^(PostTransplantFlag)) *
*((1+uDecrementInfertility)^(Infertility * ChildbearingAge)) *
*((1+uDecrementCardiacComplications)^(CardiacCompFlag)) *
*((1+uDecrementLiverComplications)^(LiverCompFlag)) *
*((1+uDecrementOtherIronComplications)^(OtherIronCompFlag)) *
*((1+uDecrementTransfFree)^(TransfusionFreeFlag)) *
((1+uDecrementTransfDep)^((1-TransfusionFreeFlag)(1-TrFailureReducedTransf)))*
*((1+uDecrementTransfRed)^((1-TransfusionFreeFlag) * (TrFailureReducedTransf)))*

Therefore, if an iron complication is present at the time of the utility update, its corresponding decrement is applied.

If cardiac complications are present at the start, then the corresponding mortality is applied there. If they are not present, then the cardiac mortality is applied when the cardiac complications event occurs. That event is called if cardiac complications are found to occur in the Complications Calculator event, which is called at the Start, at the Iron Assessment event and at the Relapse event (i.e., whenever iron load may change).

b) As noted in our Response to Question B3 (b) there are no available data to link iron levels at Time X with timing of future iron overload complications at Time Y. We believe the model appropriately links the risk of complication based on likelihood of the patient being at a given iron level (from the population distribution). Therefore, it is not appropriate to make time points amenable inputs in the model.

a) The baseline SMR (value = 3.9 --which is the value associated with transfusion dependence) is adjusted only at the time of the iron load assessments (the appropriate value to apply after baseline is stored earlier to avoid complex nested IF statements in the iron load assessment event). In the base case this event occurs only four years after transplantation in those who achieve transfusion independence or reduction.

b) All patients are assigned iron load categories by organ (1:normal, 2:Low, 3:Moderate, 4:High) at the *Start* event. They remain in these categories until the iron assessment event is called at its specified time point (4 years from *Start* and only called once in the base case). At the iron assessment event, the iron load categories are assigned using cumulative distributions that are specific to the current transfusion status (transfusion independence, transfusion reduction, or transfusion dependence). If a second iron assessment is scheduled, there will be an additional reassignment at that point. All assignments use the stored random numbers assigned at initiation.

Iron load category is also reassigned at the *Relapse* event. This event is called at a time selected from a distribution specified by the user. In the base case, those who achieve transfusion independence or transfusion reduction never relapse. The period of four years is the assumption of time taken to normalise iron levels post-Zynteglo, based on the timing in published literature regarding iron normalisation post allo-HSCT).

Population

B6. Given that 14% of patients in the chart review had osteoporosis at baseline, and approximately 40% of TDT patients have this condition (page 28 of Company Submission), please provide further justification for the exclusion of osteoporosis from the model. Please include a scenario in the economic model that includes osteoporosis as a complication of TDT.

Osteoporosis is an important condition that impacts the lives of individuals with TDT. The SLR did not identify any studies that reported on the incremental impact of osteoporosis on TDT morbidity, QoL and mortality. Therefore, the base case assumes an SMR of 3.9 for TDT which incorporates the impact of osteoporosis (and other non-cardiac conditions) on survival. In terms of morbidity and QoL impact, the disutility for TDT in the model captures the QoL impact of osteoporosis. Adding osteoporosis specifically into the model would therefore risk double-counting morbidity and mortality impacts.

B7. The baseline levels of liver iron concentration (LIC) that are applied in the model are reportedly taken from the Chart Review. However, the numbers in the model do not appear to match the numbers reported in the source document (Table 36 and 37 in Chart Review draft manuscript). Please clarify which should be the correct numbers.

There was an error in the reported percentages in Table 36 of the draft report (although the patient counts by category were accurate). Taken directly from our abstract accepted at the 2019 ASH meeting, the correct percentages were used in the model, and are as follows: “median R2 LIC closest to data collection (n=120) was 5.4 (IQR 2.9–11.5) mg/g (<7 mg/g [61%, n=73]; 7<15 mg/g [23%, n=28]; ≥15 mg/g [16%, n=19]).”

B8. Were baseline iron levels recorded in the HGB-204, HGB-205 and HGB-207 trials? If so, please described why they were not considered for use in the economic analysis, and compare the values to the matched population in the chart review.

Table 14 below compares iron distributions from the key clinical trials (HGB-204, -205 and -207; n=29 with non-β0/β0 genotype) with the UK chart review population (the full dataset as reported in the ASH abstract; as well as a column for the requested subpopulation aged 12**+** years without comorbidities that would preclude treatment with Zynteglo). The use of UK specific, contemporary iron data is more appropriate as it is more reflective of UK patient profiles, as opposed to utilising data from international studies with limited UK patients enrolled.

Table 14 Comparison of iron distributions from clinical trials with UK chart review

Iron Level*	Bluebird bio trial population (n=29)			UK Chart Review Full Population (per ASH abstract) (n=165)			UK Chart Review (Aged 12+ and excluding patients with comorbidities that would preclude treatment with Zynteglo□)		
	Serum Ferritin	Liver Iron	Cardiac T2*	Serum Ferritin	Liver Iron	Cardiac T2*	Serum Ferritin (n=[redacted])	Liver Iron (n=[redacted])	Cardiac T2* (n=[redacted])
Low	[redacted]	[redacted]	[redacted]	[redacted]	61.0%	80.0%	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	23.0%	10.0%	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]	[redacted]	16.0%	10.0%	[redacted]	[redacted]	[redacted]

*Notes:
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
□Including conditions identifiable in chart review: cardiac T2* < 10ms, pregnancy, cirrhosis

B9. PRIORITY QUESTION. Please provide the following additional scenarios within the economic model:

a) Analysis 1: Include a reanalysis of the baseline iron load distribution in terms of serum ferritin, liver iron concentration, and myocardial T2* for the chart review population, excluding any patients with comorbidities that would preclude treatment with Zynteglo (e.g. 20% of patients with hypogonadism). Please also exclude all patients with a high myocardial T2* and ensure this is reflected in the recalculated baseline distribution of SF and LIC.

b) Analysis 2: Please recalculate baseline iron load distribution in the chart review population excluding the patients outlined in Analysis 1, but also limiting the population to those aged 12-35 years.

c) Analysis 3: Please recalculate baseline iron load distribution in the chart review population excluding the patients outlined in Analysis 1, but limiting the population to all patients aged ≤18 years (including the 42 patients aged ≤12).

d) Please also undertake Analysis 1 to 3 where iron load distribution is also linked to age and gender profiles, as requested in question B4b.

Response:

a) The existence of hypogonadism would not preclude an individual with TDT from receiving Zynteglo treatment and therefore the requested scenario is not plausible. The iron distribution data from the subset of patients with comorbidities that would preclude treatment with Zynteglo are presented in Table 15 below.

Table 15 Iron distribution of patients with comorbidities that would preclude treatment with Zynteglo

Iron Level	UK Chart Review (excluding patients with comorbidities that would preclude treatment with Zynteglo)		
	Serum Ferritin (n=[redacted])	Liver Iron (n=[redacted])	Cardiac T2* (n=[redacted])
Low	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]

b) The iron distribution data from the subset of patients aged 12-35 without comorbidities that would preclude treatment with Zynteglo are presented in Table 16 below.

Table 16 Iron distribution of patients aged 12-35 without comorbidities that would preclude treatment with Zynteglo

Iron Level	UK Chart Review (Aged 12-35 and excluding patients with comorbidities that would preclude treatment with Zynteglo)		
	Serum Ferritin (n=[redacted])	Liver Iron (n=[redacted])	Cardiac T2* (n=[redacted])
Low	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]

See Table 17 for the results of the model related to this scenario.

Table 17 Iron overload distribution for TDT SoC per UK chart review reanalysis (excluding patients with comorbidities that preclude Zynteglo treatment, or high cardiac T2*)

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	37.79	17.27				
Zynteglo	[redacted]	53.63	30.43	[redacted]	15.84	13.16	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

c) The iron distribution data from the subset of patients aged ≤ 18 without comorbidities that would preclude treatment with Zynteglo are presented in Table 18 below. Please note that patients aged < 12 would NOT be eligible for Zynteglo treatment per our current indication.

Table 18 Iron distribution of patients aged ≤ 18 without comorbidities that would preclude treatment with Zynteglo

Iron Level	UK Chart Review (Aged ≤ 18 and excluding patients with comorbidities that would preclude treatment with Zynteglo)		
	Serum Ferritin (n=[redacted])	Liver Iron (n=[redacted])	Cardiac T2* (n=[redacted])
Low	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]

See Table 19 for the results of the model related to this scenario.

Table 19 Iron overload distribution for TDT SoC per UK chart review reanalysis (excluding patients with comorbidities that preclude Zynteglo treatment, or high cardiac T2*; and ages ≤ 18)

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	37.73	17.06				
Zynteglo	[redacted]	53.36	30.24	[redacted]	15.63	13.18	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

d) Per our prior responses, the available data are insufficient to provide profile-specific iron distributions

Interventions and comparators

B10. Please provide an additional scenario in the model, whereby the proportion of patients receiving each type of chelation therapy and mean number of transfusions for the transfusion-dependent population (both of which are sourced from the chart review) are re-analysed and:

a) Scenario 1: Limited to those aged 12-35 years,

b) Scenario 2: Limited to all patients aged ≤18 years,

c) Please undertake both scenarios above where these inputs are linked to age and gender profiles, as requested in question B4b.

Response:

a) Tables 15 and 16 in Appendix D provides the chelator use percentages and transfusion counts for those aged 12-35. See Table 20 for the results of the model related to this scenario.

Table 20 Proportion of chelators and mean transfusions tied to reanalysis of UK chart review limited to ages 12 to 35

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	37.79	17.2				
Zynteglo	[redacted]	53.63	30.34	[redacted]	15.84	13.14	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

b) Tables 17 and 18 in Appendix D provides the chelator use percentages and transfusion counts for those aged ≤ 18 years.

See Table 21 for the results of the model related to this scenario.

Table 21 Proportion of chelators and mean transfusions tied to reanalysis of UK chart review limited to ages ≤ 18

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	37.79	17.2				
Zynteglo	[redacted]	53.63	30.34	[redacted]	15.84	13.14	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

c) Each of the six profiles have now been assigned an age and a chelation cost, but the data are insufficient to provide for profile-specific iron distributions.

B11. The SmPC for each chelation therapy describes how the dose is linked to the underlying serum ferritin levels in the patient. However, in the model it is linked to transfusion status. Please explain how the dose of chelation therapy for each group of patients (transfusion-independent, transfusion-reduced and transfusion-dependent) was selected, taking into account their expected iron levels.

The model uses population-level iron distribution, as outlined in response to B3 (b), and is therefore not able to track ongoing changes in serum ferritin levels and adjust chelator dosage in a time- and iron-level dependent manner. Therefore, an average dose per chelator was estimated based on the corresponding SmPC.

For transfusion-reduced patients, assumptions were required as there are no real-world situations where TDT patients have had a 'transfusion-reduced' status. Once the 'threshold' transfusion reduction level of at least 60% is assumed, as outlined in response to B20, the model assumes a shift downward in the percentage of individuals with high and moderate iron levels (across each of serum ferritin, liver iron and cardiac iron). This assumed shift in population iron distribution results in an assumed corresponding reduction in the chelator dose (per review of each SmPC).

For the percentage of patients who achieve transfusion independence and utilise chelators for iron normalisation, the model assumes the same level of chelation dosing as TDT SoC until the point of iron normalisation and can be seen as a conservative assumption.

B12. Please confirm the dose of chelation therapy received by transfusion-independent patients that has been applied in the iron normalisation period in the model, and the duration for which it is applied.

Chelation during the iron normalisation period is started at the post-transplant point. The post-transplant event has been split into two to facilitate addressing the different pathways of those who achieve transfusion independence and those who do not. In the updated* Post-transplantTF event, patients who become transfusion independent are assigned a ChelationAssessCost which is set according to age (CostIronAssessByAge). This cost is a weighted average of the costs of Oral, SC, Combo and phlebotomy and includes the cost of the chelator, administration and monitoring. It is calculated in 'MRU and Costs Inputs'!H139 and 140. The cost of each chelator uses the doses in the table 'Drug Acquisition and Administration Cost'. This cost is applied until iron is normalised, which is determined at the iron assessment event. If a relapse from TI occurs, this cost is turned off and the patient resumes their original chelator cost. The definition of 'relapse' in the model is a patient who successfully engrafted, achieved transfusion independence status, and then subsequently loses that status.

B13. Please provide the following additional details of the complex PAS for Zynteglo:

a) Please comment on whether and for what the NHS is expected to pay if there is a failure during or following mobilisation, apheresis, pre-treatment conditioning or Zynteglo administration.

b) Does the price of Zynteglo also include the costs associated with mobilisation, apheresis, stem cell processing, conditioning and inpatient stay (steps 1,2,3 and 5 as stated on page 16 of the submission)? If a patient does not make it as far as step 4 (Zynteglo infusion) who pays for steps 1-3? (See also questions A16 and A17.)

Additional information is being provided by bluebird bio in discussion with PASLU, to support the complex PAS for Zynteglo, and is therefore subject to change beyond the specific points requested here

B14. PRIORITY QUESTION. Please provide cost-effectiveness analyses with [redacted] applied. It was indicated during the checkpoint meeting that this would be required.

Simple discount PAS is included in the base case and all scenario analyses throughout the response document.

Clinical Data

B15. The economic model includes a probability applied to mobilisation failure (20% of patients receive two rounds of mobilisation, 2.9% receive three rounds) but no probability of pre-treatment conditioning or Zynteglo administration failing. Please comment on the plausibility of this.

Pharmacokinetic drug monitoring is required, and a well-established practice to ensure, as far as possible, that a target area under the curve (AUC) exposure for myeloablative conditioning with busulfan is achieved. This is to ensure an appropriate level of exposure for sufficient ablation of the patient's existing marrow to make space for the graft, balanced against the risks of dose-limiting toxicity. As a result of individualised dosing of busulfan, no events of failed conditioning occurred in the clinical studies, as supported by the fact that all enrolled, consented subjects at the conditioning stage of the pathway, eligible to safely undergo myeloablation with busulfan, did so.

All trial subjects that were eligible to receive Zynteglo infusion did so successfully and no events of administration failure were observed.

B16. Please provide the following additional information on the time to assess iron levels post-transplant:

a) Please present data iron levels in patients by transfusion-reduced and transfusion-independent status in the trial (as described in page 103-108 of the Company Submission) and provide a comparison with those used in the model.

b) **PRIORITY QUESTION:** Please comment on whether we might expect the time to iron normalisation to depend on baseline levels of iron loading. It seems reasonable to expect those with higher iron levels to take longer to stabilise than those with lower iron. Please incorporate functionality in the model to model time to normalisation by the baseline iron level, to allow modelling of alternative populations with respect to their baseline iron levels in a meaningful way.

a) Table 22 below outlines the iron distribution data from the subset of patients in Zynteglo clinical trials who have achieved transfusion independence (n=[redacted]), the subset currently classified as transfusion reduced (n=[redacted]), and the UK chart review data used in the model base case analysis.

Table 22 Iron distribution data split by transfusion-reduced and -independent status

Iron Level	Bluebird bio trial population, status of transfusion independence (n=[redacted])			Bluebird bio trial population, status of transfusion reduction (n=[redacted])			UK Chart Review Full Population (per ASH 2019 abstract) (n=165)		
	Serum Ferritin	Liver Iron	Cardiac T2*	Serum Ferritin	Liver Iron	Cardiac T2*	Serum Ferritin	Liver Iron	Cardiac T2*
Low	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	61.0%	80.0%
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23.0%	10.0%
High	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16.0%	10.0%

Trial data do not indicate a noticeable trend in length of time to move from higher iron levels to lower or normal iron levels post Zynteglo (see Appendix E). There are many factors that can influence time to normalisation including physician practice style, adherence to chelation. The existing model does contain the requested functionality, allowing for two timepoint checks in terms of iron normalisation. The model also allows for scenario analyses where you can vary the amount of time to normalisation (by changing the years of the check points) depending upon the alternative populations you select regarding their baseline iron distribution.

B17. Please build functionality into the economic model for the following scenarios:

a) To return patients who 'relapse' on Zynteglo to a transfusion-reduced or transfusion-dependent state, incurring the costs and outcomes of transfusions and

chelation therapy. The current assumption of 54% mortality based on HSCT graft failure may be overly pessimistic.

b) To define an annual probability of moving from transfusion-reduced to transfusion-dependent after treatment with Zynteglo.

c) To allow a proportion of patients remaining transfusion-dependent after treatment with Zynteglo.

a) The definition of 'relapse' in the model is a patient who successfully engrafted, achieved transfusion independence status, and then subsequently loses that status. Patients who relapse on Zynteglo can return to either a transfusion reduced state (controlled by pRelapseReducedTransfOthers) or transfusion dependent (the remainder of relapsed patients). The 54% mortality given in cell 'Efficacy and Mortality Inputs'!C141 is only applied for patients who experience engraftment failure at the time of the initial transplant, set to zero in the base case. This value was chosen as the SLR did not find credible data on engraftment failure mortality outcomes following autologous transplantation for haematologic conditions. Patients who revert to transfusion reduction or dependence both revert to baseline excess mortality risks (SMR = 3.9). The post-relapse SMR for transfusion-reduced patients can be edited in cell 'Efficacy and Mortality Inputs'!E148.

b) There is no basis for defining an annual probability of relapse from either transfusion independence or transfusion reduction status. While relapse is clinically possible, it has not been observed in the trials, so no data exist to inform this parameter or justify the use of a constant annual probability. The current implementation provides a simple way to create time-dependent probabilities with flexible start and end times for the purposes of scenario analyses. Additional flexibility has been provided in the model:

- *Patients can relapse from transfusion independence to transfusion reduction (with a separate table of relapse probabilities in these patients). Patients can still relapse to transfusion dependence from either transfusion independence or transfusion reduction, as before.
- Additional timepoints can be included in each user-specified distribution (up to 10).
- Two tables* have been included for iron level distributions post-relapse in transfusion-reduced and transfusion-dependent patients, respectively. In the base case, patients who relapse to transfusion reduction achieve the same iron levels that apply to patients who become transfusion-reduced after transplant failure (see Efficacy and Mortality Inputs rows 70-73). These distributions can be modified in rows 70-73 (transfusion reduction) and patients who relapse to transfusion-dependence are conservatively assumed to return to their baseline iron levels (see Efficacy and Mortality Inputs rows 90-93).

c) In the Zynteglo trials, all patients received at least one transfusion in the immediate period after transplantation. Those who will eventually become transfusion

independent (see cell 'Efficacy and Mortality Inputs'!D98) stopped transfusions at a median time of 27 days (mean 37) post-Zynteglo treatment and a maximum of three months. To model this accurately, all patients are assigned transfusion and chelation at baseline and those receiving Zynteglo are assumed to continue in their baseline assigned transfusion and chelation status through transplant. At the transplant event, it is determined whether the patient will become transfusion independent; if so, they are sent to the new Post-transplantTF event (TF = transfusion-free).

In the Post-transplant TF event, transfusions are stopped, and the weighted average chelation costs that apply during iron assessment are applied. These persist until either an Iron Assessment event or Relapse is experienced. The [redacted]% of patients who will not achieve transfusion independence are sent from Transplant to the Post-transplantNotTF event. There they are assigned either the reduced transfusion or full dependence and all associated Conditions. The success of treatment with Zynteglo is still officially assessed at the *Transplant Success Check* event (for the purpose of applying periodic payments if applicable).

B18. Please provide further justification for the assumption of permanent engraftment with Zynteglo, and please refer specifically to the long term persistence of HSCT grafts.

a) Has the company tested for the persistence and diversity of transduced cell lines in patients over time?

b) Does the proportion of transduced CD34 cells vs non-transduced cells change over time?

a*) Has the company tested for the persistence and diversity of transduced cell lines in patients over time?*
b) Does the proportion of transduced CD34 cells vs. non-transduced cells change over time?

To achieve persistent durability of efficacy in the case of ex vivo, LVV-based gene therapies such as Zynteglo, treatment must result in the establishment of a population of undifferentiated, long-term HSCs in the bone marrow which carry the gene of interest, integrated into their genome.

Durable clinical efficacy of Zynteglo treatment has been demonstrated out to 61.3 months. During that time, the integrated transgene is stable in the HSCs. Peripheral blood vector copy number (PB VCN) serves as a surrogate marker for persistence of transduced HSCs in the marrow compartment, demonstrating that HSCT grafts containing integrated transgenes are persistent over time. No significant changes in PB VCN from Month 6 to last follow up in peripheral blood mononuclear cells have been observed. Total haemoglobin and HbAT87Q over the same time course also remain stable, indicating that the integrated lentiviral vector is not silenced and the functional beta globin protein continues to have similar stability in peripheral circulation. Therefore, it is expected that the effects of the treatment will be life-long,

and clinical data for patients that have successfully engrafted and achieved transfusion-independence across clinical studies support this view.

Integration site analysis assessment over time indicates diversity of transduced cell lines. LVV integration is generally a semi-random process, with the same genome-wide integration profile and several common integration sites identified in studies with Zynteglo. In data collected to date, the number of unique integration sites (UISs) remain stable over time, indicating that the diversity of transduced cell lines remains stable with no clonal expansion.

B19. Please clarify the reasons why all trial patients returned to chelation therapy by 48 months of follow up. It is the ERG's understanding that phlebotomy is the safest and most effective method of reducing iron load in patients producing healthy blood following HSCT; does a return to chelating agents indicate a reduction in the production of healthy haemoglobin?

Post-transplant iron management was left to investigator discretion per the clinical study protocols and was expected to be tailored to the individual patient, based on their specific iron levels/unsupported haemoglobin values (i.e. haemoglobin values observed following cessation of transfusion support). Use of chelation post-Zynteglo indicates presence of pre-transplant iron overload due to TDT and because of the hyper-transfusion regimen required prior to mobilisation, conditioning, and the temporary interruption of chelation during conditioning. Therefore, it should not be considered that a return to chelation use is suggestive of a lack of healthy haemoglobin production. Specific guidance from the study protocols on resumption of chelation therapy or the use of phlebotomy was as follows –

'Iron chelation therapy using deferasirox or deferoxamine should be restarted no sooner than after discharge from the hospital post-transplant. Deferiprone may be used no sooner than 6 months after transplant due to the potential risk of myelosuppression (as per prescribing information for Deferiprone), and alternative chelation regimens should be employed in the interim. Starting dose of chelator is recommended based on institutional protocols. Doses may need to be adjusted continuously based on serum ferritin levels to prevent toxicity. Phlebotomy can be used in lieu of chelation in subjects who have Hb consistently ≥11 g/dL and who are no longer receiving regular transfusions. To avoid toxicity, once serum ferritin is ≤1000 ng/mL, downward adjustment of dose of chelator and decreasing the frequency of phlebotomy is advised, as per institutional protocols. Chelation should be discontinued if subjects become TI, liver LIC is <5mg/g, and serum ferritin is <500 ng/mL. Subjects who are not taking chelators should be continually reassessed for chelation needs post-HSCT based on the schedule of events of the relevant protocol.'

In light of the above, chelation and phlebotomy use was variable in the Zynteglo clinical studies. As described below (further details in document B - B.2.6.4.4. Iron chelation and therapeutic phlebotomy) not all patients returned to chelation:

For subjects from Study HGB-204, there was a variable delay in restarting chelation after Zynteglo infusion, ranging from Day [redacted] to Day [redacted] after drug product infusion, but all subjects

did ultimately restart chelation after drug product infusion. All subjects from Study HGB-204 continued to receive iron chelation therapy through last study visit.

For subjects from Study HGB-205, three subjects were able to start phlebotomy as a result of achieving robust total Hb levels of [redacted], [redacted] and [redacted] g/dL, just prior to or at the start of phlebotomy. These 3 subjects were no longer on iron chelation therapy: one patient discontinued chelation prior to conditioning and did not resume after drug product infusion; another after re-starting iron chelation at Day [redacted] post-drug product infusion discontinued iron chelation during the parent study; and the final patient after re-starting iron chelation at Day [redacted] post-infusion discontinued iron chelation during long-term follow-up Study LTF-303.

For subjects from Study HGB-207, 11 of 15 patients with ≥6 months of follow-up have not reinitiated chelation therapy after drug product infusion, five of whom underwent phlebotomy treatment (bluebird bio Inc, 2019b). These five subjects have also maintained weighted average nadir Hb from [redacted] months post-drug product infusion through last follow-up >[redacted] g/dL. The length of the delay between drug product infusion and re-starting iron chelation is at the investigator's discretion, and more subjects are expected to restart iron chelation and/or undergo phlebotomy as length of follow-up increases.

B20. PRIORITY QUESTION: Please provide additional information on transfusion-reduced patients after Zynteglo:

a) The submission describes how "the inflection point for what is considered 'substantial' is when transfusion frequency is 60% reduced" (page 172, Company Submission). However, the mean reduction value doesn't fall under this cut off and only half of transfusion-reduced patients fell into this category (Table 29 in the Company Submission). Firstly, please describe why 60% is considered to be the inflection point and what are the consequences for patients who do not achieve this threshold value; and secondly please justify how the patients can be considered transfusion-reduced when their mean reduction value does not reach the cut-off point.

b) Please update the model functionality so that if we vary the mean reduction value then this change is reflected throughout the model calculations (i.e. the value isn't hard coded into any formulae, for example in the quality of life (QoL) inputs, mean number of transfusions).

Response:

a) As noted on Page 172 of the original company submission, internal clinicians at bluebird bio with expertise in chelation therapy have expressed that a reduction in transfusions of at least 60% would be clinically meaningful and can allow a TDT patient's ongoing chelation regimen to 'catch up' on existing current iron stores, and

begin reducing tissue iron more effectively, as opposed to maintaining iron at an existing level. To date there is not enough evidence to corroborate this point, however a 60% reduction in transfusion volume has been selected as the primary endpoint for the ongoing HGB-212 study, in consultation with the EMA. The assumption of 60% was not expected to hold true for all patients; but there was consensus that a substantial reduction in transfusion volume of this level would benefit the patient and allow for improved iron management. The model currently assumes that achieving the threshold has a positive impact on the following: 1) number of transfusions required, 2) level of chelation dose, 3) disutility associated with TDT SoC, 4) iron stores as measured by the iron distribution for serum ferritin, liver iron and cardiac iron, and 5) the SMR associated with TDT SoC. The consequences of not achieving the threshold value are assumed in the model to be maintaining TDT status with its associated resource use, utility decrement, and mortality decrement values.

Table 29 in the original company submission included four patients who have not achieved the trial definition of transfusion independence in the clinical trials (N=2 HGB-204; N=1 HGB-205; and N=1 HGB-207). Of these [redacted] patients, [redacted] patients achieved [redacted] than a [redacted]% reduction in transfusion frequency ([redacted] at [redacted]% and [redacted] at [redacted]%) while the other [redacted] patients achieved [redacted] than a [redacted]% reduction ([redacted] at [redacted]% and [redacted] at [redacted]%).

bluebird bio acknowledge the point raised by the ERG on the overall mean value, and therefore bluebird bio has revised the base case analysis as follows: of the percentage of patients not achieving TI status ([redacted]% in our base case), [redacted]% of these individuals ([redacted]%) are now considered TDT for the lifetime of the model, and the remaining [redacted]% ([redacted]%) will be considered to have achieved the [redacted]% transfusion reduction threshold.

b) This input has been extracted from the formula and made editable.*

B21. Inspection of the economic model indicates that iron levels in transfusion-dependent patients are not expected to change from baseline levels. Please comment on the plausibility of this, given the continual requirement for transfusion. If the ERG were to implement alternative distributions in the “Efficacy and Mortality Inputs” sheet in the model for transfusion-dependent patients and baseline iron levels, please describe how the model would implement these alternative values (i.e. transition between baseline and future levels).

At population level the continual requirement for transfusion does not imply there would be change in iron distribution. The best evidence for iron distribution status for a TDT population treated with transfusion and chelation is their current iron stores in the relevant tissues (e.g.

liver and cardiac), which have been determined through the UK chart review study. It is difficult to determine how a future TDT population iron level distribution would be impacted by improved treatment options or iron management. Current iron levels reported in the UK chart review reflect use of existing oral chelators and advanced iron monitoring approaches in the UK. The model incorporates functionality that 'adjusts' the population iron distribution at a given 'Time X' in the future. Once an individual profile with TDT reaches that time point in the model, the model would draw from the new iron distribution percentage levels assumed.

B22. The analysis currently groups together the health-related quality of life (HRQoL) and cost impact of "other" complications related to iron overload of diabetes and hypogonadism. Please create an additional scenario in the model that allows these to be modelled entirely separately.

These conditions have a low impact on costs and disutility and therefore weighted averages for both costs and disutility were used in order to take a simplified approach. However, the model does provide specific risk equations for each condition, which was deemed the most accurate clinical representation. As the related costs and disutilities are not key drivers of the results, adding this complexity into the model would not result in significantly different results but would add to the level of uncertainty.

Mortality

B23. Please confirm that patients only have an elevated risk of death in the economic model due to cardiac complications, and not liver or other complications. Please explain why the excess mortality associated with these two has been excluded, particularly in light of these patients being described as being at risk of liver cancer (page 25, Company Submission). Please include functionality in the model that allows an SMR to be applied to the mortality of patients experiencing liver complications.

The SLR only identified limited studies investigating the relationship between thalassemia-related complications (including iron overload complications) and mortality. However, clinical opinion determined that cardiac complications were the most important contributor to mortality risk. As noted in the original submission, only cardiac complications were specified in terms of the incremental mortality risk. In clinical practice, patients have a risk of death from other complications such as liver disease. It is assumed that the SMR of [redacted] in the model (for TDT patients) captures all excess mortality risk not being captured specifically by the cardiac risk inputs in the model. Specific incremental risk due to liver complications have not been investigated due to the lack of evidence from the SLR. However, the model does incorporate the functionality to adjust (upward or downward) the TDT SMR (base case value of [redacted]) to reflect the potential risk of mortality due to other complications such as liver disease.

Quality of Life

B24. PRIORITY QUESTION: Please provide a reanalysis of HRQoL data from the Chart Review to limit the included patients strictly to those who would be eligible for Zynteglo and include this reanalysis as a scenario in the model. Specifically, this analysis should involve the removal of the following patients:

a) Patients with 'high' T2* iron (≥15 mg/g)

b) Patients with hypogonadism, diabetes, or other complications whose disutility is already accounted for in the model.

Table 19 in Appendix D provide the EQ-5D utility values based on the subpopulation request outlined above in question B24.

See Table 23 for the results of the model related to this scenario.

Table 23 TDT SoC utility value based only on UK chart review patients who did NOT have high cardiac T2* (< 10 ms), NOR those with comorbidities already accounted for in model

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	37.79	19.44				
Zynteglo	[redacted]	53.63	30.59	[redacted]	15.84	11.16	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

B25. PRIORITY QUESTION: Please provide further reanalyses of the HRQoL data from the Chart Review and include these as further scenarios in the model. Specifically, these analyses should involve the exclusion of those patients described in question B23, but limits the patients to the following:

a) Analysis 1: Only include those patients aged 12 years and over

b) Analysis 2: Only include those patients aged 12-35 years

c) Analysis 3: Only include those patients under the age of 18 years

d) Analysis 4: Average the HRQoL weighted according to the age distribution in the three Zynteglo trials (i.e. the base-case model distribution)

Tables 20-22 in Appendix D provide the EQ-5D utility values based on the subpopulation requests outlined above in Question B25. Please note EQ-5D utility scores are only available for individuals ages 16+ in the chart review (given EQ-5D versions utilised in chart review study), and the sample size is very limited for ages < 18.

See Table 24, Table 25 and Table 26 below for the results of the model related to these scenarios.

Table 24 TDT SoC utility value based only on UK chart review patients ages 12 to 35 who did NOT have high cardiac T2* (< 10 ms), NOR those with comorbidities already accounted for in model

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	37.79	21.95				
Zynteglo	[redacted]	53.63	30.88	[redacted]	15.84	8.93	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 25 TDT SoC utility value based only on UK chart review patients ages < 18 who did NOT have high cardiac T2* (< 10 ms), NOR those with comorbidities already accounted for in model

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	37.79	21.39				
Zynteglo	[redacted]	53.63	30.81	[redacted]	15.84	9.42	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 26 TDT SoC utility value based only weighted UK chart review utility (weighted per Zynteglo trials age distribution) -- patients in chart review who did NOT have high cardiac T2* (< 10 ms), NOR those with comorbidities already accounted for in model

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	37.79	20.27				
Zynteglo	[redacted]	53.63	30.69	[redacted]	15.84	10.41	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

B26. Please confirm whether patients who are transfusion-independent but are within the iron normalisation period, have a disutility corresponding to chelation therapy.

Disutility due to chelation in transfusion-independent patients within the iron assessment period is applied by updating the disutility value for transfusion-independent patients, which is applied in the Utility update event. The distribution of chelator type during the assessment period is used to calculate a weighted average disutility value (similar to the method for calculating chelation costs during this time). The relevant disutility values are in the table on rows 32-39 in the Utility Inputs worksheet.

B27. PRIORITY QUESTION: Please can the company provide details of the vignette study used to calculate the utility decrements for the health states of i) transplant, ii) up to one year post-transplant and iii) transfusion-independent, that are used in the economic model. In particular, please provide:

a) A description of the health states in the study and how these descriptions were developed and validated,

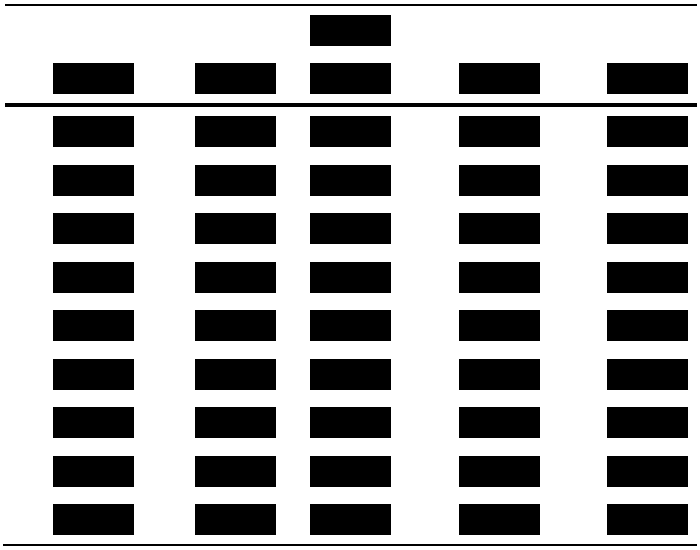
b) The number of respondents providing data for each health state,

c) A breakdown of the proportion of respondents in the following age categories: 12-17, 18-23, 24-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65+.

Response:

- **a)** Please see Appendix F which includes the manuscript for the vignette study that was recently accepted for publication by the European Journal of Health Economics. Please note that health state vignettes aren't like a PRO measure where there is a well-known formal validation process. The health states were developed via the initial interviews with clinicians, the patient, and the caregiver, and then validated via follow-up interviews in which these experts reviewed the final health states and agreed that they were an accurate representation of the typical patient experience with TDT. Multiple rounds of interviews were conducted with each person.
- **b)** The number is the same for every health state (N=207).
- **c)** Please see the table below:

Table 27 Proportion of respondents by age



Adverse Events

B28. The economic model assumes a 0% chance of veno-occlusive disease (VOD) despite the trial showing four patients having VOD related to busulfan conditioning. Can the company provide a scenario in which the costs and outcomes of VOD related to Zynteglo treatment are captured in the model?

The model does incorporate VOD prophylaxis and associated costs, as well as the occurrence of VOD post-Zynteglo treatment. However, the Zynteglo clinical trials show cases of VOD have occurred only during the Zynteglo administration hospital stay. Therefore, the model considers the VOD as part of the initial hospital episode payment (the cost impact of the VOD) and as part of the transplant utility decrement (the quality of life impact), capturing all evidence-based VOD related outcomes.

Model

B29. Please add the following functionality to the economic model:

a) The “Run model with log” function (which is distinct from the “provide profile log” function which already exists in the model)

b) Enable the scenario handler, and add back the tabs to allow this to function

c) Vertical and horizontal scroll bars, tabs and sheet headings are made visible on all sheets

d) All sampling options for the "Profile sampling method" function on the Settings sheet. This appears to include only one option at present (“Sampling from filtered profiles in the list using shares”).

If possible, please provide the model builder version of EviDICE (with all the features as available on the full DICE add-in).

We can confirm that the above-mentioned functionality requests have been incorporated into the updated model.

B30. Please provide the following supplementary documentation for the economic model, which are required for DICE reporting standards:

a) The technical description

b) User guide

c) The blueprint

d) A verification report.

All supplementary documentation have been provided as separate appendices.

B31. Priority question. There appears to be an error in how age-adjusted utilities are applied in the model, in that the utilities of patients are not updated beyond their baseline level. Please investigate and address this issue so that utilities update as patients age through the timeline of the model.

The error has been addressed in the updated version.

Section C: Textual clarification and additional points

C1. The context appears to be missing from these sentences in Document B - please clarify:

• Page 147: “A risk of bleeding exists before platelet engraftment and may continue after platelet engraftment in patients who have continued.”

- Page 46: “Emerging data from the non-β0/β0 cohort be used to support this NICE appraisal of Zynteglo as these patients become evaluable for transfusion-independence.”

Page 147: “A risk of bleeding exists before platelet engraftment and may continue after platelet engraftment in patients who have continued **thrombocytopenia**.”

Page 46: “Emerging data from the non-β^0/β^0 cohort **will** be used to support this NICE appraisal of Zynteglo as these patients become evaluable for transfusion-independence.”

References

C2. These references appear to be missing from the reference files – please provide them if possible:

i. BLUEBIRD BIO INC 2017 Standard HES Analysis β-thalassaemia study report created for bluebird bio, July 2017

ii. BLUEBIRD BIO INC 2018c Clinical study report LTF 303: Long term Follow up of Subjects with Hemoglobinopathies Treated with Ex Vivo Gene Therapy Using Autologous Hematopoietic Stem Cells Transduced with a Lentiviral Vector [draft] Data on File

iii. BLUEBIRD BIO INC 2018d Health state utilities associated with treatment for transfusion dependent β-thalassemia

iv. BLUEBIRD BIO INC 2018g Real-World Data from Existing Registries in Transfusion-Dependent β-Thalassemia Data on File

v. BLUEBIRD BIO INC 2019b June 2019 integrated TLFs for HGB-204, HGB-205, HGB-207 and LTF-303

vi. BLUEBIRD BIO INC 2019d Patient-reported burden of transfusion- dependent β-thalassemia in the USA and the UK measured using a digital app (e-diary) ISPOR EU 2019, 2019d Copenhagen, Denmark

vii. Borgna-Pignatti and Galanello (2009)

viii. The submission references Jenkinson et al. (2006), “Assessment and Evaluation of the SF36 Version II”, but the paper included in the reference pack is Jenkinson (1999), “Assessment of the SF-36 Version 2 in the UK”.

i. This reference should be changed to the Jobanputra et al. Draft Manuscript (referenced in Section B.3.3.1). The HES study reported is the original report, while the Jobanputra et al. Draft Manuscript is the draft manuscript of an updated HES analysis, currently under development.

ii. The CSR for LTF-303 was provided as part of the October submission in the confidential file 'CSRs – part of reference pack – CONFIDENTIAL' under the file name 'ltf-303_appendix_16-2-6_20180507_v2 CONFIDENTIAL'

iii. This has now been provided as pdf under the file name 'Reference 86 - bluebird bio Health state utilities 2018'

iv. This has now been provided as pdf under the file name 'Reference 38 - bbb Retrospective DB analysis summary'

v. The TLFs for the studies HGB-204, HGB-205 and HGB-207 were provided as part of the October submission in the confidential file 'TLFs – part of reference pack – CONFIDENTIAL'

vi. This reference is the Paramore C et al., draft poster (referenced in Section B.1.3)

vii. Borgna-Pignatti C, Galanello R. Thalassemias and related disorders: Quantitative disorders of hemoglobin synthesis. In: Greer JP, Foerster J, Rodger GM, Paraskevas F, Glader B, Means RT, editors. Wintrobe's Clinical Hematology. 12th ed. Philadelphia: Lippincott Williams and Wilkins; 2009. p. 1082-131.

viii. Jenkinson C, Stewart-Brown S, Petersen S. Assessment and evaluation of the SF36 Version II. Health Services Research Unit, University of Oxford, 2006, (http://www.hsruoxacuk/sf36v2.htm).

C3. The reference

BLUEBIRD BIO INC 2019a Chart Review - An observational study to evaluate the routine management, healthcare resource use and outcomes for patients with transfusion-dependent β-thalassaemia treated in the United Kingdom

is missing. We only have reference

BLUEBIRD BIO INC 2019c An observational study to evaluate the routine management, healthcare resource use and outcomes for patients with transfusion-dependent β-thalassaemia treated in the United Kingdom (TDT Chart Review)

which is in the file Chart Review, draft manuscript - CONFIDENTIAL.pdf in "Reference pack Final". If these are not the same then one of them is missing.

These are the same reference.

C4. Please provide the final versions of draft manuscripts and final conference posters for the following references:

i. UK Chart Review Draft Manuscript (referenced in Section B.3.2, B.3.3, B.3.4, B.3.5 and B.3.6)

ii. Shah et al. (referenced in Section B.1.3 and B.3.2)

iii. Jobanputra et al. Draft Manuscript (referenced in Section B.3.3.1)

iv. Drezet et al. draft manuscript (referenced in Section B.3.5.1)

v. Paramore C et al., draft poster (referenced in Section B.1.3)

The Paramore C et al., poster was presented in ISPOR Europe 2019 and the final version is provided. The remaining draft manuscripts have not yet been published. bluebird bio will update NICE if these documents are published and become publicly available during the appraisal.

Appendix A Cost-effectiveness model technical report

Appendix A cost-effectiveness model technical report is provided as a separate document and should be viewed as CIC.

Appendix B Cost-effectiveness model blueprint

Appendix B cost-effectiveness model blueprint is provided as a separate document and should be viewed as CIC.

Appendix C Cost-effectiveness model user guide

Appendix C cost-effectiveness model user guide is provided as a separate document and should be viewed as CIC.

Appendix D UK chart review selected material: An observational study to evaluate the routine management, healthcare resource use and outcomes for patients with transfusion-dependent β-thalassaemia treated in the United Kingdom

Question B4 (b):
Below are requested tables from the UK TDT chart review that provide more detail on patient weight by age and gender. Sample sizes are limited so its difficult to discern any specific trends. Given the clearer distinction between pediatric and adult weight, bluebird bio has adjusted the economic model to allow for different inputs for body weight for pediatric versus adult.

Table 1.

Age (years) and weight (kg) at baseline	n patients	n missing	Mean weight	SD	Median weight	IQR	Range
Under 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
18-23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
24-29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
30-34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
35-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
40-44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
45-50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Over 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Table 2.

Weight (kg) at start of observation (Male)	
Total patients	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
IQR	[redacted]
Range	[redacted]

Table 3.

Weight (kg) at start of observation (Female)	
Total	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
IQR	[redacted]
Range	[redacted]

Question B4 (b):
Below are requested tables from the UK TDT chart review that provide more detail on iron levels by age and gender. Given sample size issues, we report separately for age strata and then by gender. Based on these tables, there are no clear trends for iron overload status by age. Therefore, we believe it is still appropriate to handle iron overload distribution percentages at the population level, as currently modeled.

Cardiac Iron
Table 4.

Age (years) and T2* cardiac iron at baseline	n patients	Low iron, >20ms	%	Moderate iron, 10 - 20 ms	%	High iron, <10ms	%
Under 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24-29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Over 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5.

Age (years) and T2* cardiac iron at baseline	Mean	SD	Median	IQR	Range
Under 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24-29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Over 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6.

First T2* Cardiac Iron ms (Male)		n patients	% (n=[redacted])
Low iron, >20ms	>20	[redacted]	[redacted]
Moderate iron, 10 - 20 ms	10–20	[redacted]	[redacted]
High iron, <10ms	<10	[redacted]	[redacted]
No T2* result	No T2* result	[redacted]	
Total		[redacted]	
Mean (n = [redacted])		[redacted]	
SD		[redacted]	
Median (n = [redacted])		[redacted]	
IQR		[redacted]	
Range		[redacted]	

Table 7.

First T2* Cardiac Iron ms (Female)		n patients	% (n=[redacted])
Low iron, >20ms	>20	[redacted]	[redacted]
Moderate iron, 10 - 20 ms	10–20	[redacted]	[redacted]
High iron, <10ms	<10	[redacted]	[redacted]
No T2* result	No T2* result	[redacted]	
Total		[redacted]	
Mean (n = [redacted])		[redacted]	
SD		[redacted]	
Median (n = [redacted])		[redacted]	
IQR		[redacted]	
Range		[redacted]	

Liver Iron

Table 8.

Age (years) and R2 liver iron at baseline	n patients	Low iron, <7 mg/g	%	Moderate iron, 7<15 mg/g	%	High iron, ≥15 mg/g	%
Under 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24-29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Over 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 9.

Age (years) and R2 liver iron at baseline	Mean	SD	Median	IQR	Range
Under 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24-29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Over 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 10.

First R2 Liver Iron mg/g (Male)		n patients	% (n=[redacted])
Low iron, <7 mg/g	<7	[redacted]	[redacted]
Moderate iron, 7<15 mg/g	7<15	[redacted]	[redacted]
High iron, ≥15 mg/g	≥15	[redacted]	[redacted]
No R2 result		[redacted]	
Total		[redacted]	
Mean (n = 58)		[redacted]	
SD		[redacted]	
Median (n = 58)		[redacted]	
IQR		[redacted]	
Range		[redacted]	

Table 11.

First R2 Liver Iron mg/g (Female)		n patients	% (n=)
Low iron, <7 mg/g	<7		
Moderate iron, 7<15 mg/g	7<15		
High iron, ≥15 mg/g	≥15		
No R2 result			
Total			
Mean (n =)			
SD			
Median (n =)			
IQR			
Range			

Serum Ferritin

Table 12.

Age (years) and serum ferritin at baseline	n patients	low iron, ≤1,000 ng/mL	%	moderate iron, 1,000-2,500 ng/mL	%	high iron, >2,500 ng/mL	%
Under 12							
12-17							
18-23							
24-29							
30-34							
35-39							
40-44							
45-50							
Over 50							
Overall							

Table 13.

Age (years) and serum ferritin at baseline	Mean	SD	Median	IQR	Range
Under 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24-29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Over 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 14.

First serum ferritin (Male)	n patients	% (n=[redacted])
low iron, ≤1,000 ng/mL	[redacted]	[redacted]
moderate iron, 1,000-2,500 ng/mL	[redacted]	[redacted]
high iron, >2,500 ng/mL	[redacted]	[redacted]
No result	[redacted]	
Total	[redacted]	
Mean (n = [redacted])	[redacted]	
SD	[redacted]	
Median (n = [redacted])	[redacted]	
IQR	[redacted]	
Range	[redacted]	
First serum ferritin (female)	**n patients**	**% (n=[redacted])**
low iron, ≤1,000 ng/mL	[redacted]	[redacted]
moderate iron, 1,000-2,500 ng/mL	[redacted]	[redacted]
high iron, >2,500 ng/mL	[redacted]	[redacted]
No result	[redacted]	
Total	[redacted]	
Mean (n = [redacted])	[redacted]	
SD	[redacted]	
Median (n = [redacted])	[redacted]	
IQR	[redacted]	
Range	[redacted]	

Question B10:
Below are requested tables from the UK TDT chart review that provide chelator use and transfusion counts by selected age subsets.

Table 15.

Transfusions per year (aged >=12 <=35 at end of observation)	n (patients)	% (n = [redacted])
<8	[redacted]	[redacted]
8<12	[redacted]	[redacted]
12<14	[redacted]	[redacted]
14<16	[redacted]	[redacted]
16<18	[redacted]	[redacted]
18<20	[redacted]	[redacted]
20 and over	[redacted]	[redacted]
Total*	[redacted]	
Mean	[redacted]	
SD	[redacted]	
Median	[redacted]	
IQR	[redacted]	
Range	[redacted]	

Table 16.

Iron chelators ongoing at data collection (aged >=12 <=35)	n patients	% (n=[redacted])
Deferasirox	[redacted]	[redacted]
Deferiprone	[redacted]	[redacted]
Desferrioxamine	[redacted]	[redacted]
Combination (oral + sub-cut)	[redacted]	[redacted]
Combination (2x oral)	[redacted]	[redacted]
Not on*	[redacted]	
Combination therapies ongoing at data collection (aged >=12 <=35)	**n patients**	**% (n=[redacted])**
Deferiprone & Desferrioxamine	[redacted]	[redacted]
Deferasirox & Deferiprone	[redacted]	[redacted]
Deferasirox & Desferrioxamine	[redacted]	[redacted]

Table 17.

Transfusions per year (aged <=18 at end of observation)	n (patients)	% (n = [redacted])
<8	[redacted]	[redacted]
8<12	[redacted]	[redacted]
12<14	[redacted]	[redacted]
14<16	[redacted]	[redacted]
16<18	[redacted]	[redacted]
18<20	[redacted]	[redacted]
20 and over	[redacted]	[redacted]
Total*	[redacted]	
Mean	[redacted]	
SD	[redacted]	
Median	[redacted]	
IQR	[redacted]	
Range	[redacted]	

*includes all patients below the age of 19, so e.g. a patient 18 years and 6 months will be included

Table 18.

Iron chelators ongoing at data collection (aged <=18)	n patients	% (n=[redacted])
Deferasirox	[redacted]	[redacted]
Deferiprone	[redacted]	[redacted]
Desferrioxamine	[redacted]	[redacted]
Combination (oral + sub-cut)	[redacted]	[redacted]
Combination (2x oral)	[redacted]	[redacted]
Not on*	[redacted]	
Combination therapies ongoing at data collection (aged >=12 <=35)	**n patients**	**% (n=[redacted])**
Deferiprone & Desferrioxamine	[redacted]	[redacted]
Deferasirox & Deferiprone	[redacted]	[redacted]
Deferasirox & Desferrioxamine	[redacted]	[redacted]

Question B24.

Below are the requested tables on EQ-5D utility values from the UK TDT Chart Review, removing any patients with high T2* iron (≥ 15 mg/g) and patients with hypogonadism, diabetes, or other complications, whose disutility is already accounted for in the model.

Table 19.

EQ-5D utility score	
n participants	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
IQR	[redacted]
Range	[redacted]
Q1	[redacted]
Q3	[redacted]
Min	[redacted]
Max	[redacted]

Question B25.
Below are the additional requested subsets of EQ-5D utility scores from the UK TDT Chart Review.

Table 20. Patients from Table 19, but ages 12+ (matches Table 19 as only individuals aged 16+ completed EQ-5D-3L where utility score could be calculated

EQ-5D utility score	
n participants	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
IQR	[redacted]
Range	[redacted]
Q1	[redacted]
Q3	[redacted]
Min	[redacted]
Max	[redacted]

Table 21. Only those aged 12 to 35

EQ-5D utility score	
n participants	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
IQR	[redacted]
Range	[redacted]
Q1	[redacted]
Q3	[redacted]
Min	[redacted]
Max	[redacted]

Table 22. Only those aged < 18 (i.e. only 16 and 17 year olds applicable from chart review)

EQ-5D utility score	
n participants	[redacted]
Mean	[redacted]
SD	[redacted]
Median	[redacted]
IQR	[redacted]
Range	[redacted]
Q1	[redacted]
Q3	[redacted]
Min	[redacted]
Max	[redacted]

Appendix E Trials 204 and 205 iron overload status tables

Table 28 Patient level iron overload status

Patient ID	Visit	LIC (mg/g)	Model LIC Risk Category*	Cardiac T2* (msec)	Model Cardiac T2* Risk Category*	Serum ferritin (pmol/L)	Model serum ferritin Risk Category*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Notes:

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

Table 29 Patient level iron overload status

Patient ID	Visit	LIC (mg/g)	Model LIC Risk Category*	Cardiac T2* (msec)	Model Cardiac T2* Risk Category*	Serum ferritin (pmol/L)	Model serum ferritin Risk Category*
[redacted]							

[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Notes:

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

Appendix F Vignette study: Health State Utilities Associated with Treatment for Transfusion Dependent β-Thalassemia

Appendix F is the draft manuscript for ‘Health State Utilities Associated with Treatment for Transfusion Dependent β-Thalassemia’ and has been provided as a separate document and should be viewed as AIC.

Appendix G Literature Review

Appendix G systematic review is provided as a separate document and should be viewed as AIC.

Appendix H Cost-effectiveness model change log

Appendix H ‘Documentation of Model Changes Zynteglo CEM_v1.0 FINAL.pdf’ is provided as a separate document and should be viewed as CIC.

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

Clarification questions – follow-up model-related questions

December 2019

1. In question B4 (Table 13), the cost-effectiveness results are presented for a scenario whereby patient body weight is linked to age. Please clarify the values used for mean paediatric and adult body weight, as we have been unable to replicate these results.

Response: The ICER analysis presented in Table 13 of our clarification letter response (for Question B4) was based on an average paediatric weight of [redacted], rounded down from [redacted], (focusing on ages 12 to 17) and an average adult weight of [redacted], rounded up from [redacted], (resulting in an ICER of £[redacted]). These weight values were selected based on examination of the UK chart review data which was provided in Tables 1-3 of Appendix D submitted with Clarification Response 22 Nov.

2. In question B20a, the efficacy of Zynteglo has been updated so that of the patients who do not achieve transfusion independence, [redacted] Please clarify which [redacted] patients have been assumed to be transfusion reduced.

Response: The individual patient IDs considered as transfusion reduced (i.e. reduction of at least [redacted]%) are [redacted] and [redacted]

3. In question B20b, the model has amended so that the mean reduction value in transfusions for transfusion reduced patients is now an editable cell. The value in the updated model is now [redacted], instead of [redacted] that was applied in the original model. Please explain how this new value was calculated.

Response: The updated model was adapted from a global model with UK inputs populated. The [redacted]% erroneously remained from the global model. The correct value is [redacted]%, as originally submitted.

4. In question B25d, please provide the results of the analysis of utility values that were used in Analysis 4: Average the HRQoL weighted according to the age distribution in the three Zynteglo trials (i.e. the base-case model distribution).

Response: Given the trial age distribution used in base-case model ([redacted]% ages 12 to 17, [redacted]% ages 18-23, remainder 24+), and based on requested analyses of chart review data in Question B25 (shown in Tables 20-22 in Appendix, with the utility scores ranging from [redacted] to [redacted] depending on subpopulation), we utilized an average weighted utility score of [redacted] for this scenario analysis (leading to a resulting decrement of [redacted] for TDT patients in the 'Utility' tab of the model).

5. From inspection of the newly submitted economic model, we identified some unit costs that differed from those used in the originally submitted model. These include the following:

    - The post-transplant monitoring cost is half that of the originally applied value,
    - The phlebotomy cost is lower in new model (£48 in original model, £3 in updated model),
    - Administration cost of desferrioxamine is now lower (£9,220 in original model, £1461 or £913 in updated model),

Please provide an explanation for these changes.

Response: In line with the response to question 3 above, these were errors in transfer of inputs in the updated UK model. bluebird bio has confirmed that the original input values (as noted in the question) should apply. Therefore, the post-transplant monitoring costs have been doubled, the phlebotomy cost revised to £48, and the desferrioxamine administration costs revised back to £9,220. The impact of all the changes is a revised base case ICER, [redacted], of £[redacted].

Health State Utilities Associated with Treatment for Transfusion Dependent β-Thalassemia

Louis S. Matza[1] (Louis.matza@evidera.com),
Clark Paramore[2] (CParamore@bluebirdbio.com),
Katie Stewart[1] (Katie.stewart@evidera.com),
Hayley Syrad[3] (Hayley.syrad@evidera.com),
Minesh Jobanputra[2] (MJobanputra@bluebirdbio.com)
Andrew Dietz[2] (ADietz@bluebirdbio.com)

[1]Patient-Centered Research, Evidera, Bethesda, MD, USA
[2]bluebird bio, Cambridge, MA, USA
[3]Patient-Centered Research, Evidera, London, UK

For Submission to *XXX*

Word count = 4,482

Corresponding author:

Louis S. Matza, PhD
Evidera, 7101 Wisconsin Avenue, Suite 1400,
Bethesda, MD 20814
P: 301-664-7263; F: 301-654-9864;
E: louis.matza@evidera.com

ABSTRACT (current word count = 304)

Objectives

Transfusion-dependent β-thalassemia (TDT) is a rare genetic disease that affects the production of healthy red blood cells. Conventional treatment involves regular blood transfusions and iron chelation, which is associated with potential adverse events and a substantial impact on quality of life. The only available curative therapy is allogenic hematopoietic stem cell transplant (allo-HSCT), which has risk of complications, including graft-versus-host disease (GvHD). A novel treatment approach is gene therapy involving autologous stem cell transplant of the patient's own genetically modified hematopoietic stem cells. As new treatments are introduced, cost-utility analyses are needed to examine their value. The purpose of this study was to estimate utilities associated with treatment for TDT.

Methods

General population respondents in England valued eight health state vignettes (developed based on literature review and clinician, patient, and parent interviews) in time trade-off interviews. There were two pre-transplant health states, three health states describing the year in which a transplant occurs, and three post-transplant health states.

Results

A total of 207 participants completed interviews (49.8% female; mean age = 43.2 years; Newcastle, n=87; London, n=72; Bristol, n=48). Mean (SD) utilities for the pre-transplant health states were 0.73 (0.25) with oral chelation and 0.63 (0.32) with subcutaneous chelation. Mean utilities for the transplant year were 0.62 (0.35) for gene therapy, 0.47 (0.39) for allo-HSCT, and

0.39 (0.39) for allo-HSCT with acute GvHD. Post-transplant utilities were 0.93 (0.15) for transfusion independent, 0.75 (0.25) for 60% transfusion reduction, and 0.51 (0.38) for chronic GvHD. Acute and chronic GvHD were associated with significant disutility (acute = -0.09, $p<0.0001$; chronic = -0.42, $p<0.0001$).

Conclusions

Utilities followed expected patterns, with logical differences among treatment options and substantially great utility for post-transplant transfusion independence than or chronic TDT with ongoing transfusion and chelation. These utilities may be useful in cost-utility models estimating the value of treatments for TDT.

Keywords: utility, transfusion-dependent β-thalassemia, stem cell transplant, time trade-off

INTRODUCTION

Transfusion -dependent β-thalassemia (TDT) is a rare and severe genetic disease, caused by impaired β-globin production, that affects the production of healthy red blood cells (Galanello & Origa 2010). Conventional treatment for TDT involves lifelong supportive care with regular blood transfusions that lead to unavoidable iron build up (Cappellini 2007; UK Thalassemia Society 2016). Therefore, patients require continuous and rigorous monitoring of iron burden and must adhere to an iron chelation regimen. The only currently available therapy with the potential to correct the genetic deficiency is allogeneic hematopoietic stem cell transplant (HSCT), which carries the risk of serious complications, including graft-versus-host disease (GvHD), graft failure, and death (Angelucci et al. 2014; Baronciani et al. 2016; Caocci et al. 2011; Lucarelli et al. 2012).

One novel treatment approach in the investigational setting is gene addition therapy. This approach involves the addition of functional copies of the β-globin gene into the patient's own hematopoietic stem cells, ex-vivo. These stem cells are then reintroduced into the patient following myeloablative conditioning (Negre et al. 2016). Gene therapy and autologous HSCT may offer an alterative to allogeneic HSCT for TDT patients that do not have a suitably matched related donor (Sadelain et al. 2006). Gene therapy would allow these patients to avoid the risk of GvHD and would not require immunosuppression to prevent graft rejection (Sadelain et al. 2006; Roselli et al. 2010). As new treatments such as gene addition therapy are developed for TDT, cost-utility analyses (CUAs) are needed to examine their value and inform resource allocation decisions (Brazier et al. 2017; Feeny et al. 1991; Torrance et al. 2002). Such studies require health state utility values to calculate quality-adjusted life years (QALYs). Utilities are values anchored to 0 (dead) and 1 (full health) that quantify the strength of preference for health states.

Although CUAs have been conducted and published for treatments of TDT, limited utilities representing TDT health states have been published, and the available utilities have notable limitations. For example, several studies were identified that focused on utilities associated with various types of iron chelation therapy, but these studies do not appear to have quantified the burden of ongoing blood transfusion and iron chelation. Some of these studies focused on differentiating between oral and subcutaneous treatment administration, rather than quantifying the burden of transfusion and iron chelation (Karnon et al. 2008; Keshtkaran et al. 2013; Osborne et al. 2007; Seyedifar et al. 2016). Two of these publications present the health state vignettes, which appear to understate the side effects of iron chelation therapy as well as the burden of chronic transfusions (Karnon et al. 2008; Osborne et al. 2007). One of the studies derived utilities based on perceptions of nurses (rather than patients or general population respondents), which is not a generally accepted method of utility assessment (Keshtkaran et al. 2013).

Two studies were located that used the EQ-5D to derive utilities of patients with TDT, and both reported unexpectedly high utility scores up to 0.87 (Javanbakht et al. 2015; Seyedifar et al. 2016). These scores do not seem to reflect the considerable burden of this disease and its treatment, possibly because the five domains of the EQ-5D are not be sensitive to the specific impact of ongoing transfusion and iron chelation. It seems likely that the EQ-5D is underestimating the impact of these treatments on quality of life and therefore overestimating the utility of TDT.

There are studies estimating utilities of related concepts, but relevance to patients with TDT is unknown. For example, several studies have focused on utilities associated with transfusions or stem cell transplant in the context of diseases other than beta thalassemia (e.g.,

myelodysplastic syndrome) (Gidwani et al. 2012; Goss et al. 2006; Lee et al. 1997; Slovacek et al. 2005; Szende et al. 2008). One study has estimated utilities associated with GvHD, but in the context of leukemia rather than TDT (Lee et al. 1997).

In sum, few published utilities for TDT are located, and those that are available have notable limitations. Therefore, the purpose of this study was to estimate utilities associated with TDT and its treatment. Health state descriptions (often called health states or vignettes) were developed to represent TDT with ongoing blood transfusions and iron chelation therapy, as well as the period of time in which patients experience stem cell transplantation. Health states were developed to represent the experience of both allogeneic and hematopoietic transplants. In addition, several post-transplant health states were evaluated.

METHODS

Overview of Study Design

This study was designed to estimate utilities associated with treatment for transfusion-dependent β-thalassemia. Vignette-based methodology was selected for two reasons. First, the vignette approach is usually the best or perhaps the only way to estimate the utility impact associated with treatment process. In this case, the relevant treatment processes include the ongoing cycle of transfusion and chelation, as well as differences between conventional and investigational stem cell transplant procedures (Cappellini et al. 2014). While Health Technology Assessment (HTA) authorities often prefer that generic preference-based measures such as the EQ-5D are used to generate utilities (NICE 2013), generic instruments are not designed to be sensitive to treatment process variables. In contrast, vignette-based methods are useful for this purpose because health states can be designed to focus on treatment process attributes. Therefore, almost all studies estimating treatment process utilities use the vignette-

based approach (Brennan & Dixon 2013). Second, for rare diseases such as TDT (NORD 2018), it may not be feasible to have standardized preference-based instruments completed by a large enough sample of patients to represent a range of specific health states. In contrast, hypothetical health states can be drafted based on input from smaller samples of clinicians and patients, and then valued by members of the general population without requiring a large sample of patients.

Health state descriptions (often called vignettes, scenarios, or health states) were drafted based on published literature, clinician interviews, patient/caregiver interviews, and a pilot study. Eight hypothetical health states were presented during the utility interviews: five chronic (i.e., unchanging over time) health states describing patients with TDT pre- or post-transplant, as well as three "path states." Path states are vignettes that describe changes over time (Kuppermann et al. 1997; MacKeigan et al. 1999; Matza et al. 2015b). In this case, the path states describe a series of typical health-related events during the year in which stem cell transplant occurs.

Utilities for these health states were then elicited in a time trade-off (TTO) task with a 10-year time horizon for the five chronic health states and a 1-year time horizon for the three path states. The interviews were conducted with general population participants in March 2018 in three locations in England (Newcastle, London, Bristol). Participants were required to provide written informed consent before completing study procedures, and all procedures and materials were approved by an independent Institutional Review Board (Ethical & Independent Review Services; Study Number 17166).

Health State Development

A targeted literature and online search was performed to support the health state content and inform development of questions to be asked in subsequent interviews. The literature search focused on patient experiences with TDT (Angastiniotis et al. 2014; Lyrakos et al. 2012; Sohn et

al. 2013), transfusions (Javanbakht et al. 2015; Vichinsky et al. 2012; Trompeter and Cohen 2014), iron chelation (Osborne et al. 2007; Seyedifar et al. 2016; Karnon et al. 2008), hematopoietic stem cell transplant (Angelucci 2010; Angelucci et al. 2014; NHS 2015; Lucarelli et al. 2012), gene therapy (Negre et al. 2016), and graft versus host disease (GvHD) (NHS 2017; Cleveland Clinic 2018).

Multiple rounds of telephone interviews were conducted with clinicians including four hematologists and one nurse specialist, all of whom had extensive experience treating patients with TDT. Three of the clinicians were based in the UK, one in the US, and one in France. Two of the hematologists had MD degrees, one had an MBChB, and one had an MBChB and an MD. The nurse was a registered general nurse specializing in thalassemia. Interviews were also conducted with one adult patient with TDT from the US and one adult caregiver for an adolescent patient with TDT in the UK.

Health states were developed through an iterative process with the physicians, nurses, patient and caregiver. Each expert participated in up to three discussions so they could respond to multiple drafts of the health states as they developed. Initial questions focused on gathering information that should be included in the health states (e.g., patients' typical experience with TDT, transfusions/chelation, the transplant process, and GvHD). Follow-up discussions focused on reviewing and editing health state drafts to ensure that the descriptions of the treatment processes and symptoms were clear and accurate representations of the typical patient experience.

The "A" health states describe a typical patient with TDT who has never had a stem cell transplant (i.e., "pre-transplant"). These two health states have identical descriptions of TDT including symptoms, impact, and blood transfusions every three to four weeks. The only

difference between these two health states is the description of iron chelation. Health state A1 describes oral iron chelation (deferasirox) with daily oral medication; the potential side effects to liver, kidney, and gastrointestinal functioning; and typical monitoring for patients receiving this treatment. Health state A2 describes subcutaneous iron chelation (desferoxamine) using a small infusion pump about five days each week for about 10 hours. This health state includes description of potential side effects on vision and hearing, along with the typical monitoring associated with this treatment.

The three "B" health states describe a typical series of events during the transplant year. These health states include sections describing preparation for transplant, the transplant itself, the first month after transplant, and recovery after leaving the hospital. Health states B1 and B2 describe autologous and allogeneic transplant, respectively. The key differences between these health states are the immune system suppression required before and after allogenic transplant (but not before autologous transplant), time to limit exposure to others after transplant (a month or two vs. six months), and time until return to work (4 to 6 months vs. 9 to 12 months). B3 is the same as the allogeneic transplant health state (B2), except for the addition of acute GvHD symptoms and treatment.

The "C" health states describe possible post-transplant outcomes. C1 and C2 differ in the need for transfusion and chelation following a stem cell transplant. Health state C1 describes transfusion independence without anemia, regular transfusions, or iron chelation. Only annual follow up visits are required for monitoring. Health state C2 describes a reduced need for transfusion following the transplant (i.e., 60% reduction). Compared to health state A1 (pre-transplant transfusions and oral chelation), health state C2 requires transfusions less often (every six to eight weeks). Health state C2 was intended to represent the possibility of partial

engraftment with autologous stem cell transplant (Thompson et al. 2016). Health state C3 describes transfusion independence identical to health state C1, except for the addition of chronic GvHD.

For the purposes of the TTO valuation, the A and C health states are chronic states that remain stable over a 10-year period. The B health states are path states describing a series of events that occur over a 1-year period. Health states were presented to participants on individual cards with bullet point text describing each state. The path states included a timeline illustrating sequence and timing of events during the year. See Appendix A for full text of the health states used in the valuation task.

Participants

Participants were recruited from the general population and were required to be at least 18 years of age; able to understand the utility assessment procedures; willing to provide written informed consent; and a current resident of the UK. No specific clinical characteristics were required because this study was intended to estimate utilities for CUAs for submissions to health technology assessment agencies, which often prefer utilities representing general populational values (CADTH 2017; NICE 2013; PBAC 2016). Participants were recruited via local newspapers and online advertising.

Pilot Study

To assess the clarity of the health states and utility assessment methodology, a pilot study was conducted in London with 20 general population participants (55.0% male; mean age = 42.4 years; age range 21 to 73 years). The pilot began with two participants reviewing all 8 health states (A1 to C3) and ranking them in order of preference. However, participants struggled when comparing the chronic health states to the path health states. Therefore, a decision was made to

present the health states in three groups for the remaining participants: the A health states (pre-transplant), the B health states (the transplant year), and the C health states (post-transplant). Participants ranked the chronic states and path states separately. After the introductory ranking task, the health states were valued in TTO interviews. The ranking and TTO tasks were feasible for the majority of respondents, and most participants reported that the health state language and content was clear and comprehensible. Some participants suggested minor edits in formatting and word choice, and the health states were revised accordingly.

Utility Interview Procedures and Scoring

After finalizing the health states and methods based on the pilot study, health state utilities were elicited in a TTO valuation study in March 2018. After ranking the health states as described above for the pilot study, participants valued the chronic health states in a TTO task with a 10-year time horizon with six-month trading increments. For each health state, participants were offered a choice between living 10 years in the health state being rated or a shorter duration in full health. Choices were presented in an order that alternated between longer and shorter amounts of time in full health (10, 0, 9.5, 0.5, 9, 1, 8.5, 1.5...). The path health states were valued following the same procedure, but with a one-year time horizon and one-month trading increments. For health states that the respondent perceived as better than dead, utility scores (u) were calculated based on the point of indecision as the number of years/months in full health (x) divided by the number of years/months in the health state being rated, yielding a utility score on a scale with the anchors of dead (0) and full health (1).

When participants indicated that a health state was worse than dead, the task and scoring procedures were altered as described in previous literature (Rowen & Brazier 2011; Matza et al. 2015a. Participants were offered a choice between dead (choice 1) and a 10-year (or one-year

for the path states) life span (choice 2) beginning with varying amounts of time in the health state being rated, followed by full health for the remainder of the life span. The resulting negative utility scores were calculated with a bounded scoring approach commonly used to avoid highly skewed distributions for negative utility scores ($u = -x / y$, where x is the number of years/months in full health, and y is the number of years/months in the total life span of choice 2).

Statistical Analysis Procedures

Statistical analyses were completed using SAS (version 9.4). Continuous variables including utilities and differences between health state utilities are summarized in terms of means and standard deviations, and categorical variables are summarized as frequencies and percentages. Disutility for acute GvHD was calculated by subtracting the utility of the acute GvHD health state (B3) from the utility of the allogenic transplant health state (B2). Disutility for chronic GvHD was calculated by subtracting the utility of the chronic GvHD health state (C3) from the transfusion independent health state (C1). Student's t-tests and ANOVA with Scheffe's post hoc comparisons were conducted to compare utility scores among various subgroups (e.g., gender, age, geographic location). Paired t-tests were conducted to test whether there were significant differences between pairs of related health states (e.g., oral versus subcutaneous chelation for pre-transplant TDT).

RESULTS

Sample Description

A total of 250 potential participants were scheduled for interviews. Of these, 211 attended the scheduled interview. One participant was found to be ineligible after starting the

interview due to visual impairment, which made it impossible to read the health state cards. Three of the 210 eligible participants had difficulty understanding the health states and/or TTO procedures and were therefore unable to provide valid TTO data. Thus, 207 valid TTO interviews were conducted (87 in Newcastle, 72 in London, and 48 in Bristol). The sample was 49.8% female, with a mean age of 42.5 years (Table 1). The majority of participants reported ethnicity as white (84.5%). The most commonly reported health conditions were depression (21.3%), anxiety (20.3%), arthritis (9.2%), and hypertension (9.7%). No participants reported having β-thalassemia, but two participants (1.0%) reporting knowing someone diagnosed with β-thalassemia.

Health State Utilities

In the introductory ranking task, participants compared and ranked the three path states describing the year in which a transplant occurs (B1, B2, and B3). B1 (gene therapy) was always ranked as most preferable, and B3 (allogeneic transplant with acute GvHD) was always ranked as least preferable, with B2 (allogeneic transplant) in the middle. Next, participants ranked the five chronic health states with rankings ranging from 1 (most preferable health state) to 5 (least preferable). Of these five health states, C1 (transfusion independent) was always ranked as most preferable. Rankings of the other four health states varied, with mean rankings of: 2.31 for C2 (post-transplant 60% transfusion reduction), 3.14 for A1 (TDT with oral chelation), 4.08 for A2 (TDT with subcutaneous chelation), and 4.47 for C3 (post-transplant chronic GvHD).

Mean TTO utility scores are presented in Figure 1. The pre-transplant health state A1 had a higher mean utility score (0.73) than A2 (0.63). Among the transplant year health states, B1 had the highest mean utility (0.62), followed by B2 (0.47), and B3 (0.39). Among the post-

transplant health states, C1 had the highest mean utility score at 0.93, followed by C2 (0.75), and C3 (0.51).

There were no significant differences in utility by age, gender, or whether the respondents had dependents, which can sometimes affect utility valuations (Matza et al. 2014). For six of the eight health states, there were no significant utility differences across the three geographic locations. However, the Bristol subgroup's utility score for A2 was significantly lower than the utility of the London sample (0.52 vs. 0.67, $p<0.05$). In addition, the Bristol utility score for C3 was significantly lower compared to both the London and Newcastle subgroups (0.36 vs. 0.57 and 0.54, respectively, $p<0.05$).

With the exception of C1, most participants (>87%) were willing to trade time to avoid living in any of the health states. For C1, only 81 participants (39.1%) were willing to trade time to avoid this state. Nearly all participants (>95%) were willing to trade time to avoid A2, B2, B3, and C3. The great majority of participants rated each of the eight health states as better than dead (i.e., utility score > 0): A1, 99.0%; A2, 96.1%; C1, 99.5%; C2, 99.0%; C3, 92.8%; B1, 94.7%; B2, 92.3%; and B3, 91.3%.

Utility Differences

T-tests revealed that all differences between health state utility pairs presented in Table 2 were statistically significant ($p<0.0001$). For example, health states A1 and A2 had identical descriptions of TDT, except for the difference in type of iron chelation (oral vs. subcutaneous). The difference of 0.10 was statistically significant, indicating that there was a significant difference in preference between these two types of chelation. Furthermore, both acute and chronic GVHD were associated with statistically significant disutilities (0.09 and 0.42,

respectively). In addition, gene therapy was associated with a significantly greater utility than allogenic transplant (utility difference = 0.15).

DISCUSSION

In general, utilities followed expected patterns. The health state describing transfusion independence (C1), including associated benefits such as lack of symptoms and improved quality of life, had the highest utility score. The health states describing chronic TDT (health states A1 and A2) with the ongoing cycle of transfusion and chelation had substantially lower utilities. The difference in preference between health states describing transfusion independence and transfusion dependence highlights the considerable burden of this disease, as well as the benefits of potentially curative treatments such as gene therapy or stem cell transplant.

Utilities of health states differing in terms of treatment modality and treatment-related adverse events also followed logical patterns, with more difficult treatment processes associated with lower utility values. For example, TDT with subcutaneous chelation (A2) had a lower utility than an otherwise identical health state with oral chelation (A1). Furthermore, chronic (C3) and acute GvHD (B3) were both associated with significant disutility.

The utilities derived in this study may be useful in economic models examining and comparing the value of treatments for TDT. When modelers are using these values in a CUA, they should aware of the difference between the chronic health states and the path states to ensure that the utilities are used correctly. The pre- and post-transplant health states (i.e., the A and C health states) were valued as chronic health states in a TTO task with a 10-year time horizon. Because these five health states did not change over time, the resulting utilities may be applied for any length of time in a CUA, consistent with the constant proportional trade-off

assumption of the QALY model suggesting that the value of a health state is independent of the amount of time spent in that health state (Bleichrodt & Johannesson 1997).

In contrast, the three transplant states (i.e., B1 to B3) are path states each representing a 1-year time period in which the hypothetical patient proceeds through a series of health-related experiences, each of which lasts for a specified length of time. Therefore, the resulting utility values for these three path states cannot be considered independent of time, and they may only be used in a CUA to represent a 1-year period in which the transplant occurs. The advantage of this approach is that the utility represents the entire path, and respondents' valuations are based on consideration of the full sequence of events as well as the time spent in each part of the path. The disadvantage is that is not possible to identify the utility impact of individual parts of the path.

Although utilities derived in this study may be useful in economic modeling, limitations of the vignette-based methodology should be acknowledged. Several HTA guidelines, including the guide issued by NICE, advocate for use of utilities derived via generic preference-based measures such as the EQ-5D to maximize "consistency across appraisals" (NICE 2013). However, in situations when generic instruments are not sensitive to important aspects of disease or treatment, HTA guidelines allow for alternative utility assessment methodology. NICE specifies that models incorporating utilities estimated with other methodology may be acceptable when the EQ-5D is not "appropriate" (NICE 2013).

For estimating utilities of TDT, generic instruments are likely to be inappropriate for two reasons. First, because TDT is a rare condition (NORD 2018; Orphanet 2011), it may not be feasible to recruit a large enough sample of patients representing each specific health state needed for modeling. Second, treatment process attributes are a key component differentiating

among the relevant health states (e.g., oral vs. subcutaneous iron chelation; allogeneic stem cell transplant vs. gene therapy). Generic instruments such as the EQ-5D were not designed to be sensitive to treatment process attributes. However, there is growing consensus that aspects of the treatment process are important to patients and could therefore have an impact on health state preference. To estimate treatment process utilities, most researchers employ the vignette-based approach (Brennan & Dixon 2013). This approach is well-suited for assessment of process utilities because the vignettes can be drafted to represent the typical experience of patients receiving treatment.

An important limitation of vignette methods is that the resulting utility scores represent preferences for specific health states, rather than experience of an actual patient sample. Furthermore, the vignette approach cannot take into account the complexity of all possible events associated with TDT and its treatment, such as insertional oncogenesis and chemotherapy induced secondary malignancies. Therefore, the extent to which the reported utilities are comparable to values that might be derived from patients using generic instruments is not known. To mitigate this inherent limitation of the vignette approach, the TTO assessment methods were selected to maximize comparability to standardized instruments. For example, chronic health states were valued by UK general population participants in a TTO task with a 10-year time horizon, similar to methods used to derive the EQ-5D utility scoring tariffs (Dolan et al. 1996).

There may also be limitations associated with the length and complexity of some of the health states. For vignette-based utilities to be credible, is essential that the content of the vignettes is clear and comprehensible to the respondents. Health states B1 to B3, describing the year of transplant, were particularly long and complex. Although efforts were made to shorten

and clarify the health states as much as possible based on results of the pilot study, these health states remained relatively long in order to include the details that clinicians said were necessary to represent a typical transplant year. Several strategies were used to help respondents understand these relatively long health states and attend to all the information. For example, these three health states were presented separately from the others to avoid overwhelming the respondents with too much information at one time. In addition, all health states were formatted in a series of sections with headers to help organize the information. Furthermore, the three transplant health states included timelines clearly illustrating the series of events. Finally, interviewers asked the participants to explain their preferences to ensure that they understood and attended to all aspects of the health states.

Generally, it seems that these efforts to ensure participants understood the longer health states were effective because the resulting utilities followed logical patterns. The gene therapy treatment process as described in health state B1 was preferred over the allogeneic stem cell transplant in B2, indicating that most participants likely understood and considered the potential advantages of gene therapy that distinguished between the two health states (i.e., no need for immunosuppression therapy, fewer medications required after leaving the hospital, a shorter time of increased infection susceptibility in which exposure to other people must be limited, and a faster return to work). Nevertheless, it is possible that some participants may not have been able to consider all parts of the three longer health states, which could lead to some error in the resulting scores. Thus, utilities for these three longer health states should be used and interpreted with caution.

Despite limitations, the current study represents an important step forward for economic modeling of treatment for TDT. The utilities derived in this study may be used in CUAs

estimating the value of treatments that may eliminate or reduce the need for ongoing blood transfusions and iron chelation in these patients. In addition, differences among the health state utilities may be useful for distinguishing between approaches for iron chelation as well as between allogeneic stem cell transplant and the newer gene therapy approach.

ACKNOWLEDGEMENTS

This study was funded by bluebird bio. The authors would like to thank Katelyn Cutts, Milenka Jean-Baptiste, Gordon Parola, Hayley Syrad, Natalie Taylor, and Amara Tiebout for assistance with data collection; Jun Chen for statistical programming; and Amara Tiebout for editorial assistance.

REFERENCES

Angastiniotis M, Taher A, Cappellini MD. Chapter 16. Lifestyle and Quality of Life. In: Cappellini MD, Cohen A, Porter J, et al., eds. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT). 3rd Edition; 2014.

Angelucci E. Hematopoietic stem cell transplantation in thalassemia. *Hematology Am Soc Hematol Educ Program.* 2010;2010:456-462.

Baronciani D, Angelucci E, Potschger U, et al. Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000-2010. *Bone Marrow Transplant.* 2016;51(4):536-541.

Bleichrodt H, Johannesson M. The validity of QALYs: an experimental test of constant proportional tradeoff and utility independence. *Med Decis Making.* 1997;17(1):21-32.

Brazier JR, Ratcliffe J, Salomon JA, Tsuchiya A. Measuring and Valuing Health benefits for Economic Evaluation. Vol Second Edition. New York: Oxford University Press; 2017.

Brennan VK, Dixon S. Incorporating process utility into quality adjusted life years: a systematic review of empirical studies. *Pharmacoeconomics.* 2013;31(8):677-691.

Canadian Agency for Drugs and Technologies in Health (CADTH). Guidelines for the Economic Evaluation of Health Technologies: Canada — 4th Edition. Ottawa, Ontario; March 2017.

Caocci G, Efficace F, Ciotti F, et al. Prospective assessment of health-related quality of life in pediatric patients with beta-thalassemia following hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2011;17(6):861-866.

Cappellini MD. Exjade(R) (deferasirox, ICL670) in the treatment of chronic iron overload associated with blood transfusion. *Ther Clin Risk Manag.* 2007;3(2):291-299.

Cleveland Clinic. Graft vs Host Disease: An Overview in Bone Marrow Transplant. May 25, 2018; 5 pgs. Available at: https://my.clevelandclinic.org/health/diseases/10255-graft-vs-host-disease-an-overview-in-bone-marrow-transplant. Accessed October 10, 2018.

Dolan P, Gudex C, Kind P, Williams A. The time trade-off method: results from a general population study. *Health Econ.* 1996;5(2):141-154.

Feeny D, Barr RD, Furlong W, Torrance GW, S. W. Quality of life of the treatment process in pediatric oncology: An approach to measurement. In: Osaba D, ed. *Effect of Cancer on Quality of Life*. Boca Raton, FL: CRC Press; 1991.

Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis.* 2010;5:11.

Gidwani R, Khan ZM, Fenaux P, Beach CL, Pashos CL. A cost-effectiveness analysis of using azacitidine vs. decitabine in treating patients with myelodysplastic syndromes. *J Med Econ.* 2012;15(1):145-154.

Goss TF, Szende A, Schaefer C, et al. Cost effectiveness of lenalidomide in the treatment of transfusion-dependent myelodysplastic syndromes in the United States. *Cancer Control.* 2006;13 Suppl:17-25.

Javanbakht M, Keshtkaran A, Shabaninejad H, Karami H, Zakerinia M, Delavari S. Comparison of Blood Transfusion Plus Chelation Therapy and Bone Marrow Transplantation in Patients with beta-Thalassemia: Application of SF-36, EQ-5D, and Visual Analogue Scale Measures. *Int J Health Policy Manag.* 2015;4(11):733-740.

Karnon J, Tolley K, Oyee J, Jewitt K, Ossa D, Akehurst R. Cost-utility analysis of deferasirox compared to standard therapy with desferrioxamine for patients requiring iron chelation therapy in the United Kingdom. *Curr Med Res Opin.* 2008;24(6):1609-1621.

Keshtkaran A, Javanbakht M, Salavati S, Mashayekhi A, Karimi M, Nuri B. Cost-utility analysis of oral deferasirox versus infusional deferoxamine in transfusion-dependent beta-thalassemia patients. *Transfusion.* 2013;53(8):1722-1729.

Kuppermann M, Shiboski S, Feeny D, Elkin EP, Washington AE. Can preference scores for discrete states be used to derive preference scores for an entire path of events? An application to prenatal diagnosis. *Med Decis Making.* 1997;17(1):42-55.

Lee SJ, Kuntz KM, Horowitz MM, et al. Unrelated donor bone marrow transplantation for chronic myelogenous leukemia: a decision analysis. *Ann Intern Med.* 1997;127(12):1080-1088.

Lucarelli G, Isgro A, Sodani P, Gaziev J. Hematopoietic stem cell transplantation in thalassemia and sickle cell anemia. *Cold Spring Harb Perspect Med.* 2012;2(5):a011825.

Lyrakos GN, Vini D, Aslani H, Drosou-Servou M. Psychometric properties of the Specific Thalassemia Quality of Life Instrument for adults. *Patient Prefer Adherence.* 2012;6:477-497.

MacKeigan LD, O'Brien BJ, Oh PI. Holistic versus composite preferences for lifetime treatment sequences for type 2 diabetes. *Med Decis Making.* 1999;19(2):113-121.

Matza LS, Sapra SJ, Dillon JF, et al. Health state utilities associated with attributes of treatments for hepatitis C. *Eur J Health Econ.* 2015a;16(9):1005-1018.

Matza LS, Stewart KD, Gandra SR, et al. Acute and chronic impact of cardiovascular events on health state utilities. *BMC Health Serv Res.* 2015b;15:173.

National Health Service (NHS). Stem cell and bone marrow transplants - what happens. NHS Choices, 2015:2 pgs.

National Institute for Health and Care Excellence (NICE). *Process and methods guides: Guide to the methods of technology appraisal.* London, UK: NICE; September 10, 2013.

National Organization for Rare Disorders (NORD). Beta Thalassemia. Danbury, CT; 12 pgs; 2018.

Negre O, Eggimann AV, Beuzard Y, et al. Gene Therapy of the beta-Hemoglobinopathies by Lentiviral Transfer of the beta(A(T87Q))-Globin Gene. *Hum Gene Ther.* 2016;27(2):148-165.

NHS England Specialised Services Clinical Reference Group for Blood and Marrow Transplantation. Clinical Commissioning Policy: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation. NHS England; March 2017:30.

Orphanet. Rare Diseases: Beta-thalassemia. April 2011. Available at: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=848. Accessed October 10, 2018.

Osborne RH, De Abreu Lourenco R, Dalton A, et al. Quality of life related to oral versus subcutaneous iron chelation: a time trade-off study. *Value Health.* 2007;10(6):451-456.

Pharmaceutical Benefits Advisory Committee (PBAC). Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee (Version 5.0). In: Australian Government DoH. Canberra, ACT; September 2016:216.

Roselli EA, Mezzadra R, Frittoli MC, et al. Correction of beta-thalassemia major by gene transfer in haematopoietic progenitors of pediatric patients. *EMBO Mol Med.* 2010;2(8):315-328.

Rowen D, Brazier J. Health Utility Measurement. In: Glied S, Smith P, eds. *The Oxford Handbook of Health Economics*. New York: Oxford University Press; 2011:788-813.

Sadelain M, Boulad F, Galanello R, et al. Therapeutic options for patients with severe beta-thalassemia: the need for globin gene therapy. *Hum Gene Ther.* 2007;18(1):1-9.

Seyedifar M, Dorkoosh FA, Hamidieh AA, et al. Health-Related Quality of Life and Health Utility Values in Beta Thalassemia Major Patients Receiving Different Types of Iron Chelators in Iran. *Int J Hematol Oncol Stem Cell Res.* 2016;10(4):224-231.

Slovacek L, Slovackova B, Jebavy L. Global quality of life in patients who have undergone the hematopoietic stem cell transplantation: finding from transversal and retrospective study. *Exp Oncol.* 2005;27(3):238-242.

Sohn EY, Kato R, Noetzli LJ, et al. Exercise performance in thalassemia major: correlation with cardiac iron burden. *Am J Hematol.* 2013;88(3):193-197.

Szende A, Schaefer C, Goss TF, et al. Valuation of transfusion-free living in MDS: results of health utility interviews with patients. *Health Qual Life Outcomes.* 2009;7:81.

Thompson AA, Kwiatkowski J, Rasko J, et al. Lentiglobin Gene Therapy for Transfusion-Dependent β-Thalassemia: Update from the Northstar Hgb-204 Phase 1/2 Clinical Study. *Blood.* 2016;128(1175).

Torrance GW, Furlong W, Feeny D. Health utility estimation. *Expert Rev Pharmacoecon Outcomes Res.* 2002;2(2):99-108.

Trompeter S, Cohen A. Chapter 2. Blood Transfusion. In: Porter J, ed. *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT)*. 3rd Edition; 2014:12.

United Kingdom Thalassaemia Society. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK. 3rd Edition; London, UK; 2016:173.

Vichinsky E, Levine L, Bhatia S, et al. Standards of Care Guidelines for Thalassemia. In: Levine M, ed. Oakland, CA: Children's Hospital & Research Center Oakland; 2012:28

TABLES

Table 1. Demographic Characteristics

	Newcastle (N=87)	London (N=72)	Bristol (N=48)	Total Sample (N=207)	P-value[1]
Age (Mean, SD)	42.6 (16.4)	45.0 (14.2)	41.9 (15.1)	43.2 (15.3)	0.4836
Gender, n (%)					
Male	44 (50.6%)	39 (54.2%)	21 (43.8%)	104 (50.2%)	0.5335
Female	43 (49.4%)	33 (45.8%)	27 (56.3%)	103 (49.8%)	
Ethnicity, n (%)					
White	85 (97.7%)	46 (63.9%)	44 (91.7%)	175 (84.5%)	<.0001
Mixed	2 (2.3%)	3 (4.2%)	2 (4.2%)	7 (3.4%)	
Asian	0 (0.0%)	14 (19.4%)	2 (4.2%)	16 (7.7%)	
Black	0 (0.0%)	8 (11.1%)	0 (0.0%)	8 (3.9%)	
Other[2]	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.5%)	
Marital Status, n (%)					
Single	44 (50.6%)	45 (62.5%)	30 (62.5%)	119 (57.5%)	0.2305
Married/Cohabitating/Living with partner	43 (49.4%)	27 (37.5%)	18 (37.5%)	88 (42.5%)	
Employment Status, n (%)					
Full-time work	34 (39.1%)	31 (43.1%)	14 (29.2%)	79 (38.2%)	0.5599
Part-time work	24 (27.6%)	19 (26.4%)	18 (37.5%)	61 (29.5%)	
Other	29 (33.3%)	22 (30.6%)	16 (33.3%)	67 (32.4%)	
Education Level, n (%)					
University degree	28 (32.2%)	41 (56.9%)	21 (43.8%)	90 (43.5%)	0.0073
No University degree	59 (67.8%)	31 (43.1%)	27 (56.3%)	117 (56.5%)	

[1] P-values are based on ANOVAs for continuous variables and chi-square analyses for categorical variables.

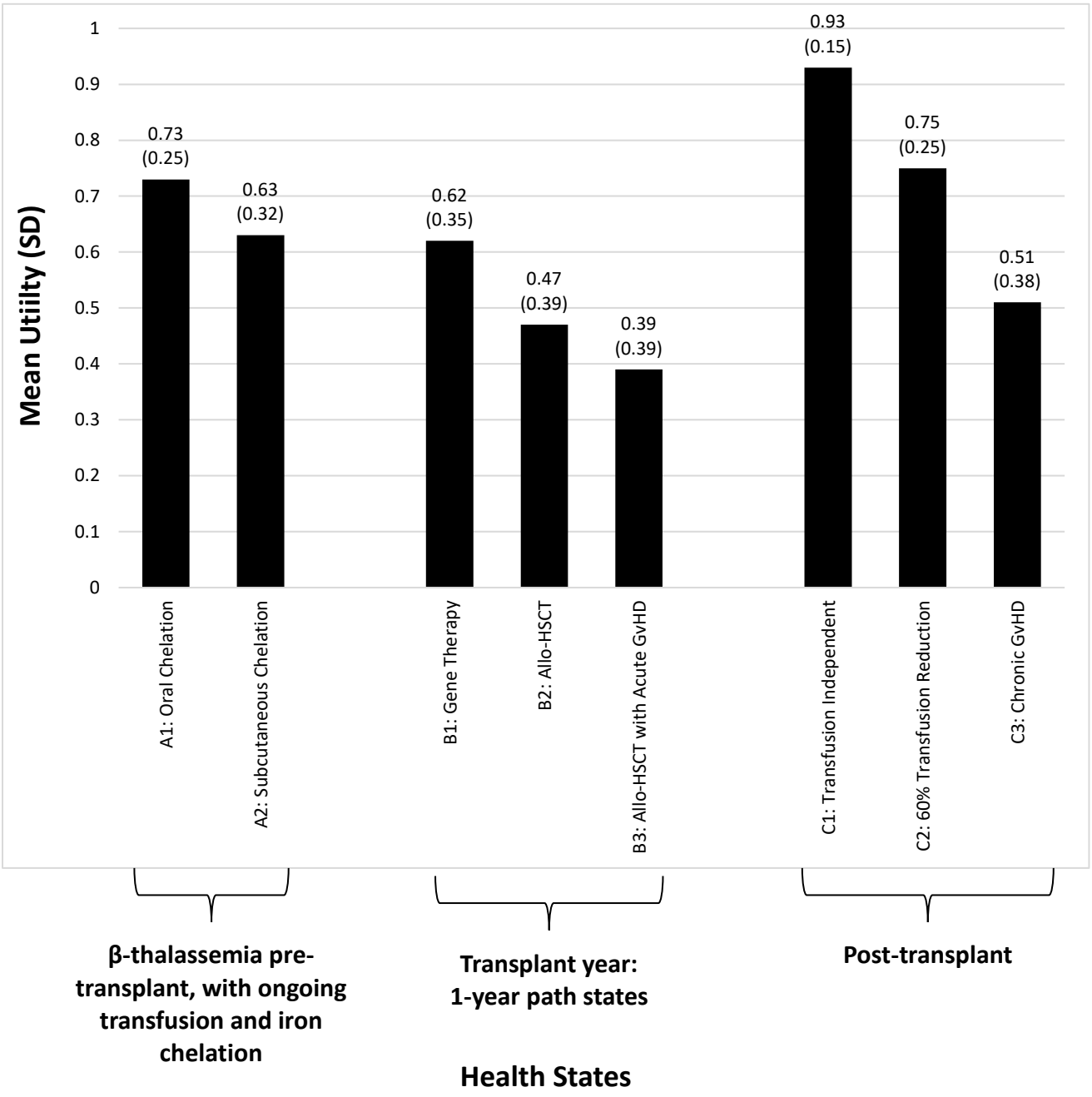
[2] Other Ethnic/Racial background included: Iranian (n=1)

Table 2. Utility Differences[1] (computed as x-y; 2 decimal places; N=207)

Health State Differences	Mean	SD	95% CI
Utility Difference: Pre-Transplant Health States			
A1 – A2: Oral chelation vs. subcutaneous chelation	0.10	0.17	0.08 – 0.12
Utility Differences: Transplant Health States			
B1 – B2: LentiG vs. Allogenic	0.15	0.17	0.13 – 0.17
B2 – B3: Allogenic vs. allogenic with acute GvHD	0.09	0.11	0.07 – 0.10
Utility Differences: Post-Transplant Health States			
C1 – C2: Transfusion independent vs. 60% reduction	0.18	0.21	0.15 – 0.21
C1 – C3: Transfusion independent vs. chronic GvHD	0.42	0.37	0.37 – 0.47
Utility Differences: Pre- vs Post-Transplant			
A1 – C1: Pre-transplant with oral chelation vs. post-transplant transfusion independent	-0.21	0.21	-0.24 – 0.18
A2 – C1: Pre-transplant with subcutaneous chelation vs. post-transplant transfusion independent	-0.31	0.29	-0.35 – 0.27
A1 – C2: Pre-transplant with oral chelation vs. post-transplant 60% reduction	-0.03	0.07	-0.04 – -0.02
A1 – C3: Pre-transplant with oral chelation vs. post-transplant chronic GvHD	0.22	0.30	0.17 – 0.26
A2 – C3: Pre-transplant with subcutaneous chelation vs. post-transplant chronic GvHD	0.12	0.27	0.08 – 0.15

[1] TTO scores are on a scale anchored with 0 representing dead and 1 representing full health.

Figure 1. Mean Health State Utilities



APPENDIX A. HEALTH STATE TEXT

For the interviews, the health state letters used throughout this article were changed so that respondents could rank the health states without being biased by the organizational structure implied by the original letters. For example, health state A1 was renamed as D, and A2 was renamed as M. The letters seen by the respondents are included in parentheses below.

Health State A1: Pre-transplant β-Thalassemia with transfusion and oral chelation (D)

Disease

- You have an **inherited blood disease** that makes it impossible for your body to make haemoglobin, which is the part of the blood that carries oxygen.
- This disease causes **severe anaemia**, which means there is not enough haemoglobin in your red blood cells to carry oxygen.
- Without regular blood transfusions, this disease would be fatal.

Blood Transfusions

- Treatment includes **blood transfusions**, which give you healthy red blood cells that are full of haemoglobin to correct your anaemia. The blood is from healthy blood donors.
- You receive these transfusions **every 3 to 4 weeks** at a hospital or transfusion unit.
- Approximately 2 days before each transfusion, you go to hospital for a blood test to make sure your blood is matched to the blood that is transfused.
- Blood transfusions are given through a tube inserted into a vein in your arm.
- Each transfusion lasts approximately **4 to 6 hours**.

Removing Iron: Tablets

- The blood transfusions cause a **build-up of iron** in your body. This iron can damage your heart, liver, hormone glands, and other vital organs.
- To reduce the amount of iron in your body, you must **take tablets daily**.
- This medication has **potential side effects** on your liver and kidney functioning, and may cause gastrointestinal upset or constipation. Therefore, your doctor will monitor you via blood tests and urine tests. Your doctor may adjust the dose as necessary. **Most patients can avoid these side effects with careful monitoring**.

Symptoms and Impact

- **In the days before your regular blood transfusions**:
  - You feel **tired and you may feel irritable**.
  - You may have **difficulty concentrating**.
  - You may not be as productive at **work or at school**.
  - Your ability to **exercise** may be limited.
  - You may feel an aching **pain** as if your bones hurt.
- You take **time off work or school** for appointments.
  - You go to the hospital for a **blood transfusion** every 3 to 4 weeks.

- You go to the hospital for a **blood test** 2 days before each transfusion.
- You have annual clinic appointments for liver and heart **scans** to check for iron build-up.
- You have bone density **scans** every 18 months to check for osteoporosis (bone weakening).

Health State A2: Pre-transplant β-Thalassemia with transfusion and subcutaneous chelation (M)

Disease

- You have an **inherited blood disease** that makes it impossible for your body to make haemoglobin, which is the part of the blood that carries oxygen.
- This disease causes **severe anaemia**, which means there is not enough haemoglobin in your red blood cells to carry oxygen.
- Without regular blood transfusions, this disease would be fatal.

Blood Transfusions

- Treatment includes **blood transfusions**, which give you healthy red blood cells that are full of haemoglobin to correct your anaemia. The blood is from healthy blood donors.
- You receive these transfusions **every 3 to 4 weeks** at a hospital or transfusion unit.
- Approximately 2 days before each transfusion, you go to hospital for a blood test to make sure your blood is matched to the blood that is transfused.
- Blood transfusions are given through a tube inserted into a vein in your arm.
- Each transfusion lasts approximately **4 to 6 hours**.

Removing Iron: Infusion

- The blood transfusions cause a **build-up of iron** in your body. This iron can damage your heart, liver, hormone glands, and other vital organs.
- To reduce the amount of iron in your body, you must take medicine **using a small infusion pump about 5 days each week**.
- This medicine is **infused into your body through a needle** just under the surface of the skin of your abdomen. You can insert the needle by yourself.
- The infusion lasts **about 10 hours**. You can do this **during the day or night**.
  - **During the day**, you can carry the pump around in a small bag attached to your belt while performing most usual activities.
  - **At night**, the pump can be next to you in bed.
- This medication has **potential side effects** on your vision and hearing. Therefore, your doctor will monitor you via blood, urine, hearing, and vision tests. Your doctor may adjust the dose as necessary. **Most patients can avoid these side effects with careful monitoring**.
- You may experience pain, discomfort, and swelling at the infusion site.

Symptoms and Impact

- **In the days before your regular blood transfusions**:
  - You feel **tired and you may feel irritable**.
  - You may have **difficulty concentrating**.
  - You may not be as productive at **work or at school**.
  - Your ability to **exercise** may be limited.
  - You may feel an aching **pain** as if your bones hurt.
- You take **time off work or school** for appointments.
  - You go to the hospital for a **blood transfusion** every 3 to 4 weeks.
  - You go to the hospital for a **blood test** 2 days before each transfusion.
  - You have annual clinic appointments for liver and heart **scans** to check for iron build-up.
  - You have bone density **scans** every 18 months to check for osteoporosis (bone weakening).
  - You have **annual clinic appointments** to check your hearing and vision.

Health State B1: Autologous Stem Cell Transplant (P)

Disease

- To treat your blood disease, you receive a **stem cell transplant**.
- The potential **benefits** of transplant are that you may no longer need blood transfusions.
- The potential **risks** are that the transplant may not work, you may need additional transfusions, and you will be susceptible to bacterial and viral infections during recovery.

Preparation for Transplant

- You need a surgical procedure to insert an **intravenous line** into a large blood vessel. This line emerges from the skin on the side of your chest.
- You make **several visits** to the hospital for blood tests.
- You **stay in hospital for approximately 10 days** while preparing for the transplant. You undergo **chemotherapy** to eliminate your bone marrow and make space for the new stem cells. The chemotherapy is administered through the intravenous line over **several hours each day for several days**.
- You experience **nausea and tiredness**.

Transplant

- One or two days after chemotherapy is completed, you receive the **stem cell transplant** by infusion through the intravenous line. This infusion occurs on **one day, and it is not painful**.

First Month after Transplant

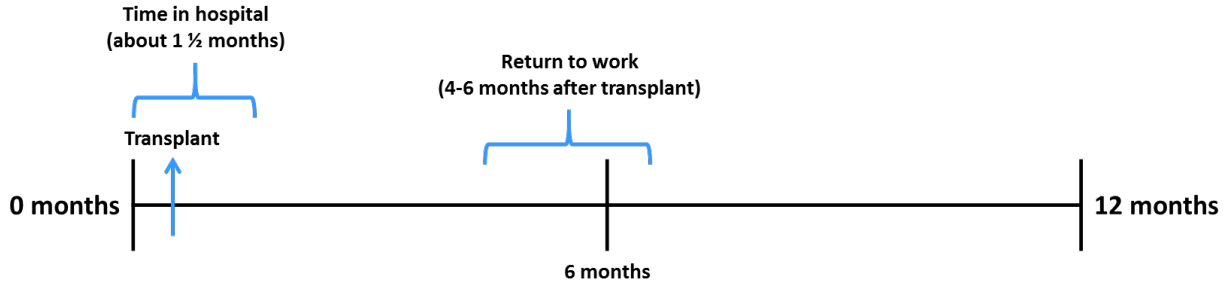
- You **stay in the hospital for approximately 1 month**. You stay in a **protective environment** because your immune system cannot fight germs.

- For the **first 2 weeks**, you experience mouth sores, sore throat, and diarrhoea. You are not able to eat or drink properly and you may need intravenous feeding. You may also have infections with fever.
- The chemotherapy can put you at risk of bleeding. To prevent this, you receive platelet infusions every few days. Platelets are a type of blood cell.
- You experience significant hair loss. Your hair starts to grow back after about 2 months.

After Hospital

- After a few months, your bone marrow produces enough red blood cells so that you **no longer need blood transfusions**.
- For **a month or two** after leaving the hospital, you try to **limit your exposure to other people** to avoid infections while your immune system is recovering from the chemotherapy.
- You take **a couple of medications** for a few months to help prevent infection during recovery.
- **Many people are re-admitted** to the hospital once or twice during the first 2 or 3 months after transplant because of complications such as infection.
- For about 3 months after leaving the hospital, you **visit the transplant unit once every week or two** for careful monitoring.
- You are able to **return to work or school approximately 4 to 6 months after the transplant**.
- Starting about 6 months after the transplant, you begin repeating all the **vaccinations** you had as a child.

Timeline



Health State B2: Allogenic Stem Cell Transplant (S)

Disease

- To treat your blood disease, you receive a **stem cell transplant**.
- The potential **benefits** of transplant are that you may no longer need blood transfusions.
- The potential **risks** are that the transplant may not work, you may need additional transfusions, and you will be susceptible to bacterial and viral infections during recovery.

Preparation for Transplant

- You need a surgical procedure to insert an **intravenous line** into a large blood vessel. This line emerges from the skin on the side of your chest.
- You make **several visits** to the hospital for blood tests.
- You **stay in hospital for approximately 10 days** while preparing for the transplant. You undergo **chemotherapy** to eliminate your bone marrow and make space for the new stem cells. The chemotherapy is administered through the intravenous line over **several hours each day for several days**.
- You experience **nausea and tiredness**.
- You receive **medication to suppress your immune system**. This prevents your body from attacking the transplanted stem cells so that new bone marrow can grow. During this time, **your immune system is seriously compromised**, and you are at risk of infection.

Transplant

- One or two days after chemotherapy is completed, you receive the **stem cell transplant** by infusion through the intravenous line. This infusion occurs on **one day, and it is not painful**.

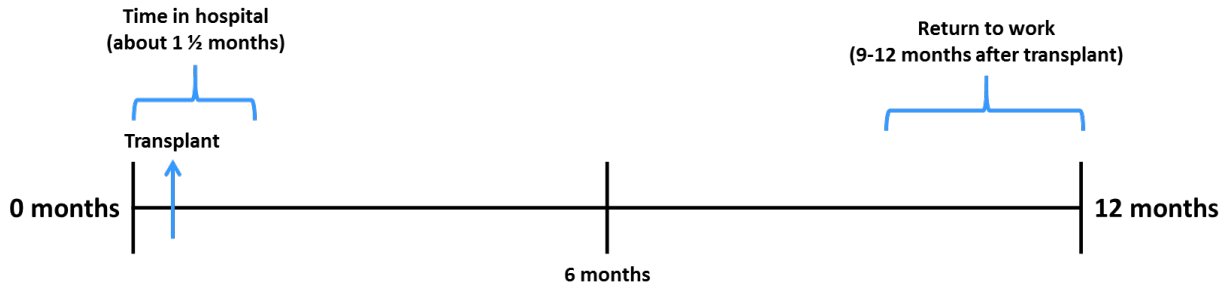
First Month after Transplant

- You **stay in the hospital for approximately 1 month**. You stay in a **protective environment** because your immune system cannot fight germs.
- For the **first 2 weeks**, you experience mouth sores, sore throat, and diarrhoea. You are not able to eat or drink properly and you may need intravenous feeding. You may also have infections with fever.
- The chemotherapy can put you at risk of bleeding. To prevent this, you receive platelet infusions every few days. Platelets are a type of blood cell.
- You experience significant hair loss. Your hair starts to grow back after about 2 months.

After Hospital

- After a few months, your bone marrow produces enough red blood cells so that you **no longer need blood transfusions**.
- You continue to take **medication to suppress your immune system** for about **6 months** after the transplant. During this time, you try to **limit your exposure to other people** to avoid infections while your immune system is suppressed.
- You take **several (up to 10) medications daily** to help prevent infection and support your body during recovery. Some of these medications can make you feel **nauseous**.
- **Many people are re-admitted** to the hospital once or twice during the first 2 or 3 months after transplant because of complications such as infection.
- For about 3 months after leaving the hospital, you **visit the transplant unit once every week or two** for careful monitoring.
- You are able to **return to work or school approximately 9 to 12 months after the transplant**.
  - Starting about 6 months after the transplant, you begin repeating all the **vaccinations** you had as a child.

Timeline



Health State B3: Allogenic Stem Cell Transplant with Acute GvHD (G)

Disease

- To treat your blood disease, you receive a **stem cell transplant**.
- The potential **benefits** of transplant are that you may no longer need blood transfusions.
- The potential **risks** are that the transplant may not work, you may need additional transfusions, and you will be susceptible to bacterial and viral infections during recovery.

Preparation for Transplant

- You need a surgical procedure to insert an **intravenous line** into a large blood vessel. This line emerges from the skin on the side of your chest.
- You make **several visits** to the hospital for blood tests.
- You **stay in the hospital for approximately 10 days** while preparing for the transplant. You undergo **chemotherapy** to eliminate your bone marrow and make space for the new stem cells. The chemotherapy is administered through the intravenous line over **several hours each day for several days**.
- You experience **nausea and tiredness**.
- You receive **medication to suppress your immune system**. This prevents your body from attacking the transplanted stem cells so that new bone marrow can grow. During this time, **your immune system is seriously compromised**, and you are at risk of infection.

Transplant

- One or two days after chemotherapy is completed, you receive the **stem cell transplant** by infusion through the intravenous line. This infusion occurs on **one day, and it is not painful**.

First Month after Transplant

- You **stay in the hospital for approximately 1 month**. You stay in a **protective environment** because your immune system cannot fight germs.
- For the **first 2 weeks**, you experience mouth sores, sore throat, and diarrhoea. You are not able to eat or drink properly and you may need intravenous feeding. You may also have infections with fever.
- The chemotherapy can put you at risk of bleeding. To prevent this, you receive platelet infusions every few days. Platelets are a type of blood cell.

- You experience significant hair loss. Your hair starts to grow back after about 2 months.

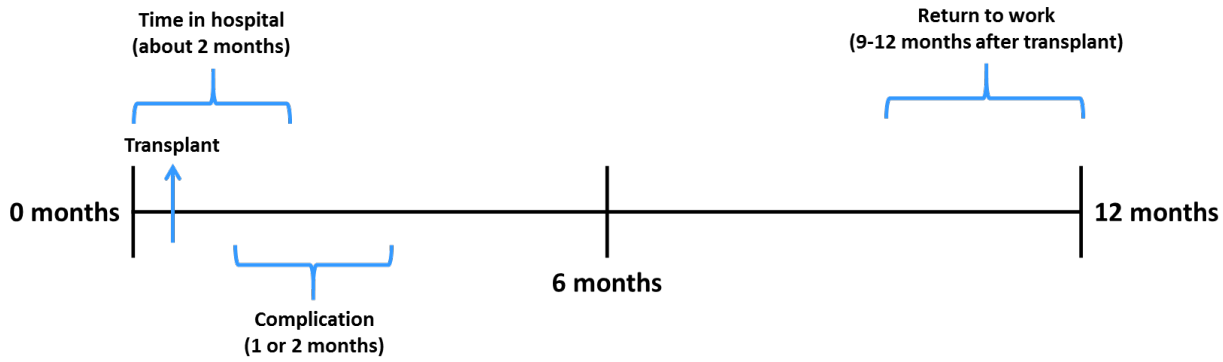
Complication

- About 3 weeks after the transplant, **the transplanted cells begin to attack the cells in your body**. This keeps you **in the hospital for an extra 2 weeks**.
- This causes a skin rash, sickness, weight loss, loss of appetite, severe diarrhoea, and severe abdominal pain.
- You are treated with intravenous steroids for a few days, followed by oral steroids for about 2 months. This condition resolves in a month or two.

After Hospital

- After a few months, your bone marrow produces enough red blood cells so that you **no longer need blood transfusions**.
- You continue to take **medication to suppress your immune system** for about **6 months** after the transplant. During this time, you try to **limit your exposure to other people** to avoid infections while your immune system is suppressed.
- You take **several (up to 10) medications daily** to help prevent infection and support your body during recovery. Some of these medications can make you feel **nauseous**.
- **Many people are re-admitted** to the hospital once or twice during the first 2 or 3 months after transplant because of complications such as infection.
- For about 3 months after leaving the hospital, you **visit the transplant unit once every week or two** for careful monitoring.
- You are able to **return to work or school approximately 9 to 12 months after the transplant**.
- Starting about 6 months after the transplant, you begin repeating all the **vaccinations** you had as a child.

Timeline



Health State C1: Post-Transplant, Transfusion Independent (U)

Disease Status

- **You received a stem cell transplant in the past.**
- Your bone marrow now produces normal red blood cells full of haemoglobin.

- You **do not** have anaemia.

Blood Transfusions

- You no longer need to receive blood transfusions.

Removing Iron

- You **do not** require treatment to remove excess iron from your body.

Symptoms and Impact

- You **do not** have any symptoms of your previous blood condition.
- Your history of the blood disease does not affect your current ability to work or engage in your usual activities.
- You have **annual follow-up visits** with your doctor to monitor the long-term effects of chemotherapy and stem cell transplant.

Health State C2: Post-Transplant, 60% Transfusion Reduction in Terms of Volume (Y)

Disease Status

- **You received a stem cell transplant in the past**.
- Your bone marrow now produces **some** normal red blood cells full of haemoglobin, **but you still have anaemia**.
- Without regular blood transfusions, this disease would be fatal. This condition requires ongoing treatment and hospital visits.

Blood Transfusions

- Treatment includes **blood transfusions**, which give you healthy red blood cells that are full of haemoglobin to correct your anaemia. The blood is from healthy blood donors.
- You receive these transfusions **every 6 to 8 weeks** at a hospital or transfusion unit.
- Approximately 2 days before each transfusion, you go to hospital for a blood test to make sure your blood is matched to the blood that is transfused.
- Blood transfusions are given through a tube inserted into a vein in your arm.
- Each transfusion lasts approximately **4 to 6 hours**.

Removing Iron: Tablets

- The blood transfusions cause a **build-up of iron** in your body. This iron can damage your heart, liver, hormone glands, and other vital organs.
- To reduce the amount of iron in your body, you must **take tablets daily**.
- This medication has **potential side effects** on your liver and kidney functioning, and may cause gastrointestinal upset or constipation. Therefore, your doctor will monitor you via blood tests and urine tests. Your doctor may adjust the dose as necessary. **Most patients can avoid these side effects with careful monitoring**.

Symptoms and Impact

- **In the days before your regular blood transfusions**:
  - You feel **tired and you may feel irritable**.
  - You may have **difficulty concentrating**.
  - You may not be as productive at **work or at school**.
  - Your ability to **exercise** may be limited.
  - You may feel an aching **pain** as if your bones hurt.
- You take **time off work or school** for appointments.
  - You go to the hospital for a **blood transfusion** every 6 to 8 weeks.
  - You go to the hospital for a **blood test** 2 days before each transfusion.
  - You have annual clinic appointments for liver and heart **scans** to check for iron build-up. You have bone density **scans** every 18 months to check for osteoporosis (bone weakening).

Health State C3: Post-Transplant, Chronic GvHD (R)

Disease Status

- **You received a stem cell transplant in the past**.
- Your bone marrow now produces normal red blood cells full of haemoglobin.
- You **do not** have anaemia.

Blood Transfusions

- You no longer need to receive blood transfusions.

Removing Iron

- You **do not** require treatment to remove excess iron from your body.

Symptoms and Impact

- **The transplanted cells attack the cells in your body**. This causes a range of symptoms:
  - You experience a **skin rash** with skin thickening and tightening. The skin rash affects your appearance.
  - You have **chronic diarrhoea**, unintentional weight loss, and abdominal pain.
  - You experience **stiffening of your joints**. This is painful and persistent, and it causes you to limit your physical activity.
  - You have **dry mouth and dry eyes**. This can be uncomfortable.
- You are **prone to infection**, including respiratory and fungal infections.
- Your symptoms interfere with your ability to be productive at work and school.
- You are not very active because you **often feel sick**.
- You take time off work or school for appointments associated with treatment.

Treatment

- You take **oral medication daily to suppress your immune system**. This may include oral steroid medication.

- You also receive intravenous infusions once **every 6 weeks** to help strengthen your immune system.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	United Kingdom Thalassaemia Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The UKTS is the only thalassaemia charity which operates throughout the UK and with all the various communities affected by thalassaemia. **The aims and objectives of the Society are as follows:** 1. Support of individuals and families affected by thalassaemia – individual, confidential advice and support service (public can self-refer), production of educational materials, organisation of national and local family-centered meetings. 2. Support of health care professionals – production of educational materials, organisation of national medical conferences, distribution of information. 3. Policy making and consultation – UKTS is an active consulting member of national bodies such as: the All Party Parliamentary Group for Thalassaemia, the UK Forum on Haemoglobin Disorders, the NHS Sickle Cell & Thalassaemia Screening Programme, the Clinical Reference Group for Haemoglobinopathies, National Haemoglobinopathy Registry, Quality Review Service of Haemoglobinopathy treating centres. 4. Raising awareness and knowledge of thalassaemia in the general public (especially the communities highlighted as the most prevalent) and informing them of the availability of preconception testing for the carrier state. This includes the production of educational materials, presentations to students and community groups, distribution of information at events such as melas, health fairs etc. **Funding** 1. UKTS holds regular fund raising events such as sponsored walks, gala balls, soul nights, marathon runners etc. 2. For specific projects (e.g. medical conferences) we apply to pharma companies for unrestricted

	grants (i.e. the grant is given on condition that the pharma company has no involvement in the project other than the acknowledgement of their support). 3. For other projects we have received support from grant making bodies e.g. RDMCC, Genetic Alliance UK. 4. In recent years UKTS has received some financial support for awareness/public outreach work from the NHS Sickle Cell and Thalassaemia Screening Programme. 5. Membership fees and personal donations from supporters. 6. UKTS owns the freehold of its office premises and the upper part of the building is let. The UKTS has a unique database containing contact details of over 800 families affected by thalassaemia (estimated total number of thalassaemia major patients is 1200) located throughout the UK. We also keep contact databases of doctors and nurses who have a special interest in thalassaemia.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Over the past 12 months, the UKTS facilitated a series of focus groups as part of four patient and carer education awareness days, to gather qualitative data specifically on quality of life data on the views and experiences of patients and their families affected by a form of thalassaemia. The educational awareness days took place throughout England and was attended by over 200 people in total.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Beta thalassaemias (intermediate and major) can be a life-threatening form of anaemia in which patients living with the condition are unable to produce normal adult haemoglobin (Ahmed, Petrou and Saleem, 1996). As a result, people become fully dependent on regular blood transfusions, ranging from every two to four weeks depending on the severity of their case, in order to have a normal chance of life. Additionally, due to excess iron accumulated during regular blood transfusions over time, people with transfusion dependent beta-thalassaemia can also develop multi-organ damage and failure such as heart and liver failure, diabetes, osteoporosis, pancreatic insufficiency, liver carcinoma, hypotrophic gonadism

	amongst others. Long term treatment with iron chelation medication can also result in growth delay, ophthalmic and audiologic issues, in addition to nephrology toxicity if not managed well. The comments below summarises the discussion that took place with patients and their loved ones. Patients spoke about how difficult life was with thalassaemia. While they spoke about the importance of maintaining a positive attitude, most people with thalassaemia felt that keeping up with their vigorous treatment plans were extremely difficult and time consuming. Some patients described their treatment as "never ending" and even expressed the wish to know what it would be like to not need transfusions or take medication every day. Everyone commented on the difficulty of keeping up or administering iron chelation medication. Patients and carers who administered the subcutaneous pumps everyday spoke of the difficulty with keeping up with the treatment plan. They added that they would quickly run out of injection sites due to the fact that the medication caused large painful lumps and had to be administered everyday over an 8-12 hour rate. Both groups spoke about the side effects of oral iron chelators and the impact they had on their stomachs, immune system and overall health. Patients also commented on the additional time it took out of their family/educational/ working life to cater to the demands of their condition. With regards to having blood transfusions, all patients spoke about the extreme fatigue, exhaustion, breathlessness, palpitations, bone pain (due to the bone marrow going into overdrive), cognitive disturbances, low mood, anxiety and insomnia they felt when they were due for a transfusion. They all described the pain as "a throbbing, sharp like pain which constantly strikes deep within your bones" and also commented on experiencing headaches varying in severity and the difficulty in trying to cope with everyday tasks due a lack energy and concentration. Some patients felt that as they got older, they required more time to recover from their blood transfusions. They recalled feeling great after a blood transfusion when they were younger but noticed as they grew older, they began to experience bone pain and extreme exhaustion which could take up to four days to resolve. Additionally, patients spoke of the extra care they needed for coping with secondary conditions and felt that they needed to dedicate more time to meet their additional treatment needs.

	All patients and carers felt a sense of guilt for requiring time to be taken off education and work in order to meet to their/ their children's daily treatment demands. They added that they did not just need time off for blood transfusions, but they also needed time off for MRIs and other diagnostic scans and consultations with their expanding team of specialists including haematologists, endocrinologists, cardiologists, nephrologists, orthopaedic surgeons etc. Both patients and their carers felt that thalassaemia was a progressive condition and felt that there was not enough research in treating bone pain in thalassaemia. Patients felt this was being overlooked and dismissed. In addition, some patients and carers felt that there was little knowledge and experience on treating patients in their late fifties and above. These mature patients identified themselves as feeling anxious about their future. Parents disclosed experiencing an overwhelming sense of guilt when it came to having children with thalassaemia. They all expressed concerns about the type of care their children would receive in the future. Some parents and carers disclosed the feelings of sadness their experienced when their children were not eligible for bone marrow transplants due to not having a HLA match and expressed their desire to see their children 'cured' one day. Parents spoke about how difficult it was to see their children unwell and in pain and also expressed their heartbreak of having to administer painful subcutaneous infusions on their children and also having to look on as doctors and nurses cannulated their children. Parents and carers described this as a "painful experience". Both patients and carers discussed the lack of psychological care and support offered to those affected by thalassaemia. Some patients commented on the lack of self-esteem and body confidence they experienced due to delayed puberty and the way in which it affected their future relationships. Some patients and their carers spoke about the stigma that is still affecting certain communities. These families felt they were unable to inform anyone outside of their immediate family in fear that they (patient) or their children (parent) would be victimised or wrongly judged.

	Both patients and carers felt the unpredictable nature of thalassaemia means there is an inability to predict and plan for the future.
T	
7. What do patients or carers think of current treatments and care available on the NHS?	All patients and their families were appreciative of the care they received from the NHS. However, they wished more would be done to improve their quality of life. Some patients and families spoke about the need to take annual leave to attend their blood transfusions and other appointments because hospitals did not offer any out of hours service. Patients also spoke of being turned down for bone marrow transplants due to age or not having a matched relative and wished the NHS would do more to look into other treatments that could improve their health.
8. Is there an unmet need for patients with this condition?	Yes. Presently in England only paediatric beta thalassaemia major patients under the age of nine are usually considered for a bone marrow transplant depending on their HLA matched donor status. At the moment, only ten percent of cases are classed as suitable to have a bone marrow transplant. Unfortunately, there is no other 'curative' option offered to the other ninety percent of patients who live with the condition or with another form of transfusion-dependent beta thalassaemia.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients and Carers thought the advantages of this technology were: 1) Not needing a donor 2) Correcting the patient's own gene 3) Less risk of developing Graft Versus Host Disease and other reactions 4) Available to adults with thalassaemia

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Parents and carers expressed their concern for undergoing chemotherapy as part of the treatment for "Zynteglo". The group talk about the impact chemotherapy could have on their/ their children's fertility and the risk of developing cancer secondary to chemotherapy in the future. Additionally, both groups disclosed concerns over the accuracy of the gene editing/ correcting procedure and the contingency plan to ensure the right genetic material is transported to where it is desired. Furthermore, patients and carers also expressed concern with regards to the use of viral vectors and the possibility of being infected in anyway by the virus. Lastly, all patients and carers spoke of the possibility in which this new technology may not work or improve their children's prognosis at all.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who do not meet the current criteria for bone marrow transplants due to not having a suitable match or age (i.e. 90% of patients) could benefit from this new technology. Additionally, patients who experience frequent blood transfusion reactions due to the development of antibodies and other agents may also benefit from this.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No
Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • This new technology may benefit patients lives and change the future of thalassaemia • The new technology may not be suitable for all transfusion dependent beta thalassaemia patients • If successful, this new technology may decrease the demand for blood donation on the NHS • If successful, this new technology may decrease cost to the NHS in the long term (in treating secondary conditions and appointments)	

- This new technology may increase the quality of life of people living with thalassaemia

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Professional organisation submission

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**RCPath and BSH**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Current therapies are supportive- blood transfusions, medications to remove excess iron and for a small number bone marrow transplant. The proposed therapy is potentially curative
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Transfusion independence

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, the only curative option (bone marrow transplantation) is only available to a minority of patients
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Blood transfusion, iron chelation treatment
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	National guidelines http://ukts.org/standards/Standards-2016final.pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Patients are reviewed by network centres so care should be co-ordinated. However there are still variations in care.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Potentially lifesaving option would eliminate the need for standard therapy
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Novel therapy not currently available as part of current care
• How does healthcare resource use differ between the technology and current care?	Initially there will be increased use of health care resources at the time of the intervention. However if the procedure works this will reduce.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Under the direction of specialist clinics only
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training of medical personnel

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes as it is potentially curative
• Do you expect the technology to increase length of life more than current care?	No impact of length of lifeq
• Do you expect the technology to increase health-related quality of life more than current care?	Improvement in QOL
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As per the genotype of the patient population
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology which is complex should be limited to 2-3 centres. Patients who are considered eligible should be discussed in national MDTs proposed as part of the Haemoglobinopathy commissioning framework
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Additional testing will be required to determine genotyping
15. Do you consider that the use of the technology will result in any substantial health-	no

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Innovative therapy reducing the need for allogeneic stem cell donors and potentially curative
• Is the technology a 'step-change' in the management of the condition?	New therapy with new mechanism of action not previously used
• Does the use of the technology address any particular unmet need of the patient population?	Yes as described above

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Most side effects are short term. Longer term concerns re fertility
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Transfusion independence which is the most important clinical outcome
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. How do data on real-world experience compare with the trial data?	Therapy currently only available as part of a trial
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- innovative
- potentially curative
- manageable side effect profile
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England & NHS Improvement**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NHS England and NHS Improvement** NHS England and NHS Improvement leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are published clinical guidelines – the National Thalassemia Guidelines, 2016, 3rd edition http://ukts.org/standards/Standards-2016final.pdf. Under the current commissioning arrangements, adults (over 19 years of age) in the UK do not have access to stem cell transplant as an alternative treatment option.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is defined and has been further clarified following the national service review of haemoglobinopathy services which concluded in 2019. Implementation of the model of care to deliver this pathway is underway and will be fully operational by 2020. There is good consensus on the pathways between professionals across the NHS.
8. What impact would the technology have on the current pathway of care?	NHSE&I understand that this technology may stop or significantly reduce lifelong transfusions for patients, which may in turn reduce the level of co-morbidities experienced by patients due to iron overload from the transfusions. This could significantly reduce patient need for transfusion and follow up, although the extent to which this would be reduced is yet unknown. A reduction in transfusions could also reduce the use of iron chelation (treatment used to manage the side effects of iron build caused by transfusions), which are high cost drugs. The technology is expected to require new pathways for the preparation of patients, the transfer of the medicine from the manufacturer, clinical delivery of the medicine and long-term monitoring of the patient. This would have a significant impact on specific services that would be part of the pathway for the delivery of this technology. As this is a new technology and it is not a full cure for the disease it is unknown what the level of uptake would be and therefore the scale of impact on the overall pathway and service.

The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Currently, this product is available through research trials only. If the technology receives a positive recommendation from NICE, it will be used in accordance with its MA in those patients who are eligible for treatment and who want to undertake the treatment. However, the infrastructure to support the implementation of this technology will need to be in place before access can be allowed, which may require a variation to the funding requirement and may require additional time to fully implement so the capacity and capability is available to support delivery of this technology. Consideration will also need to be given to the concentration of expertise to enable safe access to this technology. Work is underway with clinicians, providers, commissioners and the company to prepare for a possible positive recommendation from NICE.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This technology uses techniques that are already utilised in some specific centres but could require an expansion of these services both in terms of capacity and capability across more centres. In this population apheresis is not regularly used to gather and infuse stem cells, but this is a technique used to gather and infuse stem cells for other indications. Cell management (which includes the processing of stem cells in and out of the country including transport, quality management and tracking) is an additional requirement that would require capacity to be developed, and an increase in capability to comply with the specific requirements for this technology. The technology also requires a storage of back up copies of stem cells, which is not routine practice for stem cell transplants for this population, so additional capacity would need to be developed to accommodate this requirement.
• How does healthcare resource use differ between the technology and current care?	For patients who may be eligible for this technology, current healthcare resource focuses on managing the condition through regular transfusions and management of the complications associated with these. This technology would move patients to a new treatment pathway that would involve resources that currently have restricted use within NHS care, and are not for this indication. This includes additional high cost drugs that are not currently commissioned for non-malignant indications to mobilise cells and the

	increased demand on stem cell collection, cell storage and cell management (including transportation, tracking and quality management).
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology would only be available in those specialised centres that have co-located haemoglobinopathy and allogenic stem cell transfer services to ensure the right expertise is available to manage any complications associated with the use of this technology. Centres would be identified from those currently commissioned by NHS England to provide these services, using an appropriate provider selection approach based on understanding and developing the market over time to match demand and capacity.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment would be required to train staff to deliver this technology and support patients in receiving this technology. Staff on site will need to be trained on the handling and provision of the product and we understand this should be provided by the company as part of regulatory requirements. This will need to include training for laboratory and pharmacy staff who will be handling and storing the final product, including QA processing before administration to the patient, in accordance with the regulation of medicines. There would be an increased pressure on apheresis, cell storage and cell management services that would be required to deliver this technology. Once the likely uptake of this technology is understood then a capacity / infrastructure analysis can be undertaken to determine the scale of any additional investment required to deliver this specific technology. It should be noted that the infrastructure requirements for this technology is the same as for a number of other ATMPs and therefore there may be a cumulative effect that will require investment in future.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	The rules around starting treatment with this technology are defined in the licencing and by the commissioned pathway, so it is restricted to patients with beta thalassemia with a specific genotype where the patient does not have a sibling match for a stem cell transplant (or the patient is over the age where this is commissioned). As this is a one-off treatment there are no stopping criteria. All patients being considered for treatment with this technology will need to be referred to the National Haemoglobinopathy MDT Panel that has been commissioned on an ongoing basis as part of the national

	service review to oversee and advise on all complex cases and the use of new technologies for haemoglobinopathy patients. The testing required to diagnose the specific genotype of a patient's thalassemia is part of the pathway of care for all patients, which is being reinforced through the designation of specialist centres following the national service review for haemoglobinopathy services. This is coming into place across the country and is already routinely undertaken as part of the initial diagnosis process in many specialist clinics, so there will not be additional genetic testing required for the incident population. However, there will be a requirement for genetic testing of the prevalent population who have not previously been tested to enable access to this technology.
11. What is the outcome of any evaluations or audits of the use of the technology?	No audits have been undertaken by the NHS on the use of this technology, but we believe the company have undertaken some that they will be submitting to NICE.
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	We understand the new treatment will not be available to children under the age of 12. Children meeting commissioning criteria do currently have access to the alternative treatment of allogeneic HSCT. Allogenic HSCT is not currently commissioned for adult patients, based on published data which indicates difference in the balance of risk and benefit between adults and children in relation to allogeneic HSCT. This condition affects more people from specific ethnic groups and only those with the specific genotype would qualify for treatment, so this could disadvantage those from ethnic groups who are not eligible for this treatment through not having the relevant genotype. Other groups with protected characteristics may have been excluded from clinical trials based on the agreed protocol and this may result in exclusions at licensing due to lack of data. The National Haemoglobinopathies Panel would oversee all referrals to identify any inequalities seen in the patients referred for or accepted into treatment with this technology.

	The use of this technology (either specifically the technology or the myeoablative conditioning used as part of the preparation for this technology) is contra-indicated in certain co-morbidities, including those considered a long term condition and therefore would have an additional element of restricting access to this treatment for these patients. The new treatment requires the use of chemotherapy drugs which could affect fertility, this consideration may impact decisions about uptake by groups with protected characteristics.
12b. Consider whether these issues are different from issues with current care and why.	The above issues are different from the current care as the current care pathways are not genotype specific and therefore applicable to all patients with the condition. As noted above, this condition adversely impacts people from certain ethnic groups. This technology would be available to a wider age range of patients (from 12 years of age upwards, as opposed to the 19 years and under the current commissioned policy for stem cell transplantation), which would help address an inequality in the current pathway for patients over the age of 19 years.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Clinical expert statement

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Kate Ryan**
2. Name of organisation	**Manchester University Hospitals Trust**
3. Job title or position	**Consultant Haematologist**

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Beta thalassaemia is a lifelong genetic disorder causing ineffective red cell production, chronic haemolysis, and profound anaemia with a requirement for blood transfusions. Severe anaemia causes fatigue and leads to poor growth and development, organ enlargement and skeletal abnormalities. Although beta thalassemia may vary in severity, the most severe forms require regular blood transfusions from infancy. This is known as Transfusion Dependent Thalassaemia (TDT). Repeated blood transfusion leads to accumulation of iron which is toxic to organs, particularly the liver, heart and endocrine glands; it requires

	removal by iron chelation drugs. Thalassaemia and its treatment, including iron chelation, carries significant physical and psychological morbidity and leads to a reduced life expectancy. Zynteglo is a therapy which aims to improve the production of haemoglobin in red cells to a level that will improve the clinical complications of chronic anaemia and thereby avoid or significantly reduce, the need for blood transfusions and iron chelation. This will lead to a reduction of morbidity and mortality.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Correction of anaemia to a level which prevents symptoms and complications and is associated with transfusion independence.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. While improvements in red blood cell transfusion and chelation practices have improved their prognosis, patients with transfusion-dependent β-thalassemia continue to suffer organ damage due to iron overload and other complications of their disease. Allogeneic hematopoietic stem cell transplantation (HSCT), while curative, confers significant risks of morbidity and mortality and is limited by donor availability for patients 12-18years. It is not currently offered to patients >18years in the UK.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	TDT patients are treated with regular blood transfusions together with iron chelating drugs which have to be taken daily. They have regular monitoring for assessment of iron burden and toxicity from chelation agents; end organ damage requires management in specialist clinics. A recent UK chart review of 165 adult and paediatric TDT patients showed that they had a median of [redacted] transfusion episodes/patient/year (Abstract accepted ASH 2019) receiving a mean of [redacted] units of blood per year. All patients were taking iron chelation drugs with 20% needing to take more than 1 drug. Clinically significant cardiac and liver iron overload, outside safe targets, was seen in 20% and 30% patients respectively.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	UK Thalassaemia Society Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK (3rd Edition, 2016) details all aspects of care including transfusion policy, assessment and treatment of iron overload and management of complications. NHS England (2016) Clinical Commissioning Policy: Treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias . Reference: NHS England: 16070/P. August 2016
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes. Infants with beta thalassaemia major are identified through the national Newborn Bloodspot Screening Programme and should enter clinical follow up by a specialist paediatric haemoglobinopathy team within 90 days. The decision to commence regular transfusions is determined on clinical grounds, namely anaemia, failure to grow and develop appropriately and/or significant organ enlargement. Once started on transfusion, treatment is lifelong. Transfusions are given every 3-6 weeks to maintain a target haemoglobin. They are administered on day units or wards in a process that takes several hours, usually needing a whole day. While some patients are able to get transfusions at nights/weekends, many are only possible in routine working hours. Blood tests are needed before each transfusion to ensure suitable blood is obtained; this often requires a separate visit from the transfusion episode. Patients are regularly seen for follow up in haematology and other specialist clinics such as endocrine, cardiology, diabetes and liver. Investigations are undertaken to measure iron levels, detect the development or progression of end organ damage and to monitor for chelator toxicity. Specialist investigations include regular cardiac and liver MRI imaging for quantification of iron. Thalassaemia care is commissioned as a Specialist Service by NHS England. Care is delivered via a clinical network. Transfusions and routine monitoring are undertaken as close to the patients home as possible, either at a local haemoglobinopathy or specialist haemoglobinopathy centre (SHC) but care is overseen by a designated SHC who is responsible for oversight of iron chelation therapy, specialist investigations and undertaking annual review. A National Haemoglobinopathy Panel has recently been set up to provide an MDT for management of complex clinical cases and consideration of patient suitability for new treatments as well as ensuring consistency between different parts of the country.

	Clinicians caring for thalassaemia patients meet regularly for educational and governance meetings and there is widespread support for clinical standards and assessment through peer review. Almost all patients are entered into the National Haemoglobinopathy Registry (NHR) which provides demographic and treatment data for England as well as clinical data from annual review.
• What impact would the technology have on the current pathway of care?	The treatment would avoid the need for transfusion and iron chelation treatment thereby avoiding repeated episodes of day care and clinic visits. Ongoing outpatient follow up would still need to be maintained for monitoring for ongoing efficacy of the treatment and any late effects.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	This is a new treatment and completely different to current treatment. It will require clinical and psychological assessment of patient suitability and collection of autologous cells with storage of these cells as a back-up. The treatment itself requires a period of inpatient admission with conditioning treatment pre infusion of the product and supportive care until engraftment has taken place and the patient has recovered their blood counts. The care requirements may be considered similar to that of autologous HSCT for malignant haematology indications.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Treatment will be carried out in designated centres which have both the national accreditation and regulatory requirements for stem cell collection, gene therapy and SCT, and have thalassaemia expertise. In practice, it may be that centres achieving accreditation for CAR-T cell therapy are a good proxy, as the requirements will be similar. They must have a Thalassaemia Specialist Team on site. The number of centres needed would be determined by NHSE commissioners.
• What investment is needed to introduce the technology? (For	It is likely that this treatment would be given in centres which already meet the regulatory requirements for HSCT and genetic therapies (see above).

example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes. Although current transfusion and chelation management has improved over the years, there are still a significant proportion of patients who find it difficult to adhere to the lifetime requirement for iron chelation and multiple hospital visits. These patients have a reduced life expectancy compared to a matched non-thalassaemia population.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Thalassaemia carries a lifetime burden for patients in terms of clinical symptoms and the requirement for multiple hospital visits necessitating time off work, education and family life. This impacts not only on the patient but other family members. A recent UK chart review of 165 adult and paediatric TDT showed that a health-related utility score (EQ-5D) for adults was [redacted] compared with population norms of 0.93 (ASH 2019 Abstract accepted). Work Productivity and Activity Impairment results suggested that activity impairment, at 50%), was comparable to or higher than reported in other chronic conditions, such as rheumatoid arthritis (33%) and chronic pain (38%) (ASH 2019 Abstract accepted) .
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	At present the treatment is proposed only for non β^0/β^0 genotypes which account for about 50% TDT patients in the UK. The risks associated with the conditioning treatment would be increased in patients with significant end organ damage (e.g. cardiac and liver dysfunction) and these would impact on the eligibility for this treatment. Each patient would undergo clinical assessment to ensure a favourable benefit: risk ratio and be discussed in the National MDT.
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This is a completely different approach to treatment from current care. It will be undertaken in designated units meeting the clinical commissioning criteria (see above). Patients will be jointly managed by Specialist HSCT and Thalassaemia teams. The treatment will require a period of intensive inpatient based treatment and increased hospital visits in the pre-treatment and immediate post treatment phase which will likely need a period of time off work or education and increased family support. These may deter some patients, for instance those who are undertaking higher education. The proposed conditioning regimen with busulphan is likely to cause infertility. Many patients with thalassaemia already have impaired fertility due to endocrine dysfunction and need assisted conception. Concerns about fertility may also deter patients (or they may defer until they have completed their family) and will require individual assessment and counselling. For some patients, egg or sperm storage may be considered. Patients will be given full information regarding the risks and requirements of the treatment to ensure informed consent. Once treated, patient will still need clinical follow up for assessing its effectiveness and any residual iron overload will continue to need iron chelation until it reaches safe levels. Such clinic visits will, however, be less frequent and less time consuming than current hospital attendances.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patient eligibility will be specified in the commissioning criteria which will be decided by the Haemoglobinopathy and Stem Cell Transplant Clinical Reference groups. Patients fulfilling the eligibility criteria will be identified by the Specialist Haemoglobinopathy Team and discussed at the National MDT to ensure clinical appropriateness and equity of access across England. Representatives of Stem Cell Transplant (SCT) and haemoglobinopathy will be on this panel.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are	

unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Zynteglo offers the potential to free patients from chronic blood transfusions which will transform their quality of life over their whole lifetime. They will not be at risk of further iron overload with organ damage and this will prolong survival.
• Is the technology a 'step-change' in the management of the condition?	Yes. Zynteglo is a highly innovative life -changing treatment which, by allowing the production of functional haemoglobin will reverse the underlying pathophysiology of beta thalassaemia, treating anaemia and its complications and avoiding the need for chronic blood transfusions with consequent iron overload. By using the patient's own haemopoietic stem cells it avoids the immunological risks associated with conventional transplant from a matched donor. This represents a step change in the current treatment paradigm.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. It will free then from lifelong blood transfusion and iron chelation treatment.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Treatment associated adverse events are those typically seen with autologous stem cell transplant and relate to the use of myeloablative drugs for conditioning. These risks include liver veno-occlusive disease (VOD), neutropenia and thrombocytopenia and are limited to the period of treatment. Longer term side effects include infertility. There are no adverse events related to Zynteglo to date. The long-term effects of Zynteglo are unknown.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	This is a novel treatment unlike standard management . Then UK experience is limited to one participating centre in the clinical trials
• If not, how could the results be extrapolated to the UK setting?	If successful Zynteglo would be offered to all patients within its market authorisation and who meet the clinical commission criteria.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are: • Safety: This was assessed and is planned to continue for a period of 15years post infusion of the product. To date there has been no transplant related mortality and no adverse events attributed to Zynteglo. There is no evidence of clonal dominance related to vector integration. • Improvement in Hb levels and transfusion independence: In the Northstar HGB-204 study 8/10 patients with non β^0/β^0 genotypes were transfusion independent at a median follow up of 40.7months (EHA 2019 Abstract S141) In the Phase 3 HGB207 Study, 13/14 non β^0/β^0 patients with ≥ 3 months follow-up were transfusion free and 4/5 evaluable patients achieved the primary endpoint of transfusion independence for >12 months (EHA 2019 Abstract S1362) • Sustainability of the gene product (HbA T87Q): HbA stabilizes approximately 6 months after LentiGlobin infusion T87Q and it appears that these responses are durable. • Health related Quality of Life:
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Iron related clinical complications are the major cause of reduced life expectancy in this group of patients and reduction to safe levels is extremely important. In the HGB-204 study there was a 56% reduction in liver iron from baseline to month 48 and cardiac iron remained stable. Patients were restarted on iron chelation to reduce iron levels. Follow up data will establish how many patients are able to stop chelation completely once target iron levels are achieved.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware of any. Regular follow up monitoring is ongoing.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	This is new treatment and not given, to my knowledge, outside of clinical trials.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Thalassaemia is found in individuals whose origins are from Mediterranean, Middle east, South Asia and S E Asia. In the UK, transfusion-dependent beta-thalassaemia is mostly seen in ethnic minority populations, the largest groups being Pakistani, Indian and Bangladeshi.
22b. Consider whether these issues are different from issues with current care and why.	No. All patients meeting clinical criteria would be considered for gene therapy.
Topic-specific questions	
23. Are deferasirox, deferiprone, desferrioxamine and the combinations deferiprone/desferrioxamine,	Yes. All regularly transfused patients currently receive one or more iron chelation agents. NHSE clinical commissioning policy makes all of these treatments available as treatment options for patients with thalassaemia who have iron overload (caused by transfusions) as set out in the commissioning criteria.

deferiprone/deferasirox and deferasirox/desferrioxamine considered to be established clinical practice for chelating in the NHS for treating transfusion-dependent beta-thalassaemia?	
24. How often do people with transfusion-dependent beta-thalassaemia receive blood transfusions?	Every 2-6 weeks most typically every 4 weeks. A recent chart review shows that 82% patients had more than 12 transfusions/year (mean 13.7).

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Transfusion Dependent Thalassaemia requires lifelong treatment with regular blood transfusion and a need to take iron chelation. Even with improvements in standard therapy, there remains substantial morbidity and a reduced life expectancy.
- Health QoL measures show significant impairment and impact on working life in children, adults and their carers.
- Zynteglo offers a curative option for adults >18y and children 12-18y with non for whom stem cell transplant is not possible.
- To date almost all patients with the subtype of non β^0/β^0 thalassaemia treated with Zynteglo have shown improvement of Hb levels to enable transfusion independence and these effects appear to be sustained for the current period of follow up.
- Zynteglo has a good safety profile with no adverse events attributable to the treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Clinical expert statement

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Emma Drasar**
2. Name of organisation	**Whittington Health and UCLH**

3. Job title or position	**Consultant Haematologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment is to make transfusion dependant thalassaemia patients transfusion independent. Although this treatment only corrects the gene in the bone marrow this has the potential to correct the main abnormality in thalassaemia namely ineffective erythropoiesis caused by an imbalance in globin chains. It will improve anaemia and prevent the sequaelae of transfusion, most of which are related to iron overload but also include the risk of receiving infected blood products. The aim is that it will therefore reduce the need for chelation treatment and other medications used to treat the impact of iron loading on the various organs in the body
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Patients need to become truly transfusion independent. I would also like to see a significant reduction in ineffective erythropoiesis – an Hb of 80 while potentially NTDT would fundamentally be an “intermedia” phenotype. This condition has it’s own complex pathology which can develop over time.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – speaking to my patients options are limited to transfusion life-long or transplant at a young age (usually under 9 years of age). This adds to the treatment options and also removes the need for a matched sibling or unrelated donor to be found. It also removes the risk of GVHD which is highly attractive in treatment of non malignant conditions.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Life-long transfusion every 3-4 weeks with another visit (usually) for cross match, chelation to remove iron, hormone treatment, bone protection, other supportive medications to treat complications e.g. previous iron in the heart may require treatment for arrhythmias
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	UKTS standards of care of thalassaemia BSH chelation guidelines (most recent version in process) Local guidelines shared nationally
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes the pathway is well defined. Some areas use different approaches but a more standardised national approach is being developed as the result of recent NHSE changes and the formation of the haemoglobinopathy coordinating centres and the national haemoglobinopathy panel
• What impact would the technology have on the current pathway of care?	This would enable patients to become transfusion independent and “cured” from their need for regular transfusions and down stream treatments
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This depends – there are risks to the treatment and some patients may not wish to participate in it. There are also contraindications to treatment e.g. significant cardiac or iron loading

• How does healthcare resource use differ between the technology and current care?	This would be an intensive “up front” cost – fundamentally the resource is directed at developing the infusion product and the initial transplant and management of post transplant complications, probably with late effects monitoring. In contrast current treatment is a regular but smaller resource burden on the healthcare system, however it has the potential to increase throughout the patients life as complications develop
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics and discussion at the National Haemoglobinopathy Panel
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Existing transplant facilities would be used – I assume that the product production facilities may need to be upscaled
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	This is difficult to judge as our oldest patients are pre chelation era and have accrued a large burden of morbidity due to this. However I would expect, due to human nature, that this would have a positive impact on length of life.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes – this would be highly likely. The removal of the burden of 3-4 weekly hospital attendances and the constant use of medication I would have thought will be significant on QOL
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those patients who do not have a sibling donor or the adult patient population. Consideration could be given to those patients who are difficult to transfuse due to reactions/complications from blood transfusion.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	The treatment is a stem cell transplant (myeloablative), albeit an autologous one. The technology would have to be delivered in a specialist setting with transplant and red cell teams working together. There would be all the usual con meds required during transplantation. There is an impact on fertility and fertility preservation will be an additional factor

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	National Haemoglobinopathy panel will review requests for this therapy I believe. I assume the criteria used for entry into the trial will continue but the majority of these investigations are part of routine monitoring of the patients.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I think relief from the burden of transfusion will be incalculable to some patients
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes entirely new approach
• Does the use of the technology address any particular unmet need of the patient population?	Yes – the potential for cure
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As per above the risk of death, complications from chemotherapy and infertility are all things that the patients need to consider when making their decision to access this treatment
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK	Yes

clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The potential for transfusion independence and end Hb and lack of ineffective erythropoiesis Yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes – reduction in chelation usage
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not to my knowledge

21. How do data on real-world experience compare with the trial data?	N/A
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No – just need to have a red cell team and transplant team. If patients and clinicans both educated about this as an option there should be no issues
22b. Consider whether these issues are different from issues with current care and why.	Similar – important that the clinicians caring for the patient have a good understanding of thalassaemia and its complications and issues
Topic-specific questions	
23. Are deferasirox, deferiprone, desferrioxamine and the combinations deferiprone/desferrioxamine, deferiprone/deferasirox and deferasirox/desferrioxamine	Yes

considered to be established clinical practice for chelating in the NHS for treating transfusion-dependent beta-thalassaemia?	
24. How often do people with transfusion-dependent beta-thalassaemia receive blood transfusions?	Every 2-4 weeks. 3 weekly is probably the most common in my cohort.

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- This is a potentially “curative” treatment for thalassaemia
- This treatment will not be appropriate for, or desired by, all patients with thalassaemia
- This will reduce blood demand for this patient population
- It has the potential to reduce associated costs associated with long term complications and treatment of thalssaemia
- There may be a significant positive impact on patients quality of life

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Patient expert statement

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Roanna Maharaj**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	UK Thalassaemia Society
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Thalassaemia is a challenging condition to live with. Whilst there is some stability and consistency when it comes to treatment options, it has a huge impact on everyday life. Having to attend hospital for regular blood transfusions, is not always a pleasant experience for everyone living with thalassaemia. When an individual has an infection or becomes anaemic, it can result in an exacerbation of their symptoms. Often, this necessitates the care and support of a carer or member of their family/ to help them complete the basic everyday tasks. Some people may also experience difficulties with aspects of personal care and moving around may be which may be worse during days /weeks before transfusion. Patients can suffer from extreme fatigue, exhaustion, breathlessness, palpitations, bone pain (mostly due to the bone marrow going into overdrive), headaches, lack of concentration, cognition disturbances, low mood, anxiety, depression and insomnia.

	Additionally, there is a huge issue with cannulation and as years progress, the scarring of peripheral veins worsens which results in multiple attempts by the most experience health care professionals. This can be very distressing for patients as it is not only painful but can result in temporary nerve damage which can affect patient's use of their hands for up to three months. This is extremely painful and can really impact on a person's ability to complete everyday activities. Over the years I have heard and observed patients becoming needle phobic because of the trauma they have endured over the years. When peripheral cannulation is no longer an option, patients are offered central lines/ catheters which help to alleviate some of the cannulation issues but comes with its own challenges in maintaining an infection free line. This is not always possible and can easily result sepsis which can be life threatening. Having central lines in situ can impact on patients' ability to partake in exercise, sports etc. Some people with thalassaemia also experience transfusion reactions with each transfusion. This can be life- threatening and also very unpleasant and disheartening for patients as the therapy they need to sustain their lives causes them harm. Transfusion reactions range from fever, rigors, urticaria, oedema, severe debilitating bone pain, haemolytic reactions, anaphylactic reactions and transfusion related graft version host disease. Due to the severity of the reactions, some people with thalassaemia, transfusion burden also increases which not only affects their quality of life but also affects their iron burden. If this is not addressed adequately, it can result in severe iron overload in organs. Iron Chelation- People with transfusion dependent thalassaemia are prescribed iron chelating agents to remove excess iron received from blood transfusions. Whilst treatment options have improved greatly over the year, adherence to medication is still a major issue affecting people with thalassaemia. In the UK, there are three chelating agents available which is prescribed according to patient needs. For those on subcutaneous therapy which is infused over 12-24 hours up to seven days a week, patients are required to self- administer the injection. This is painful and after repeated needle punctures, the injection sites become painful, inflamed and left with painful bumps and scarred tissue. Over time it becomes difficult to find viable injection sites. This can severely impact on a person's quality of life and their ability to comply with their treatment. With regards to the oral iron chelators, whilst this has been described by patients as being "life changing", adherence is also an issue as patients are required to take medication several times a day which is not always convenient for them. As with any medication, oral chelators cause a variety of side effects which

hinders people's ability to comply with treatment. Often if the side effects are severe and they can result in organ damage, patients are then required to go back on subcutaneous therapy rather than have the combination which is offered to most patients.

People with thalassaemia are also advised to attend regular hospital appointments outside their transfusion routine for monitoring for iron overload, side effects and other routine tests. These are in the form of Cardiac MRIs, ECHOS, liver MRIs, DEXA scans, CT and XRAY scans, audiology, ophthalmology etc. it should be noted that having to manage everyday treatment, transfusion therapy and routine monitoring is like a full-time job.

People with thalassaemia also develop a myriad of secondary conditions due to the nature of the condition and implications of iron overload. Some of the secondary conditions are:

Liver and Gall Bladder Diseases

a. Hepatitis or hepatic dysfunction
b. Hepatitis B and/or Hepatitis C
c. Gall bladder disease
d. Liver Fibrosis
e. Liver Failure
f. Hepatocellular Carcinoma

1) Endocrine and Metabolic Dysfunction

a. Diabetes mellitus
b. Low bone mass (osteoporosis)
c. Growth hormone deficiency
d. Hypogonadism
e. Hypothyroidism
f. Hypoparathyroidism
g. Adrenal insufficiency

	2) Cardiac Dysfunction a. Tachycardia b. Atrial Fibrillation c. Pulmonary Hypertension d. Cardiac Failure **3) Pulmonary Care** **4) Thrombosis/ Thrombotic Events** **5) Spleen** a. Enlargement b. Splenectomised c. **6) Pain Syndrome- Mostly Join and bone pain** **7) Dental Issues** **8) Chelator Side Effects and Toxicity** a. Audiology disturbances b. Ophthalmology c. Nephrology d. Neutropenia e. Growth Retardation f. Local and allergic reactions g. Over-chelation - toxicity **9) Rheumatology** a. Rheumatoid arthritis b. Auto immune conditions- Raynaud's syndrome

10) Psychological

a. Anxiety
b. Depression
c. Lack of Self Esteem/ Self confidence
d. Guilt
e. Post Traumatic Disorder

Having to cope with the daily implications of thalassaemia in addition to having one or more conditions identified above can seriously impact a patient's quality of life. The majority of patients with thalassaemia have secondary conditions.

Due to the iron over-load in the pancreas, some patients often suffer from diabetes mellitus and may struggle to consume the right diet. Increasingly, the prevalence of pancreatic insufficiency is on the amongst the older patients, which can cause severe weight loss and malnutrition as they are unable to absorb nutrients. This in turn can exacerbate symptoms of their secondary conditions and decrease their overall health and quality of life.

Patients with thalassaemia are also prone to developing bone disease (osteopenia/ osteoporosis syndrome) due to bone marrow expansion and as a result, are more susceptible to falling and fracturing bones. This is not visible; however, it can result in patients becoming frail and anxious about managing around their daily lives. Many patients may also require bone replacement surgery over their lifetimes and have difficulty with their mobility.

Iron overload can also cause hormonal and fertility issues. Most men with thalassaemia have low testosterone levels and thus requires treatment with testosterone injections every three months. Low testosterone can cause a myriad of problems such as decrease muscle mass/ strength, decreased body hair, swelling/tenderness of the breast tissue, increased fatigue, hot flashes, sleep disturbances, impotency and fathering children. Not only does this cause physical complications it can also result in psychological

	issues such as memory/ concentration loss, depression, lack of self-esteem, body issues and even put pressure on relationships. Patients can be very embarrassed to talk about these issues. In women, menstrual cycles are disrupted and irregular, affecting fertility. Patients may find this hard to express / openly discuss and may not have come to terms with what this means for their future life choices. Individuals with thalassaemia are often underweight and can be short in stature. As puberty is often delayed, people with thalassaemia can look very young in appearance. Consequently, they are often treated or spoken to like children which can often cause them some distress in wanting to disclose their need to rely on others when they are unwell. They can often feel very embarrassed about talking about how reliant they are on others and have often spoken about the guilt they feel on not being able to care of provide for themselves. Those who live alone may find it difficult to disclose that they would benefit from extra support. The nature of thalassaemia means there is an inability to predict and plan future. People with thalassaemia cannot go on holidays for an extended period of time or seek opportunities outside of the hospital catchment area due to the need for regular treatment and monitoring. The nature of thalassaemia care and treatment has significant logistical and financial implications that include a heavy burden of travel to a specialist regional centre or clinic, difficulties gaining insurance for travel and critical illness cover. Stress, anxiety, low self-esteem, feelings of isolation and depression are all elements of an individual's condition that must be monitored and managed. **Hospital Admissions** When faced with acute issues, patients are usually admitted to hospital. This can be a challenging experience as health professionals outside of the thalassaemia/ haematology units are not aware of the condition or how to treat them. This can cause a delay in treatment which can result in serious life changing consequences. This is a national problem that as has been reported from patients throughout the UK.

	Carers Thalassaemia can have a major impact on carers and loved ones. Most parents are not aware of thalassaemia until they are pregnant or after the birth of their child is. The birth of a child is a life changing event, but receiving a diagnosis of a life long condition can be heart-breaking. There still is not adequate support for carers in terms of handling the diagnosis and how to manage their children's condition. Carers also suffer experience psychological issues such as anxiety, depression etc from trying to help their love ones manage their condition. The diagnosis also changes their lives not only on an emotional perspective but also from a financial perspective as managing their loved one conditions can be a full time job and many have to terminate their employment to take their loved ones to hospital appointments. Thalassaemia also affects their social lives, as planning holidays or trips become centred on the needs of the person with thalassaemia.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers are appreciative of the care they receive. However, it is important to note that care and patient statisfaction differs greatly throughout the UK based on patient numbers and the experience and knowledge of health care professionals with regards to thalassaemia. UKTS is part of the steering committee for peer reviews in haemoglobin disorders which is organised by the UK Forum for haemoglobin disorders. The findings of the last peer review season completed in June 2020 found there were huge disparities in parent care throughout the UK. It was concerning to learn about the issues patients were experiencing in other parts of the country as some units were not able to meet the quality standards. Access to the peer review reports can be found on the Quality Review website. Both patients and carers spoke about not being able to access bone marrow transplants due to age or not having a matched relative and wished the NHS would do more to look into other treatments that could improve their health outcomes.

	Other issues relate to having to take time off to attend treatment and appointments which causes patients and carers the need to take annual leave to attend which can affect their education and employment opportunities. Patients and carers also spoke about the need to purchase medication after they turn 18 as thalassaemia was not included in the list of conditions deemed exempt by the Government. This results in a financial strain to some families.
10. Is there an unmet need for patients with this condition?	Yes. Bone marrow transplantation is currently the only "curative" treatment for thalassaemia but the majority of patients do not quality for it due their age, secondary conditions and suitable match. As such this new therapy may give other patients a normal chance of living a thalassaemia free life.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	1) A chance of living a thalassaemia free life- with no blood transfusions and iron chelation therapy 2) The chance of not developing other secondary conditions 3) Not needing a donor 4) Correcting the patient's own gene 5) Less risk of developing Graft Versus Host Disease and other reactions 6) Less overall burden on the NHS 7) More freedom- more control on life
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The disadvantages highlighted by patients and carers are: 1) Concerns about the myeloablative conditioning 2) Fertility implications 3) The risk of becoming transfusion dependent again 4) The efficacy of the new treatment with those of a more severe genotype

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who do not meet the current criteria for bone marrow transplants due to not having a suitable match or age (i.e. 90% of patients) could benefit from this new technology. Additionally, patients who experience frequent blood transfusion reactions due to the development of antibodies and other agents may also benefit from this.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No**
Other issues	
15. Are there any other issues that you would like the committee to consider?	No

Topic-specific questions	
16. How often do people with transfusion-dependent beta-thalassaemia receive blood transfusions?	Typically, people with transfusion dependent thalassaemia receive blood transfusions every 2-4 weeks. However, this can vary with incidence of transfusion related reactions where blood transfusions may be required more often or based on the person's genotype.

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- This new technology could give people the chance to live thalassaemia free lives
- This new technology could help patients reduce iron burden and the need for iron chelation medication
- This new technology may help decrease the need for blood transfusions
- This new technology may help decrease the overall financial burden on the NHS
- This new technology may not be suited to everyone

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report

Zynteglo for treating transfusion-dependent beta-thalassaemia

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Lindsay Claxton, Research Fellow, CRD
	Mark Corbett, Research Fellow, CRD
	Matthew Walton, Research Fellow, CRD
	Peter Murphy, Research Fellow, CRD
	Sumayya Anwer, Research Fellow, CRD
	Melissa Harden, Information Specialist, CRD
	Sofia Dias, Professor of Health Technology Assessment, CRD
Correspondence to	Sofia Dias, Professor of Health Technology Assessment, CRD, University of York, York YO10 5DD
Date completed	20/01/2020

Source of funding

This report was commissioned by the NIHR Systematic Reviews Programme as project number 18/54/11.

Declared competing interests of the authors

None

Acknowledgements

We thank Professor Sally Kinsey at Leeds Teaching Hospitals NHS Trust for her expert advice throughout this project.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Claxton L, Corbett M, Walton M, Murphy P, Anwer S, Harden M, Dias S. Zynteglo for treating transfusion-dependent beta-thalassaemia: A Single Technology Appraisal. CRD and CHE, University of York, Technology Assessment Group, 2020.

Contributions of authors

Lindsay Claxton, Peter Murphy and Matthew Walton wrote the cost effectiveness sections and conducted the ERG economic analyses. Lindsay Claxton provided advice, commented on drafts of the report and took overall responsibility for the cost effectiveness sections. Mark Corbett and Sumayya Anwer wrote the clinical effectiveness sections of the report. Mark Corbett took overall responsibility for the clinical effectiveness sections. Melissa Harden wrote the sections on the search strategies. Sofia Dias provided advice, commented on drafts of the report and took overall responsibility for the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

Copyright statement

Table of Contents

Table of Tables

Table of Figures

List of abbreviations

CS	Company submission
AE	Adverse event
BBTS	British Blood Transfusion Society
BSH	British Society for Haematology
CMR	Cardiovascular magnetic resonance
CSR	Clinical study report
DICE	Discretely integrated condition event
DSA	Deterministic sensitivity analysis
EMA	European Medicines Agency
eMIT	Electronic market information tool
ERG	Evidence review group
G-CSF	Granulocyte-colony stimulating factor
GvHD	Graft-versus-host disease
Hb	Haemoglobin
HCV	Hepatitis C virus
HES	Hospital episode statistics
HLA	Human leukocyte antigen
HLA	Human leukocyte antigen
HRQoL	Health related quality of Life
HSC	Haematopoietic stem cells
HSCT	Haematopoietic stem cell transplant
HST	Highly specialised technology
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
LIC	Liver iron content
LVV	Lentiviral vector
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
PAS	Patient access scheme

PASLU	Patient access scheme liaison unit
PB VCN	Peripheral blood vector copy number
PFC	Point for clarification
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALY	Quality adjusted life-year
RCPath	The Royal College of Pathologists
SAE	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SoC	Standard of care
TDT	Transfusion dependent thalassaemia
TI	Transfusion independent
TP	Transplant Population
UKTS	United Kingdom Thalassaemia Society
VCN	Vector copy number
VOD	Veno-occlusive disease
WTP	Willingness-to-pay

1 Summary

1.1 Critique of the decision problem in the company's submission

Both the NICE scope and the Zynteglo marketing authorisation refer to a ≥ 12 years β-thalassaemia population for which hematopoietic stem cell transplantation (HSCT) is appropriate, but a matched related donor is not available. The ERG considers that the reference to HSCT being 'appropriate' should primarily be interpreted as relating to fitness to receive conditioning chemotherapy prior to an autologous cell therapy (such as Zynteglo) – rather than allogeneic HSCT, because for the overwhelming majority of NHS patients ≥ 12 years allogeneic HSCT will not be considered appropriate. Allogeneic HSCT is not recommended for adults in the UK, and it is very rarely considered in patients aged ≥12 years, as the risks outweigh the benefits. In light of this, the ERG has some concerns about the interpretation of the restriction of "a matched related donor is not available" in the ≥12 years β-thalassaemia population, as it could leave some patients without a viable transplant option if they are ≥12 years old but have a matched related donor.

For the Zynteglo clinical trials, transfusion-dependent β-thalassaemia (TDT) was defined as requiring 8 or more transfusions per year or ≥100ml /kg/year of packed red blood cells. Patients excluded from the trials were those with evidence of severe iron overload, or with hepatitis B or C, or other clinically significant active infections. The ERG's clinical adviser thought these were appropriate criteria.

The EMA SmPC noted that only a few patients homozygous for IVS-I-110 or IVS-I-5 mutations were included in the Zynteglo studies. As part of the conditional license, the EMA require the company to submit interim and final data from such patients with severe non-β^0/β^0 genotypes. These patients may be under-represented in the Zynteglo trials, considering their prevalence in the NHS population.

The intervention in the company submission was the same as that specified in the final scope. Patients may only be treated with Zynteglo once. None of the Zynteglo trials had a control arm, so the company identified data on comparator therapies through systematic reviews and their own studies. The systematic reviews were often too limited in their search dates to identify suitable studies so additional 'targeted reviews' were undertaken, but detailed methods were not reported.

The outcomes specified in the company submission (CS) matched the NICE scope, with the exception of 'symptoms of anaemia'. However, symptoms of anaemia are a consequence of low haemoglobin levels and both total haemoglobin levels and haemoglobin A (HbA^{T87Q}) levels were reported as outcomes in the CS.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness data on Zynteglo presented in the CS were derived from two phase 1/2 studies in patients with any genotype (studies HGB-204 and HGB-205), and one ongoing phase 3

study in patients specifically with non-β^0/β^0 genotypes (HGB-207). Of the patients recruited, [redacted] were Asian, [redacted] were white and [redacted] were classed as 'other' race.

For the primary outcome – transfusion independence (TI) – a response rate of 83% (20/24 patients) was seen in the 'transfusion evaluable' population. No events for loss of TI have been recorded so far with patients showing generally stable levels of vector copy number (the average number of vector copies per cell) in peripheral blood and HbA^{T87Q} (the haemoglobin derived from the modified stem cells). Of the four patients who did not achieve TI in the transplant population, two had 'substantial' transfusion reductions (≥60% reduction in frequency) and two were transfusion dependent.

For adults with baseline HRQoL measurements, the CS noted a general trend of [redacted]. The company concluded that the EQ-5D data collected in the Zynteglo trials may not accurately reflect the HRQoL of patients treated with Zynteglo.

The company used summary data from both their own studies and identified published studies to derive outcomes for patients receiving comparator treatments (transfusions and chelation) in the economic model. One identified study led the company to conclude that the conditioning chemotherapy associated with Zynteglo therapy would increase infertility by 24% in men and 57% in women when compared to transfusion-dependent patients.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company stated that 31 articles were included "for qualitative synthesis" in their systematic review but no such synthesis of these articles was presented. The CS synthesis focussed on the trials HGB-204, HGB-205, and HGB-207 but no reference was made to existing conference abstracts on study HGB-212, and no unpublished data on this trial were presented.

The ethnicity distribution of the Zynteglo trial population does not appear to well represent the UK TDT population. In the UK, around 10-15% of patients with thalassaemia are white, while [redacted] of the trial patients were white. This may mean that the proportion of the trial population with a severe non-β^0/β^0 IVS-I-5 genotype is not representative of the UK setting, since IVS-I-5 mutations are quite common in thalassaemia patients of Indian or Pakistani descent. Furthermore, patients with an IVS-I-110 severe non-β^0/β^0 genotype were excluded from HGB-207. While most patients appear to respond well to Zynteglo, the small subgroup of patients who are homozygous for these mutations, or heterozygous for IVS-I-110 or IVS-I-5 together with a β^0 mutation, appeared less likely to achieve transfusion independence than other non-β^0/β^0 genotype patients. The ERG is concerned that there is very little evidence (both now and expected in the future) for a key subgroup of patients seen in the

NHS – those with IVS-I-5 mutations – and believes that the possible impact of heterogeneity across trials on transfusion outcomes should have been considered by the company.

The Zynteglo manufacturing processes have evolved during the trial programme with the aim of [redacted]. It is possible that [redacted] may increase the probability of achieving TI in patients with severe non-β^0/β^0 genotypes (compared to the previous processes used in the trial programme) but only results from the study HGB-212 and further data from HGB-207 can resolve this uncertainty. The primary outcome of HGB-212 is transfusion reduction (in HGB-207 it was transfusion independence) suggesting lower expectations of a TI response in patients with more severe genotypes.

The trials results remain immature, and the number of patients treated is small, so uncertainty exists regarding the persistence of the Zynteglo treatment effect, and the possibility of adverse events in the medium-to-long term. Zynteglo appears to have an acceptable short-term safety profile.

The company's systematic reviews to identify comparator group data were restricted to studies published from 2007 onwards and review articles appear to have been excluded. These criteria proved to be too restrictive as the company had to undertake additional "targeted reviews" to identify sufficient evidence. The justification for selecting specific studies from these reviews was often not presented. The ERG considers that the applicability of the comparator data is not optimal as some studies do not reflect the improvements in TDT patient treatment and management achieved over the last 10-20 years. This was exacerbated by the limited or absent critiques of the likely limitations of many studies, and their possible implications. The company commissioned a 'chart review' of the medical records of UK patients with TDT. However, the Chart Review also had limitations in how well it reflected the Zynteglo trial population [redacted]

1.4 Summary of cost effectiveness submitted evidence by the company

The company's submission of economic evidence included a systematic review to identify previous economic analyses. One overall search was used to identify studies on the cost-effectiveness of treatments, health-related quality of life (HRQoL), and cost and resource utilisation in patients with TDT. The review identified five cost-effectiveness models and one cost-of-illness model. The remaining nine publications were resource use/cost studies. Two of the identified cost-effectiveness analyses were used to inform clinical parameters in the company's model.

The company presented a *de novo* economic analysis of Zynteglo compared with the standard of care (SoC), consisting of blood transfusions and iron chelation therapy, in transfusion-dependent beta thalassaemia. Treatment effectiveness was assessed through the achievement of transfusion-independence. Total costs and QALYs were assessed over a lifetime time horizon, and discounted at a rate of 1.5% for each arm.

The model used a discrete event simulation structure, implemented through the discretely integrated condition event (DICE) simulation framework. The model structure was driven by the transfusion status of patients, which determined their tissue-specific iron levels. A patient's iron level then determines the risk of developing complications attributable to iron overload, also influences mortality risk, quality of life, and chelation requirements.

Zynteglo, as implemented in the model, consists of three stages, each comprising distinct processes and treatment costs. These include patient stem cell mobilisation and apheresis, myeloablative conditioning, and administration of the transduced cells. The comparator considered in the company's model was 'current care', which consists of regular transfusions and iron chelation therapy. In the economic model, patients were allocated to either oral (deferasirox, deferiprone), subcutaneous (desferrioxamine) or a combination of two different chelation therapies.

The clinical effectiveness of Zynteglo in the model is assessed by the proportion of patients achieving transfusion independence. This was estimated from pooled results in all non-β^0/β^0 genotype subjects from studies HGB -204, HGB-205, and HGB-207. The engraftment procedure was assumed to be successful in all patients. In the long-term, it was assumed that there would be no loss of graft, i.e. transfusion independence status was permanent, and that transfusion-reduced patients would not experience an increase in the need for transfusions or return to transfusion dependence over time.

Modelled baseline levels of iron overload are based on the mean of the Chart Review population, with each simulated patient randomly assigned to an overload risk category (low, medium, high) for the cardiac, liver, and endocrine systems. To predict the complications of iron overload, the model uses literature-based rates and risk equations to estimate the rate of developing complications based on distribution of iron levels in the heart, liver, and serum (ferritin).

In the absence of direct long-term survival data for the transfusion dependent population after treatment with Zynteglo, the company used a range of external sources to predict long-term survival. The company applied a standardised mortality ratio based on transfusion-dependence status to general population mortality rates. Mortality following the development of cardiac complications was modelled separately, to account for the specific impact of this aspect of the condition.

The health-related quality of life (HRQoL) estimates used in the company's base-case analysis for patients achieving transfusion independence were based on a vignette study conducted by the company. Owing to a perceived lack of appropriate HRQoL data for transfusion dependent patients, the company commissioned the Chart Review of the medical records of UK TDT patients. Patients' EQ-5D-3L and EQ-5D-Y questionnaire data were used to generate utility scores. The mean of these scores was applied to transfusion dependent patients in the model. The model also incorporates disutility increments associated with chelation, infertility, cardiac complications, liver complications, and endocrine complications.

Resource use and costs include: drug acquisition costs; Zynteglo pre-treatment and administration costs; post-Zynteglo infusion monitoring costs; treatment and monitoring costs for blood transfusions and iron chelation therapy; costs associated with managing iron overload-related complications; and the costs of managing adverse events associated with iron chelation therapy.

The company found Zynteglo to be more costly (cost difference of [redacted]) and more effective (13.14 QALYs gain) compared to SoC. The deterministic base case incremental cost-effectiveness ratio (ICER) for Zynteglo was [redacted] per QALY gained, the mean probabilistic ICER was [redacted] per QALY gained. The majority of the additional QALYs were generated as a result of additional life years; however, improvements in quality of life also had a considerable impact on the incremental QALYs. The company reported that the most influential parameters in the one-way sensitivity analysis included the iron chelation acquisition cost and the distribution of oral iron chelation therapies across patients.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG highlights a significant number of issues that contribute to uncertainty in the cost-effectiveness results presented by the company.

By reflecting iron overload complications in only the liver, cardiac and endocrine systems, the company's model may have omitted important aspects of the condition, such as splenectomy and the development of osteoporosis. These were included in other cost-effectiveness analyses for this condition, and clinical advice suggested that improvements in patient care mean treating the consequences of TDT in older patients (such as osteoporosis) is increasingly important.

The ERG did not consider the model to adequately correlate patient characteristics and key outcomes. Historic iron levels were not considered in rate of complication development, or time to iron normalisation, which was assumed to be four years in TI patients regardless of prior iron levels. Furthermore, the risk of developing iron overload-related complications depended only upon the current iron load category, rather than accounting for the severity or duration of historic iron overload,

or the patient's age. This meant that very few patients in the Zynteglo arm developed cardiac complications, as they were assumed to be at no risk after four years.

The ERG identified several issues regarding the composition of the modelled population. These include the age, weight, iron load, comorbidities, and genotype of patients. The age of patients included in the Chart Review (the source of comparator HRQoL data and resource use) did not match the NICE Scope or the Zynteglo trial population. A large proportion of Chart Review patients were aged over 35, with some over 60 years of age, had a number of co-morbidities that would have precluded treatment with Zynteglo, and had other complications whose disutilities would be double counted by the model, thereby introducing bias in favour of Zynteglo. Modelled patient weight was assumed to be [redacted] throughout the lifetime of both paediatric and adult patients, which the ERG considered an oversimplification and an overestimation. Finally, the ERG considered the modelled population to underrepresent severe non-β^0/β^0 genotypes covered by the marketing authorisation, and may be more highly prevalent in the UK.

The intervention as implemented in the economic model matches the product licence. However, the distribution of chelating agents may not represent current clinical practice in this population. The relatively recent development of the evidence around the safety and efficacy of using a combination of agents, means there may not yet be a consensus on best clinical practice, adding further uncertainty.

The ERG has a number of concerns regarding the company's justification for the use of the non-reference case discount rate of 1.5% in the economic evaluation. The company argue that Zynteglo restores people who would otherwise die or have a very severely impaired life to full or near full health. The ERG highlighted the age of the literature cited in support of this assumption, and identified recent sources stating that patients optimally managed with currently available therapies could have a near-normal life expectancy. A number of evidence sources, including the company's own Chart Review and HGB trials, supported the notion that the impact of TDT and current management on HRQoL was not as severe as argued by the company. Furthermore, the ERG did not consider there to be sufficient evidence to conclude with certainty that Zynteglo restores individuals' health to full or near full in terms of length and quality. It is also therefore uncertain whether or not Zynteglo will commit the NHS to significant irrecoverable costs.

The ERG highlighted a number of uncertainties in the modelled treatment effectiveness, including uncertainty around the generalisability of the trials to the UK, given the potential underrepresentation of IVS-I-110 or IVS-I-5 genotypes. This may impact the overall rate of achieving transfusion independence. The ERG also highlight that there is insufficient evidence to support the assumption of permanent engraftment and an indefinite treatment effect in all patients. Furthermore, the ERG considers that cited evidence did not support the assumption of iron normalisation in all transfusion

independent patients, and that the four year time frame may be too optimistic. The source of assumptions surrounding the modelling of complications from iron overload and the mortality rate of transfusion dependent patients also may have introduced uncertainty.

A number of issues regarding the modelled HRQoL result in uncertainty in the company's results. Firstly, an inappropriate value set was selected as the basis of the general population utility estimates. The company selected a subset which excluded all individuals with a history of a health condition meaning that the baseline utility of a patient aged 75 was higher than someone aged 30 in the general population. Secondly, the utility of transfusion dependent patients was based on the full Chart Review population, despite its demographics differing substantively from patients included in the Zynteglo trials. As a result, the ERG requested the company re-analyse HRQoL data in the Chart Review, limiting the population to only those aged from 12-35 years, and excluding patients with comorbidities already separately accounted for in the model. This resulted in a higher utility for TDT patients, comparable to other literature-derived estimates.

The economic model failed to account for patients withdrawing from treatment during the pre-transplant stage. The company's submission showed one patient from the ITT population in HGB-204 discontinued Zynteglo due to inadequate stem cell mobilisation. The potential costs of this are not captured in the model, which prospectively selects only those who successfully received Zynteglo infusion. Furthermore, uncertainty remains around the cost of chelation therapy, given the uncertainty around the weight of modelled patients.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The effectiveness of Zynteglo was compared against SoC (transfusions and iron chelation), and the outcomes assessed were appropriate.

In the company's economic model, the impact of a range of uncertainties were explored using sensitivity and scenario analysis. The company also addressed numerous additional uncertainties in response to ERG requests and clarifications. Where there was a lack of appropriate data for use in the submission, the company also endeavoured to generate appropriate evidence, notably commissioning of the Chart Review of the medical records of patients with TDT.

1.7 Weaknesses and areas of uncertainty

The main weaknesses and areas of uncertainty identified by the ERG include:

The representativeness of the trial population

The Zynteglo trial results have uncertain applicability to the population likely to receive Zynteglo in the NHS as the trial population might under-represent certain genotypes which are prevalent in the UK.

Heterogeneity of effect

The level/extent of heterogeneity of effect (i.e. in achieving TI) remains an area of uncertainty. Heterogeneity based on genotype and the evolving manufacturing process is not addressed in the evidence.

Immaturity of the data

The trials results are still immature, and the number of patients treated is small, so uncertainty exists regarding the longevity of the Zynteglo treatment effect, and the possibility of adverse events in the medium-to-long term.

Model structure and parameters

There is a lack of interaction between patient characteristics and key outcomes in the economic model. The model uses mean cohort values for all patients and fails to adequately account for interaction between age, weight, event risk, and events themselves. Uncertainty also exists regarding the validity/appropriateness of many of the comparator data used in the model.

The use of the Chart Review

The Chart Review provided the source of many of the model inputs, including HRQoL data for transfusion dependent patients, the proportion of patients on chelation therapy and the average weight of patients. However, the Chart Review included patients outside of the NICE scope as well as patients with comorbidities, which would preclude them from treatment with Zynteglo.

The non-reference case discount rate

The company's use of a non-reference case discount rate of 1.5% in the economic evaluation has a considerable impact on the incremental costs and QALYs of Zynteglo compared to SoC. The 1.5% discount rate leads to a substantial underestimate of the company's ICER. Considerable uncertainty remains regarding the company's justification for using this discount rate.

The modelled HRQoL

Due to the use of utility values for transfusion independent patients being derived from a vignette study; the selection of an inappropriate general population utility value set; and the use of utility values for transfusion dependent patients with questionable internal and external validity, considerable uncertainties remain regarding the HRQoL of Zynteglo and SoC patients.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The key uncertainties addressed by the ERG scenario analyses relate to:

- The baseline characteristics of the modelled population
- The discount rate
- The use of the Chart Review as the modelled comparator
- The modelled utility decrements

The company presented additional analyses as part of their points for clarification response which include age category specific body weights; alternative proportions of chelation therapy, and alternative utility values based on the age- and comorbidity-adjusted Chart Review reanalysis.

The results of these scenario analyses, including the ERG's alternative base-case are summarised in Table 1. Due to time constraints and the nature of the model structure, deterministic ICERs are presented throughout unless otherwise stated.

The ERG alternative base-case analysis incorporated a number of alternative assumptions, a number of which were also explored by the company in scenario analyses. The changes made by the ERG include:

- Alternative discount rate of 3.5%,
- Age category specific body weight (paediatric and adult),
- 20% of the population have hypogonadism at baseline,
- Age-adjusted proportions of chelation type from the Chart Review,
- Age and comorbidity-adjusted utility values from the Chart Review,
- Age-adjustment of utilities based on values for the full general population,
- Alternative utility decrement for transfusion independent patients on subcutaneous chelation ,
- electronic market information tool (eMIT) drug acquisition costs.

Under the ERG's alternative set of assumptions, the ICER for Zynteglo versus SoC is [redacted] per QALY gained.

A scenario analysis is provided on the ERG's base case in which a discount rate of 1.5% is used for costs and QALYs. The resulting deterministic ICER is [redacted] per QALY gained. Further analyses undertaken by the ERG on their alternative base-case suggested that the mortality rate for transfusion-dependent patients was also an influential parameter in the analysis.

Table 1 Summary of ERG exploratory analyses

	Incremental costs	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	13.13	[redacted]
Scenario 1: Age category-specific body weight (paediatric and adult)	[redacted]	13.13	[redacted]
Scenario 2: 20% of population have hypogonadism at baseline	[redacted]	12.98	[redacted]
Scenario 3: Adjusting clinical effectiveness data for underrepresented genotypes	[redacted]	12.45	[redacted]
Scenario 4: Adjusted chelation therapy distribution	[redacted]	13.13	[redacted]
Scenario 5: Engraftment failure – 1%	[redacted]	13.03	[redacted]
Scenario 6: Engraftment failure – 5%	[redacted]	11.81	[redacted]
Scenario 7: 5% relapse every 10 years	[redacted]	11.26	[redacted]
Scenario 8: 10% relapse every 10 years	[redacted]	9.51	[redacted]
Scenario 9: Alternative SMR of 2 (transfusion dependent)	[redacted]	11.99	[redacted]
Scenario 10: Time to iron normalisation – 5 years	[redacted]	12.85	[redacted]
Scenario 11: Time to iron normalisation – 7 years	[redacted]	12.01	[redacted]
Scenario 12: Time to iron normalisation – 10 years	[redacted]	11.28	[redacted]
Scenario 13: Patients with normalised levels of iron face a residual risk of developing iron overload-related complications	[redacted]	9.13	[redacted]
Scenario 14: Alternative discount rate - 3.5%	[redacted]	7.29	[redacted]
Scenario 15: Age-related disutilities taken from full Ara and Brazier population	[redacted]	11.32	[redacted]
Scenario 16: Age- and comorbidity-adjusted Chart Review utility values	[redacted]	8.92	[redacted]
Scenario 17: Cumulative impact of 15 and 16	[redacted]	7.11	[redacted]
Scenario 18: Subcutaneous chelation therapy decrement for TI patients	[redacted]	13.07	[redacted]
Scenario 19: No infertility disutility	[redacted]	13.71	[redacted]
Scenario 20: eMIT drug acquisition costs	[redacted]	13.13	[redacted]
Scenario 1: Age category-specific body weight (paediatric and adult)	[redacted]	13.13	[redacted]
ERG Alternative base case analysis (deterministic)	[redacted]	**3.05**	[redacted]
ERG Alternative base case scenario analysis - 1.5% discount rate for costs and outcomes	[redacted]	6.71	[redacted]
ERG Alternative base case scenario analysis - SMR of 2 for transfusion dependent patients	[redacted]	2.48	[redacted]

2 Background

2.1 Description of the technology being appraised

Zynteglo is a gene therapy that provides functional β-globin to patients with TDT using the patient's own cells ex-vivo to correct the underlying cause of the disease. Zynteglo is an autologous $CD34^+$ cell enriched population that contains haematopoietic stem cells (HSCs) transduced with lentiviral vector (LVV) encoding the $\beta^{A\text{-}T87Q}$ globin gene. Zynteglo is administered as a single intravenous infusion, where copies of the functional $\beta^{A\text{-}T87Q}$ establish a population of undifferentiated, long-term HSCs in the bone marrow, integrating the β-globin gene into the patient's genome.

Zynteglo should be administered in a specialised treatment centre by physicians with experience in treating patients with TDT and HSC transplantation.[1] The company expressed a preference that treatment centres are co-located with haemoglobinopathy medical expertise as patients will need to be heavily chelated before treatment, to prevent complications. The processes involved in manufacturing and administering Zynteglo include mobilisation and apheresis to harvest stem cells from the patient, cryopreservation of stem cells and a back-up collection, shipping between treatment centres and the manufacturing facility, purification of stem cells and transduction of cells using a viral vector. The treatment process from mobilisation to the end of the hospital stay lasts 13-19 weeks and depends greatly on the number of cycles of mobilisation and apheresis the patient undergoes.

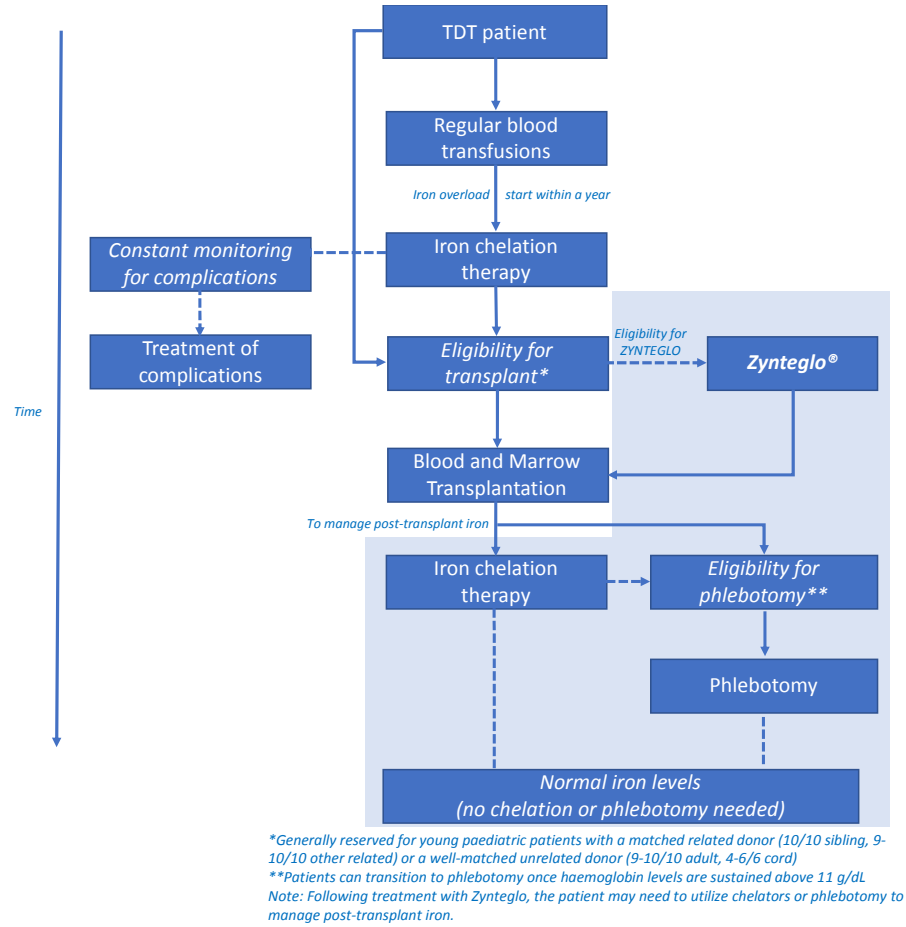
Prior to the infusion of Zynteglo, patients undergo full myeloablative conditioning using chemotherapy with busulfan to destroy the existing bone marrow stem cells. A description of the treatment process is detailed in Table 2 (p12-17) of the CS. Post infusion, iron loading in patients is managed through either phlebotomy – if the patient's unsupported haemoglobin levels reach a certain threshold – or chelation therapy if phlebotomy is not feasible. This is necessary because while transfusion-independent patients do not experience additional iron loading after infusion, previously stored iron levels need to be actively reduced.

In their submission on Zynteglo, NHS England emphasised the importance of establishing the infrastructure necessary to support treatment implementation. While the techniques used are not novel or exclusive to Zynteglo, there may be a need to expand existing services, such as apheresis, which is currently already used to gather stem cells, albeit not in TDT patients undergoing HSCT. Cell management strategies, tailored to the specific treatment would need to be established, as well as a capacity to store back-up copies of stem cells. The submissions from the Royal College of Pathologists (RCPath) and British Society for Haematology (BSH) stated that additional testing (which is not offered at present) would be required to determine patient eligibility for the treatment, though this is funded by the company.

2.2 The health condition and position of the technology in the treatment pathway

The company submission provided an overview of the standard care pathway for TDT, adapted from UKTS's guidelines (Figure 3, p 21 of CS). In Figure 14 (p 44 of the CS), reproduced here as Figure 1, the company also highlighted the position Zynteglo would occupy in the treatment pathway, where it is presented as an option for patients eligible for HSCT but without a matched, related donor.

Figure 1 Treatment pathway for TDT patients including Zynteglo (Fig 14, CS)



The scope of the population as ascertained by the company is patients aged over 12 years with TDT with a non-β^0/β^0 genotype. The maximum age a patient can receive Zynteglo is unspecified, though it is unlikely that many older patients would receive Zynteglo since eligibility is linked to the physical condition of the patient and iron damage tends to accumulate with age. Currently the oldest patients treated with Zynteglo were [redacted] years old. Zynteglo is also a potential treatment for older patients who are ineligible for allogeneic-HSCT according to current guidelines, due to an increased risk of graft rejection and graft-versus-host disease (GvHD).

3 Critique of company's definition of decision problem

3.1 Population

The population specified in the NICE scope was "*People aged 12 years and over with transfusion-dependent beta-thalassaemia with a non-β^0/β^0 genotype, who are eligible for hematopoietic stem cell transplantation but do not have access to a matched related donor*". This is very similar to the wording of Zynteglo's licensed indication: "*...patients 12 years and older with TDT who do not have a β^0/β^0 genotype, for whom HSC transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available*." For the Zynteglo clinical trials, TDT was defined as requiring 8 or more transfusions per year or ≥100ml /kg/year of packed red blood cells, which the ERG's clinical adviser thought was an appropriate definition.

The reference to HSC transplantation in the marketing authorisation and the population described in the NICE scope can be read as mainly encompassing autologous HSC therapies – such as Zynteglo – rather than allogeneic HSCT, and relates to patient fitness to receive conditioning chemotherapy. Allogeneic HSCT is not recommended for adults in the UK, regardless of donor availability, and is rarely considered in patients ≥ 12 years, due to the risks outweighing the potential therapeutic benefit. The risks associated with allogeneic HSCT are greater than those associated with autologous HSCT therapies (such as Zynteglo) because the former carries the risk of severe immune reaction from GvHD and the risk of infection as a result of taking immunosuppressive agents. Autologous transplants do not carry these particular risks.

The summary of product characteristics (SmPC) for Zynteglo states:

"*Contraindications to the mobilisation agents and the myeloablative conditioning agent must be considered*", adding that:

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

The Zynteglo trials excluded patients with cardiac T2* <10 msec by MRI and patients with evidence of liver disease defined by MRI evidence or specific elevated liver function tests (e.g. 3 times the upper limit of normal). Patients with any other evidence of severe iron overload, and patients with hepatitis B, hepatitis C or other clinically significant active infections were also ineligible for the

trials. The ERG's clinical adviser thought these were appropriate criteria for considering fitness to receive Zynteglo, since the main risks from the myeloablative conditioning would be liver failure and infections such as sepsis (which the heart must be strong enough to withstand).

The mutations which cause β-thalassaemia are regionally specific, based on four groups: Mediterranean, Asian Indian, Southeast Asian, and sub-Saharan African. Each country in a group displays a few common alleles but also a larger number of alleles are found at much lower gene frequencies.[2] It is important to consider this heterogeneity of mutations because certain mutations – such as IVS-I-110 and IVS-I-5 – are associated with dramatically reduced β-globin production, behaving phenotypically as β^0 genotypes (despite being classed as β^+genotypes). Patients with a β^0/β^0 genotype are not covered by the marketing authorisation, but 'severe' non-β^0/β^0 genotypes are covered (such as homozygous IVS-I-110 and IVS-I-5 genotypes, and IVS-I-110/β^0 or IVS-I-5 /β^0 genotypes). This despite the fact that in Zynteglo trial HGB-207, IVS-I-110 mutations were considered as being "equivalent to a β^0 mutation" and were grounds for exclusion from the study, if paired with another IVS-I-110 mutation, or a β^0 mutation.

Moreover, there is heterogeneity of response to Zynteglo in patients with β^0/β^0 genotypes (not covered by the MA) and patients with severe non-β^0/β^0 genotypes deemed equivalent to a β^0 mutation (which are covered by the MA), when compared with patients with other non-β^0/β^0 genotypes (see Section 4.2.2). Severe non-β^0 mutations are quite prevalent in UK patients, based on a study which found IVS-I-5 to be the most common mutation (22.5% and part of the 'Asian Indian' group of mutations) and IVS-I-110 the fourth most common mutation (5.5%, and part of the 'Mediterranean' group of mutations) in 1,712 unrelated β-thalassaemia carriers who required screening for antenatal diagnosis in the UK.[2] The ERG also asked the company to comment (in a point for clarification) on whether the proportion of patients with IVS-I-110 or IVS-I-5 mutations in the Zynteglo studies adequately reflects the proportion likely to be eligible in the NHS. The company stated that specific genotype data from a bluebird bio sponsored study of genotyping adult patients with β-thalassaemia from the Manchester centre for Genomic Medicine found 4 of 14 patients with non-β^0/β^0 genotypes with an underlying IVS-I-110 or IVS-I-5 mutation. The EMA's SmPC noted that only a few patients homozygous for IVS-I-110 or IVS-I-5 were included in the Zynteglo studies. As part of the conditional license the EMA require the company to "submit interim and final data from patients with a severe non-β^0/β^0 genotype such as IVS-I-110 included in Study HGB-212". Although there are prevalence estimates for individual mutations in the UK, the prevalence of severe non-β^0/β^0 genotypes appears unclear. The ERG also has concerns that severe non-β^0/β^0 patients who had IVS-I-110 mutations were excluded from one of the pivotal Zynteglo trials (HGB-207) which contributed to the submission efficacy data, even though these patients are covered by the marketing authorisation. It is acknowledged that an ongoing trial (HGB-212) is studying such patients but these data were deemed by the company to be

too immature to contribute to the CS. Of the Zynteglo trial cohort 'transplant population', [redacted] had severe non-β^0/β^0 genotypes.

Routine genotype testing is not part of usual NHS practice. The introduction of testing will be needed to identify patients who may be eligible for Zynteglo, which will have implications for infrastructure. The ERG notes that costs for genotype testing are incurred by the manufacturer (Table 58, CS).

3.2 Intervention

The intervention in the CS was as specified in the scope: Zynteglo gene therapy (previously known as LentiGlobin) which is administered as a single-dose and which should only be administered once. The therapy involves transplantation of autologous $CD34^+$ haematopoetic stem cells which have been transduced by a lentiviral vector encoding the $\beta^{A\text{-}T87Q}$-globin gene. The minimum recommended dose is 5.0 x 10^6 $CD34^+$ cells/kg.

Zynteglo therapy is comprised of multiple interacting components and processes and should therefore be considered a complex intervention. The CS reported that the complete treatment process lasts 13-19 weeks; Table 2 of the CS presented details of the various stages involved, which are:

1. Mobilisation and apheresis, in which stem cells are mobilised from the bone marrow using granulocyte-colony stimulating factor (G-CSF) and plerixafor, and are harvested via apheresis. This also includes collection of back-up cells for rescue treatment. This is followed by shipment of cells to the manufacturing facility for stem cell processing.
2. While the extracted cells are undergoing processing, the second stage, pre-treatment and myeloablative conditioning, occurs. Prior to treatment with Zynteglo, patients undergo hypertransfusion to maintain haemoglobin levels during the period in which transfusions are stopped, iron chelation is also discontinued prior to myeloablative conditioning. Patients then begin prophylaxis for veno-occlusive disease (VOD) with ursodeoxycholic acid, and for seizures using clonazepam. When the transduced cell product has been successfully manufactured and received by the administration site, patients undergo myeloablative conditioning using busulfan over the course of four days.
3. The third stage comprises the administration of the transduced cells, which is performed in a <30 minute intravenous infusion in a specialist treatment centre. This is followed by an inpatient stay of 21-42 days until engraftment of the infused cells has occurred.

Where necessary, patients may need to undergo one or more additional cycles of mobilisation and apheresis, separated by at least 14 days, in order to obtain enough cells for manufacture.

The EMA designated Zynteglo as an orphan medicine in 2013. Marketing authorisation for Zynteglo was granted by the EMA on 29th May 2019. The approval is conditional, meaning the company must

provide the EMA with results of ongoing studies to allow annual assessment of effectiveness and safety data (beginning on 29th May 2020). Zynteglo was evaluated through the EMA Adaptive Pathways programme so data will continue to be generated and re-evaluated by the EMA.

Gene therapies are different to pharmacological therapies in that they are often not fixed, but may change over time. It was evident from section B.2.1.2 of the CS that this is happening with Zynteglo (and is discussed further in this report in Section 4.2.1).

3.3 Comparators

The scope comparators were defined by NICE as "*established clinical management including blood transfusions and chelating agents*". None of the Zynteglo trials had a control arm, so data from conventional direct comparisons with Zynteglo were not available. However, the CS noted that, for the primary and key secondary outcomes of transfusion independence and transfusion reduction, a comparator cohort of patients receiving transfusions and chelation therapy would not be appropriate since patients with TDT receiving established clinical management do not spontaneously achieve transfusion independence or have significant reductions in their transfusion requirements. Consequently, the company utilised the before-and-after treatment dataset from the single-arm Zynteglo trials population. The ERG concurs with this approach for these transfusion outcomes.

For the remaining outcomes the company undertook systematic reviews to identify appropriate comparator datasets of TDT patients to evaluate:

- The clinical safety of iron chelation and transfusion therapies
- The impact of TDT and iron chelation and transfusion therapies on health-related quality of life
- How iron overload-related complication rates vary by iron levels

To obtain further comparator data the company also undertook an observational Chart Review study of UK TDT patients with the aim of describing: transfusion requirements, patient demographics and baseline clinical characteristics, routine management, clinical outcomes, quality of life and complications related to iron overload and iron chelation therapy.

Comparator data were therefore derived from a variety of sources, depending on the outcome in question. The relevance and usefulness of a given comparator study depends largely on how closely the cohort matches either the Zynteglo trial cohort, or an NHS cohort, in important factors which can affect outcomes – such as fitness for autologous HSCT transplantation and applicability of clinical management to current NHS practice, particularly with respect to chelation therapies and iron-overload monitoring. A critique of the identification of comparator data is in Section 4.3.

3.4 Outcomes

The outcomes specified in the CS matched the NICE scope outcomes with the exception of 'symptoms of anaemia'. Although the company stated this was covered in Table 1 of the CS the ERG could not find outcome data on symptoms of anaemia in the CS. Nevertheless, the ERG does not see this as an important issue since symptoms of anaemia are a consequence of low haemoglobin levels and both total haemoglobin levels and haemoglobin A (HbA^{T87Q}) levels were reported as outcomes in the CS. Only one small paragraph of the CS was used to describe growth and development outcomes. The ERG therefore requested more detailed results via a point for clarification (see Section 4.2.2.4). The primary efficacy outcomes of the single-arm Zynteglo trials varied, reflecting both the various stages of product development and the differing populations recruited (see Section 4.2.2).

4 Clinical Effectiveness

This section contains a critique of the methods of the systematic reviews of clinical effectiveness and safety data on Zynteglo and on comparators, followed by a description and critique of the included studies.

4.1 Critique of the methods of the Zynteglo review

The CS did not include a systematic review of Zynteglo studies as the company stated that this was not required since no Zynteglo studies had been conducted outside of bluebird bio. In a point for clarification (PfC) the ERG requested a systematic review of Zynteglo studies, which was subsequently provided. Separate reviews were also conducted to identify outcome data for patients receiving established clinical management (i.e. blood transfusions and chelation). These are discussed in Section 4.3).

4.1.1 Searches

Searches to identify studies of Zynteglo for the treatment of TDT were not provided in the original CS. In the points for clarification, the ERG requested that the company provide a systematic review to demonstrate that they had identified all studies of Zynteglo (Question A23, p20). The company provided a systematic literature search document containing details of the searches in Appendix G of their clarification response.

The company reported searches of the following databases on 13th November 2019: PubMed, Embase (Ovid) and the Cochrane Library (Ovid). Retrieval was limited to English language studies. In addition, the following conference websites were searched on 19th November 2019 to identify more recent conference abstracts not yet available via Embase: American Society of Hematology (ASH 2018, 2019), European Hematology Association (EHA 2019), British Blood Transfusion Society (BBTS), European Society for Blood and Marrow Transplantation (EBMT 2019) and the International Society of Blood Transfusion (ISBT 2018).

The database search strategies were clearly reported in Table 1 of Appendix G of the clarification response, with 67 studies found in total after deduplication. The terms used within the strategies for Zynteglo could potentially have been expanded to include title and abstract searches of bb305 and T87Q to ensure comprehensive retrieval of all relevant studies. Retrieval may also have been improved by searching for the specific trial codes (HGB-204, HGB-207, HGB-212) and the trial names (Northstar), particularly in EMBASE, to ensure that all relevant conference abstracts were retrieved. Indexing terms were not included in the search of PubMed and the Cochrane Library. This was most likely because both databases do not contain any specific indexing terms for Zynteglo yet. However, to ensure studies were not missed by the searches, it would have been appropriate to include some broader indexing terms for Zynteglo, such as genetic therapy, lentivirus, and beta-

globins and combine those with terms for thalassaemia. A similar approach could have been adopted for the search of Embase. Although the search of Embase included the indexing term lentiglobin bb305 this has only been available since 2017. Prior to this, broader indexing terms would have been used to index articles about Zynteglo, therefore it would have been beneficial to include some of the broader indexing terms in the strategy. The ERG ran a search in EMBASE (Ovid) including these additional terms detailed above, but did not identify and further relevant studies of Zynteglo.

The search for conference abstracts via conference websites was clearly reported in Table 2 (of Appendix G of the clarification response), detailing the specific URLs, search terms and results. However, the search of the BBTS website was missing from the table. Additional searches by the ERG identified 3 relevant conference abstracts.[3-5] These 3 conference abstracts do not appear to have been identified by the searches provided by the company.

A search of trial registers was not reported in the systematic literature search document, therefore it was not clear to the ERG that all ongoing or completed but not yet published trials of Zynteglo for beta thalassaemia had been identified. The ERG carried out searches of ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform and the EU Trials Register to identify any trial register records of Zynteglo for beta-thalassaemia. The ERG searches were carried out on 18th October 2019 and retrieved 75 records: no previously unidentified trials were found.

4.1.2 Inclusion criteria

The Zynteglo review eligibility criteria were presented in Appendix G (Table 3) of the company's response to the ERG's points for clarification. These were suitably broad to allow identification of relevant studies. Appropriate screening methods were reported as being used for minimising the possibility of reviewer errors and biases affecting the final list of studies included.

4.1.3 Critique of data extraction

As mentioned in Section 4.1 the company did not initially undertake a systematic review of Zynteglo studies. The review document (Appendix G of CS) provided by the company as a response to an ERG point of clarification only went as far as the study selection phase, and did not include data extraction tables.

4.1.4 Quality assessment

The company presented the results of quality assessment for Zynteglo trials HGB-204, HGB-205 and HGB-207 as Tables 1-3 in Appendix D of the company submission. No quality assessment was provided for the ongoing study HGB-212, which is at an earlier stage than the ongoing HGB-207 study. The company did not indicate which tool had been used for quality assessment, but the ERG identified it as a modified version of the GATE framework[6] which is recommended by NICE for evaluating studies of public health interventions.[7] The methods of quality appraisal were not

described, including what the symbols represented in the "response" column of the CS Appendix D tables. To provide clarity when interpreting the company's quality assessment results the ERG looked into how the GATE framework is used. The appraisal checklist consisted of items categorised into five sections: section 1 attempts to assess external validity, whereas sections 2-4 aim to assess internal validity. Each item was assigned one of the five possible responses described in Table 2 and the reasoning behind the decision was explained in the corresponding "comments" column. In the final section, each study was awarded a grade for the overall quality with respect to the internal and external validity individually. The validity grades are described in Table 3.

Table 2 List of possible responses for the NICE quality appraisal checklist

Response	Description
++	Indicates that for that particular aspect of the study design, the study has been designed or conducted in such a way as to minimise the risk of bias.
+	Indicates that either the answer to the checklist question is not clear from the way the study is reported, or that the study may not have addressed all potential sources of bias for that particular aspect of study design.
-	Should be reserved for those aspects of the study design in which significant sources or bias may persist.
Not reported (NR)	Should be reserved for those aspects in which the study under review fails to report how they have (or might have) been considered.
Not applicable (NA)	Should be reserved for those study design aspects that are not applicable given the study design under review (for example, allocation concealment would not be applicable for case control studies).

Table 3 Description of overall study quality grading for validity

Response	Description
++	All or most of the checklist criteria have been fulfilled where they have not been fulfilled the conclusions are very unlikely to alter.
+	Some of the checklist criteria have been fulfilled, where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter
-	Few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

Overall, the results of the quality assessment were not very informative or particularly well-reported. Details about the quality assessment process, such as how many researchers were involved and whether their appraisals were conducted independently, were not provided. Additionally, many items on the checklist were assigned a response without providing sufficient explanation to justify the decision. This lack of transparency in reporting the quality appraisal process means the possibility of errors or bias affecting the assessments cannot be ruled out. Some obvious inconsistencies were identified in the appraisal results. Firstly, the heading for 'Section 2' in all three appraisals was

assigned a quality assessment response. Secondly, identical explanations in the comments section were assigned different responses across studies. For instance, when asked in item 1.2 whether the eligible population was representative of the source population, the comment for all three studies was "Yes, the criteria set represent TDT patients". For studies HGB-204 and HGB-207, this item was given a response of '++', whereas for HGB-205 was given '+'. Similar inconsistencies also occurred in items 1.3, 3.4, 4.2, and 4.4.

There are no tools specifically to assess the quality of single-arm studies. The checklist used by the company is not strictly appropriate either, as many of the items were deemed 'not applicable' for all three studies. Although section 1 of the checklist assesses the external validity of the study population, the information provided was quite basic and did not describe how representative the study population would be to the eligible NHS population (e.g. in terms of genotypic and ethnicity distributions) or which effect modifiers/confounders may potentially be important.

4.1.5 Evidence synthesis of Zynteglo studies

The company stated that 31 articles were included "for qualitative synthesis" in their Zynteglo systematic review (Appendix G of the clarification response). However, no such synthesis of these articles was presented. This is likely a consequence of the company not initially undertaking a systematic review of Zynteglo studies. The CS synthesis instead focussed on the trials HGB-204, HGB-205 and HGB-207. No references were made to conference abstracts on study HGB-212.

The CS did not present a description nor a rationale regarding how data from the three Zynteglo trials were synthesised. Data from the three studies were pooled directly, without adjustment. Given that the included studies all had single-arms and small sample sizes the ERG can understand why this approach was adopted. However, the ERG believes that the issue of population and intervention heterogeneity across trials should have been considered and its possible impact discussed (see Section 4.2 of this report).

The CS reported that the individual trials were analysed according to:

- Intention-to-Treat (ITT) Population datasets i.e. all subjects who initiated any study procedures, beginning with mobilisation, and
- Transplant Population (TP) datasets i.e. all subjects who received Zynteglo treatment

The CS added that the ITT population was the primary population for the analysis of safety parameters and the TP was the primary population for the analysis of efficacy and pharmacodynamic parameters. The ERG requested ITT data on the flow of participants from screening to receipt of Zynteglo, including any reasons for withdrawal. The ERG noted that the safety dataset appears to use a different definition of ITT as it includes patients who signed informed consent forms but were yet to

begin the cell mobilisation stage. The ERG considers this to be the true ITT dataset i.e. all patients who signed informed consent to be included in the study.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Overview of the Zynteglo trials

The submission referred to two phase 1/2 Zynteglo trials in patients with any genotype (HGB-204, aka 'Northstar' and HGB-205), one ongoing phase 3 trial in patients specifically with non-β^0/β^0 genotypes (HGB-207, aka 'Northstar-2'), and one ongoing phase 3 trial in patients with "both non-β^0/β^0 and β^0/β^0" genotypes (HGB-212, aka 'Northstar-3'). All the studies were single-arm, open-label trials and are broadly summarised in Table 4 (adapted from Table 8 of the CS). Patients from these trials were followed up long-term in a separate study (LTF-303).

Study HGB-212 is the most recently initiated study in the Zynteglo trials programme but very limited study details were presented in the CS. The ERG requested further methods details on study HGB-212 via a point of clarification request. These were provided (see Table 4), with the company adding that the "data was not yet mature to provide meaningful results" for use in the submission. This seems an inconsistent approach as the company did report some immature results for ongoing study HGB-207 (p89, CS). The ERG also notes that two conference abstracts exist which report interim results for HGB-212.[3, 4] The most recent abstract indicated that, so far four patients had been recruited who had severe non-β^0/β^0 genotypes: two β^0/IVS-I-110, and two homozygous IVS-I-110.[4] The ERG believes that early efficacy data for these patients may help to resolve some of the uncertainty about the efficacy of Zynteglo in patients with severe non-β^0/β^0 genotypes.

The company stated (in Table 1 of their PfC response) that the HGB-212 study population was of TDT patients of "any genotype". When the ERG examined the relevant clinicaltrials.gov record and conference abstracts (one identified in the company's systematic review[4] and one identified by the ERG[3]) it appears that this study was, more specifically, of patients with "either a β^0 or IVS-I-110 mutation at both alleles".[3, 4] However, on the clinicaltrials.gov record, the exclusion criterion which relates to genotype reads: "Presence of a mutation characterized as other than β^0 (e.g., β^+, β^E, β^C)". It appears therefore that in study HGB-212 an IVS-I-110 mutation was deemed "equivalent to a β^0 mutation", as was the case in study HGB-207. However, given that "*certain β^+ genotypes such as the IVS-I-110 and IVS-I-5 mutations are associated with dramatically reduced β-globin production behaving phenoptypically as a β^0 genotype despite being grouped non-β^0/β^0 genotypes*" (CS, p19) it is unclear why IVS-I-5 mutations were not also specified as being eligible for study HGB-212.

The CS reported basic baseline data in terms of the race of patients included in the Zynteglo trials: [redacted] Asian, [redacted] white and [redacted] other (Table 18, p75 of CS). In the UK the largest group of patients with thalassaemia are those of Pakistani ethnicity and around 10-15% of patients are white.[8] Patients

in the Zynteglo trials were recruited in: Australia, France and the US in HGB-204; France in HGB-205 and Germany, France, Greece, Italy, Thailand, the UK and the US in HGB-207. The table of baseline characteristics presented in the CS was limited in allowing comparison of characteristics across studies because it also included data from six patients aged <12 years (from study HGB-207) who are not covered by the marketing authorisation. Also, no data were presented on the different genotypes across studies. In a point for clarification the ERG requested genotype data. The company stated that the genotypes included in the submission for the ITT population were: 6 β^{+}/β^{+} subjects (of which [redacted] are IVS-I-110), 15 βE/β0 subjects and 10 β^{0}/β^{+} subjects. The proportions of β^{E}/β^{0} and β^{0}/β^{+} patients [redacted]. The clinical implications of this are uncertain, although the CS baseline characteristics table suggested that [redacted] (though this was not a statistically significant difference).

Another source of heterogeneity across studies is the Zynteglo manufacturing process, which has changed over time. [redacted] due to "inherent subject-to-subject variability in transduction efficiency of HSCs". Ultimately, the changes in manufacturing processes were driven by a desire to [redacted].[9] This again highlights the importance of considering severity of genotype as an important subgroup. This has the potential to introduce heterogeneity of results across trials – with severe genotype response rates possibly varying depending on the manufacturing process used. Similarly, the ERG notes the dose difference between the early trials (≥3 x 10^{6} CD34+ cells/kg in HGB-204 and HGB-205) and later trials (≥5 x 10^{6} CD34+ cells/kg in HGB-207 and HGB-212) which may also be a source of heterogeneity of effect. On p189 of the CS it was reported that in the clinical studies, [redacted] of patients underwent one additional cycle of mobilisation and apheresis and [redacted] underwent a total of three cycles, in order to obtain more cells for additional manufacture.

Table 4 Overview of the Zynteglo trials (adapted from Table 8, CS)

Study, status, manufacturing process	**Population eligibility criteria, dose, and planned n (actual n for completed studies)**	**Primary endpoint(s)**
HGB-204 (Northstar) Completed February 2018 [redacted]	TDT (any genotype) Age ≥18 to ≤35 years Dose: ≥3 x 10^6 CD34+ cells/kg n=18 (10 non-β^0/β^0 genotype and 8 β^0/β^0 genotype)	**Safety:** Success and kinetics of engraftment, survival, incidence of AEs, monitoring for RCL, and insertional mutagenesis leading to clonal dominance or leukemia **Efficacy:** Proportion of patients with sustained production ≥2.0 g/dL HbA containing HbA^{T87Q} for the 6 months between months 18 and 24 post-transplant
HGB-205 Completed February 2019 [redacted]	TDT (any genotype) or severe SCD Age ≥5 to ≤35 years Dose: ≥3 x 10^6 CD34+ cells/kg n=7 (4 non-β^0/β^0 genotype TDT patients and 3 severe sickle cell disease)	**Safety:** success and kinetics of engraftment, survival, incidence of AEs, monitoring for RCL and insertional oncogenesis leading to clonal dominance or leukemia **Efficacy (TDT):** RBC transfusion requirements post-transplant; in-patient hospitalisation days (post-transplant discharge)
HGB-207 (Northstar-2) Ongoing [redacted]	TDT, non-β^0/β^0 genotype Age ≤50 years Dose: ≥5 x 10^6 CD34+ cells/kg n=15 (all belong to non-β^0/β^0 genotype)	**Efficacy:** Proportion of patients achieving transfusion independence (TI).
HGB-212 (Northstar-3) **Ongoing** [redacted]	TDT patients with "either a β0 or IVS-I-110 mutation at both alleles" Age ≤50 years Dose: ≥5 x 10^6 CD34+ cells/kg n=14 (5 non-β^0/β^0 and 9 β^0/β^0 genotype TDT patients)	**Efficacy: Proportion of patients achieving transfusion reduction, defined as demonstration of a ≥60% reduction in the annualised volume of packed red blood cells transfusion requirements (in mL/kg) in the post-treatment time period from 12 months post-drug product infusion through Month 24 (approximately a 12-month period), compared to the annualized mL/kg pRBC transfusion requirement during the 2 years prior to study enrollment.**
LTF-303 Ongoing	TDT: long-term follow up of patients in the above studies	Long-term safety and efficacy

4.2.2 Summary of the pooled dataset effectiveness results

The CS reported that the data presented related to a data-cut of June 2019, although this was contradicted in Table 21 of the CS, which stated that the data from HGB-207 were from an interim analysis dated 22nd February 2018. Results from p89 of the CS indicated that the June 2019 data were used for the primary endpoint (transfusion independence).

4.2.2.1 Transfusion and haemoglobin outcomes

The primary outcome was stated as the proportion of patients achieving transfusion independence. This was defined as a weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months at any time during the study after Zynteglo transfusion. Twenty-four patients were classed as being "TI-evaluable" (i.e. patients who had either completed their parent study, or achieved TI, or won't achieve TI due to insufficient remaining follow up time). For the transplant population the rate of TI was 83% (20/24 patients). No results were presented for the ITT population. The ERG estimates this as [redacted]. For the 20 TI patients, no events for 'loss of TI' have been recorded so far.

[redacted]

[redacted]

Genotype heterogeneity in TI response

In light of the possibility of a heterogeneity of response based on genotype (see Section 4.2.1), the ERG requested transfusion independence and transfusion reduction results data for all patients with IVS-I-110 or IVS-I-5 mutations via a PfC. The ERG cross-referenced the company's response with data in the respective trial clinical study reports (CSRs) and in the CS. The aim was to collate the outcomes on all patients with severe non-β^0/β^0 genotypes. The company's response to the PfC identified different IVS-I-110 or IVS-I-5 patients from those previously identified by the company in their submission and from the patients identified by the ERG from the CSRs. The differences are documented in Table 5 and indicate the CSRs and the CS as being the best sources of data to investigate Zynteglo's efficacy in severe non-β^0/β^0 genotypes.

Table 5 Patients in Zynteglo studies with an IVS-I-5 or IVS-I-110 mutation

Study	Data from CSR or CS	Data from PFC response	Conclusion
HGB-204	[redacted]	[redacted]	Use CSR data
HGB-205	[redacted]	[redacted]	Use CSR data
HGB-207	[redacted]	[redacted]	Use CSR data – patients with severe non-β^0/β^0 genotypes which incorporated IVS-I-110 were excluded from HGB-207

Of the [redacted] patients identified in Table 5 as having severe non-β^0/β^0 genotypes – i.e. homozygous for IVS-I-110 or IVS-I-5, or heterozygous for IVS-I-110 or IVS-I-5 together with a β^0 mutation – [redacted]. An initial reading of these data suggests that the likelihood of achieving TI in patients with severe non-β^0/β^0 genotypes [redacted] to that for patients with β^0/β^0

genotypes i.e. [redacted]. For comparison, Study HGB-204 included 8 patients with β^0/β^0 genotypes (these patients are not included in the marketing authorisation). [redacted].[10]

However, the changes in the manufacturing processes, and doses, across the trials (discussed previously in Section 4.2.1) should also be considered with respect to efficacy. The CS points out (p89) the importance of the combination of transgene expression (i.e. Zynteglo-derived β-globin) and endogenous β-globin production in determining the probability of achieving TI, and that high levels of gene-derived haemoglobin production are needed to achieve TI (p170). [redacted], although study HGB-207 is still ongoing and is recruiting a more selective population than HGB-204. Nevertheless, this suggests that Zynteglo [redacted].

The TI response of the two IVS-I-5 patients with severe non-β^0/β^0 genotypes in study HGB-207 is encouraging, although patients with severe IVS-I-110 genotypes are excluded from this study. Therefore, the uncertainty surrounding the proportion of patients likely to achieve TI in the important subgroup of severe non-β^0/β^0 genotypes will only be clarified by results from the ongoing study HGB-212 (and further results from HGB-207). However, it is unclear whether IVS-I-5 patients are eligible for study HGB-212 so the number of patients recruited with severe non-β^0/β^0 genotypes may be small. The severe non-β^0/β^0 genotype subgroup appears likely to be important as taken together, the IVS-I-5 (in particular) and the IVS-I-110 alleles are quite common in the TDT UK population (see Section 3.1). With these issues in mind it is also worth noting that the primary outcome of study HGB-212 is transfusion reduction (in HGB-207 it was transfusion independence) suggesting lower expectations of a TI response in patients with more severe genotypes.

New data from studies HGB-207 and HGB-212 may also be complicated by the fact that the results from some patients may be affected by [redacted]

[redacted]. The CS stated (on p52) that the EMA conditional marketing authorisation decision included an approved commercial manufacturing process that "increased the acceptable range of transduction parameters compared to those used for the majority of subjects within studies HGB-207 and HGB-212".

[redacted]. The company has therefore proposed to the EMA that

[redacted].

Figures 22 and 23 of the CS indicate

[redacted]. Beyond this time point the patient numbers are very limited so there is some uncertainty about the longevity of transduced HSC engraftment in bone marrow and subsequent expression of HbA^{T87Q}.

4.2.2.2 Post-Zynteglo Iron levels

The company assumed an iron normalisation period of 4 years, following treatment with Zynteglo. However, results from section B.2.6.4 of the CS indicated this to be a simplistic assumption with wide variation in results across the small number of TI patients who had results at the 4-year timepoint. Data on iron levels are only available for a limited number of patients, as they have not yet been analysed for HGB-207. For example, some patients had an increase in liver iron content (Table 31, CS)[redacted] when compared with baseline levels. Table 33 in the CS shows that serum ferritin levels at 4 years were still clinically significantly high in some patients; the mean serum ferritin level was 1437ng/ml and the median 937 ng/ml for the 7 patients with available data. The company also stated that, out of the 11 non-β^0/β^0 patients that have achieved TI from Studies HGB-204 and HGB-205, all continued to have "normal" cardiac T2* values at their last follow-up, and maintain cardiac T2* values well above 20 msec (p105, CS). However, the company describe a cut-off of "normal" cardiac T2* of 40 msec, which only [redacted] patient appeared to achieve, and the lower limit of cardiac T2* was not significantly above 20 msecs, at [redacted] at 48 months. Post-transplant chelation guidelines were provided in the study protocol. However, resumption of iron chelation therapy was done at the investigator's discretion and in accordance with institutional protocols so there will have been variation in the timings and intensities of chelation.

4.2.2.3 Health-related quality of life

The Zynteglo health-related quality of life (HRQoL) data reported in the CS were limited because several patients from studies HGB-204 and HGB-205 did not have baseline measurements. The HRQoL tools used within and between trials varied widely, with the following being used: EQ-5D-3L, EQ-5D-Y, SF-36v2, PedsQL, and FACT-BMT. For adults with baseline HRQoL measurements, the CS noted a general trend of [redacted]. The company concluded that the EQ-5D data collected in the Zynteglo trials may not accurately reflect the HRQoL of patients treated with Zynteglo. Later in the submission (p182) the company discussed the problematic issues of ceiling effects and adaptation bias when evaluating HRQoL in patients with β-thalassemia. These also [redacted] from the results of the UK patient (and caregivers) preference study the company undertook, which suggested that TDT patient uptake of Zynteglo treatment would be somewhat limited. The study was an online survey of [redacted] TDT patients and [redacted] caregivers (total n=[redacted]), [redacted] of which had been living with beta-thalassaemia for [redacted] years or more. Of the [redacted] survey responders only [redacted] of patients agreed with the statement "Beta thalassaemia significantly impacts my quality of life" and only [redacted] indicated they would immediately accept a referral (to see a transplant specialist) and accept Zynteglo, were it offered.

4.2.2.4 Growth & Development

The company's results on growth and development outcomes in patients aged <18 years were restricted to one short descriptive paragraph (p113) so the ERG requested data on the growth and development endpoints detailed on p72 of the CS. [redacted] subjects underwent Tanner staging at screening: [redacted] males ranging from 8 to 15 years of age, and [redacted] females ranging from 5 to 17 years of age. [redacted] subjects were considered pre-pubertal at the time of Zynteglo Infusion: [redacted] males and [redacted] female. [redacted] subjects ([redacted]) were undergoing puberty, and one was post-pubertal at the time of drug product infusion. The other [redacted] subjects who underwent Tanner staging did not have data for the screening visit. For the [redacted] subjects with data after screening, [redacted] showed a [redacted] over time, with the exception of [redacted] who was already post-pubertal at the time of screening. Of note, a [redacted], was assessed as Stage II/I pubic hair/genitalia at screening, then assessed as Stage I/I pubic hair/genitalia at Month 6 but had [redacted] to Stage III/III pubic hair/genitalia by Month 18.

4.2.3 Adverse Events

Reporting clarity by company

At the FAC stage, the company acknowledged inconsistencies in the CS and PFC response regarding the population included in the safety assessment. Some confusion whether the AEs reported were exhaustive remains, due to differences in cut-off points used for ongoing studies and the lack of a CSR for HGB-212. A systematic review requested by the ERG via a PFC question referenced a

conference abstract reporting interim results of study HGB-212,[4] which gave an overview of AEs observed up to April 2019. One patient, genotype not reported, experienced congestive heart failure where the left ventricle ejection fraction fell. This was associated with the worsening of cardiac iron pre-engraftment. No further information was provided for this patient either to recommend inclusion or exclusion in AEs or to detail the patient's condition. The ERG considered it likely that this patient had a β^0/β^0 genotype, as the company excluded β^0/β^0 patients from the intention-to-treat (ITT) population. However, the ERG questions the rationale to include only non-β^0/β^0 patients for safety assessments, since in HGB-207 a severe non-β^0 allele (IVS-I-110, in particular) was considered equivalent to a β^0 mutation, which is a relationship that would apply in both directions.

Adverse Event data

Adverse event data were reported on pages 114-143 of the CS. Adverse events (AE) were assessed in the ITT population of 35 patients with non- β^0/β^0 genotypes aged ≥ 12 years from studies HGB-204 (n=11), HGB-205 (n=4) and HGB-207 (n=16) and HGB-212 (n=4). TDT patients with the β^0/β^0 genotype in HGB-204 were excluded by the company from the safety data as they were not part of the population of interest.

In Table 37 of the submission, the company reported the incidence of all AEs categorised by system organ class and pre-decided intervals in the treatment period. AEs have not been reported for all 35 patients in some of the later time intervals since not all patients in the ongoing HGB-207 and HGB-212 studies had progressed to these later stages.

[redacted] of all patients experienced at least one AE and [redacted] experienced at least one serious adverse event (SAE); [redacted] reported as being Zynteglo related.

[redacted] The fewest

[redacted] reported after 24 months post Zynteglo infusion. In addition to standard safety outcomes, patients were monitored for any sign of AEs caused by gene therapy using the BB305 vector.

Safety of the BB305 lentiviral vector

There were no safety issues related to the BB305 LVV in HGB-204, HGB-205 or HGB-207.[11, 12] The company did not mention HGB-212 in the relevant section of the CS. There was no evidence of clonal dominance (which indicates whether the insertion of a therapeutic gene could be a precursor to a haematological malignancy). No malignancies related to LVV were reported, including leukaemia or

lymphoma where the longest follow-up was 61.3 months after drug infusion. One patient who received Zynteglo experienced an occurrence of HIV-1 infection, but this was later confirmed to be wild-type HIV-1 and not due to lentiviral vector (LVV) recombination.

Engraftment and transplant-related complications

Engraftment of the gene-modified autologous cells was successful in all patients treated with Zynteglo across all the clinical trials up to the latest follow-up at 61.3 months.[11, 13, 14] There were no incidents of transplant-related mortality, graft rejection or GvHD.[14, 15]

Mobilisation and apheresis

Most AEs attributed to mobilisation and apheresis in TDT patients occurred [redacted]. AEs attributed to mobilisation and apheresis were summarised in Table 38 (pp 128-129) of the CS. Most were non-serious events: [redacted]. [redacted] serious adverse events (SAEs) were attributed to mobilisation and apheresis, an event each of: [redacted]

Conditioning

AEs attributed to busulfan conditioning that occur in at least 3 patients were summarised in Table 39 (pp 131-134) of the CS. Most events were not serious and expected from treatment with an alkylating agent such as busulfan, according to the prescribing information including [redacted].[16] Some observed AEs that were not part of the prescribing information were: [redacted] have been documented as potential side effects of busulfan. According to the latest data available, [redacted] patients reported at least one AE attributed to conditioning where [redacted]

Adverse events by ≥ Grade 3 severity

The incidence of all ≥ Grade 3 AEs were summarised in Table 40 (pp 137-139) of the CS. [redacted] experienced at least 1 AE ≥ Grade 3. [redacted]

[redacted]

There [redacted] drug-product related Grade 3 SAE in [redacted].

[redacted]

Serious adverse events (SAEs)

The incidence of all SAEs in TDT patients was presented in Table 41 (pp 141-142) of the CS. The overall survival was 100% and no transplant-related mortality was observed. Approximately [redacted] of the patients experienced an SAE,

[redacted] was deemed Zynteglo-related. [redacted] experienced SAEs prior to neutrophil engraftment which were attributed to study procedures, mobilisation, apheresis, or reasons unknown.

[redacted] which were all resolved

[redacted]. There were

[redacted]. In addition to the

[redacted] All cases were resolved with defibrotide.

[redacted]

4.2.4 Summary

Observations on how the Zynteglo trial programme has evolved – such as study variation in production processes, doses, eligibility criteria, primary outcomes, and results – suggests an ongoing drive to improve transfusion independence response rates. While most patients appear to respond well to Zynteglo, some patients, in particular those with a genotype deemed very similar or equivalent to a β^0/β^0 genotype (i.e. "severe" non-β^0/β^0 genotypes, who are covered by the marketing authorisation) and patients with a β^0/β^0 genotype (who are not covered by the marketing authorisation) tend not to

respond as well as other genotypes. [redacted] may increase the probability of achieving TI in patients with severe non-β^0/β^0 genotypes (compared to [redacted]) but only results from ongoing study HGB-212 and further data from the ongoing HGB-207 study can help to resolve this uncertainty. The company did not submit results for HGB-212, stating that the data were too immature, but the ERG considers that initial results on total Hb levels, HbA^{T87Q} levels and number and frequency of transfusions, for each of the non-β^0/β^0 patients would nevertheless be useful and could be submitted at the technical engagement stage of the appraisal.

The ethnicity distribution of the Zynteglo trial population is not a particularly good representation of the UK TDT population. The main implication of this is the possibility that the proportion of patients with severe non-β^0/β^0 genotypes in the trials is not representative of the UK setting. This was exacerbated in one trial by an eligibility criterion which excluded patients with a specific severe non-β^0/β^0 genotype. The longest follow up period for an individual patient is 5 years. Consequently, there is uncertainty about whether Zynteglo confers benefit to patients in the much longer term i.e. whether it truly is a curative therapy. It is possible that the transformed cells may not persist long-term. This may mean that some patients revert to needing regular transfusions long after they have achieved transfusion independence. Such future outcomes could also open the possibility of re-treatment with Zynteglo, although re-treatment is not currently part of the license. Zynteglo appears to have an acceptable safety profile in the short-term, though uncertainty exists about its long-term safety.

4.3 Critique of the systematic reviews for comparator data and Zynteglo proxy data

Only single-arm data were available on the effectiveness and safety of Zynteglo. Therefore, to compare the outcomes of patients receiving Zynteglo with those receiving transfusions and chelation therapy (in the economic model) the company undertook several systematic reviews to identify appropriate comparator datasets of TDT patients to evaluate:

- The clinical safety of iron chelation and transfusion therapies
- How iron overload-related complication rates vary by iron levels

The company provided the 120-page systematic review as a supplementary document (EVA-20726-04).[17]

To obtain further comparator data the company also undertook a "Chart Review" observational study of UK TDT patients with the aim of describing:

- Transfusion requirements,
- Patient demographics and baseline clinical characteristics,
- Routine management,
- Clinical outcomes,
- Complications related to iron overload and iron chelation therapy,
- Impact of TDT on quality of life.

This study was submitted by the company as a draft manuscript.[18]

4.3.1 Searches for comparator studies

The company conducted two searches for evidence on the following:

- What is the clinical safety of iron chelation and transfusion therapies in patients with TDT,
- How do iron overload-related complication rates vary by iron levels in TDT in Europe.

The searches for the above reviews were included in the 2018 report by Evidera in Section 3.1, p. 14-15.[19] These searches were updated in 2019 and included in the 2019 report by Evidera, with a description of the searches on p5 and full search strategies contained in Appendix D, p111-115.[17]

The following databases were searched in May 2017: MEDLINE (via PubMed.com and Embase.com) and Embase (via Embase.com). Retrieval was limited to English language studies with an abstract, published from 2007 to 31st December 2017. The searches of MEDLINE and Embase were updated in April 2019 along with a search of CENTRAL via the Cochrane Library (searched from 2007 to 1st April 2019).

Specific conferences taking place from 2015 onwards were searched via Embase.com to identify relevant conference abstracts or posters: American Society of Hematology (ASH), European Hematology Association (EHA), British Blood Transfusion Society (BBTS), European Society for Blood and Marrow Transplantation (EBMT) and the International Society of Blood Transfusion. In addition, the following online conference websites were searched: ASH (2018), EHA (2018) and the International Society of Blood Transfusion (2018). Further unpublished studies were identified through searches of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform.

The databases and other sources searched were appropriate to locate both published and unpublished studies of comparator treatments (iron chelation and transfusion therapies), and iron overload-related complications in patients with TDT. However, the Cochrane Database of Systematic Reviews (CDSR) is missing from Table D.1. Data Sources (p111. Appendix D, 2019 Evidera report) although it does appear to have been searched (Table D.6, p114, 2019 Evidera report). The results from CDSR could have identified any Cochrane Reviews relevant for SLRs 1 and 2.

The search strategies for all databases (MEDLINE, Embase, and the Cochrane Library) were structured appropriately using terms for thalassaemia combined with terms for either transfusion or iron chelation therapies. The term 'thalassemia major' has been included within the intervention terms in most of the database search strategies. This appears to be a mistake, though it would not have caused relevant studies to be missed. A lack of truncation was noted throughout all database strategies for some search terms – thalassemia and thalassaemia, anemia and anaemia. These terms could have been truncated as follows: thalassemi$, thalassaemi$, anemi$, anaemi$, to allow maximal retrieval of relevant records that use the same word stem in the title and abstract but have different endings eg: thalassaemic, thalassaemias, anaemic, anaemias etc.

Subject headings for iron chelation therapies and blood transfusion were missing from the MEDLINE, Embase and Cochrane Library search strategies. It is usual practice for systematic review searches to include both text word searches of the title and abstract fields as well as relevant subject headings to ensure all relevant studies are retrieved.

The search strategies for EMBASE were limited by publication type to records that have been assigned as articles or articles in press e.g. line #7, Table 2, p. 15 in the 2018 report by Evidera.[19] This may have omitted errata or corrections to published articles as well as other publication types such as book chapters, short surveys, reviews and conference papers.

Some minor reporting errors were found by the ERG relating to the searches. The PRISMA flow diagram (Figure 1, p. 9, 2019 report by Evidera), had typing errors in the first box – the 2017 searches

of PubMed retrieved 2398 results and the 2017 searches of Embase retrieved 2372 results.[17] The flow diagram was also missing the search results obtained from the Cochrane Library.

4.3.2 Selection of comparator studies

The eligibility criteria for the systematic reviews of comparator studies were presented in Table 1 of the separate systematic review document.[17] The screening methods used were appropriate for minimising the possibility of reviewer errors and biases affecting the final list of included studies. The eligibility criteria appeared broadly appropriate, although it appeared that systematic reviews were not eligible, which seems like an oversight. Moreover, the selection approach when several studies were identified was not reported, and little was presented in terms of a synthesis. The ERG considers that the validity of some of the comparator data is uncertain, as the justification for selecting specific studies from these review for use in the CS was often not presented.

4.3.3 Quality assessment of comparator studies

The quality of the single-arm studies in isolation is only one aspect of the critical appraisal of the clinical evidence submitted by the company. The appropriateness and relevance of the comparator studies which were used in the model should also be justified, but this was not included in the systematic literature review (SLR).[17, 19] The quality of some of the included studies was assessed using the Cochrane Risk of Bias Tool 2.0,[20] though no explanations were provided for the decisions made regarding bias judgements.[17] The review and the submission did not discuss how the characteristics of comparator study populations compared with the corresponding Zynteglo trials cohort, so it was not easy to evaluate the level of appropriateness of the comparator studies selected. This was particularly important for studies which reported outcomes likely to be affected by the way chelation therapy was managed. Similarly, external validity was largely overlooked for comparators studies i.e. generally, there was a lack of consideration and discussion about whether interventions and populations were adequately representative the TDT population in the UK.

4.3.4 Results

Mortality

Cardiac iron overload is the major cause of death in β-thalassaemia. The company's systematic review found cardiac-related mortality to be reported in 18 studies[17] though the CS added that no studies reported mortality based on the presence or absence of cardiac complications. The CS stated that two economic studies 'identified in the literature' reported cardiac and non-cardiac mortality. It is unclear how these studies were identified as they were not mentioned in the systematic review.[17] For transfusion-dependent patients without cardiac disease, a standardised mortality ratio (SMR) of 3.9 was used based on a paper published in 1996 which was referenced and used in a 2007 economic study.[21] The ERG considers the 1996 paper[22] to be an obsolete reference in terms of its relevance to current NHS practice because subcutaneous chelation was used, whereas the introduction of oral iron

chelators (deferiprone and deferasirox) in recent years has led to improvements in mortality rates in β-thalassaemia patients. Subcutaneous chelation has been found to be associated with poorer compliance than oral chelators[21] and improved compliance of chelation therapy has been found to be associated with the avoidance of complications associated with iron overload and subsequently survival and quality of life may approach a normal pattern. Some evidence exists showing that oral chelators have a protective effect on the heart compared with subcutaneous chelation.[23, 24]

In the model, patients who acquire cardiac disease were assumed to have an annual mortality rate of 13%. This was based on a study of 52 patients with β-thalassemia and heart failure who were treated in the mid-to-late 1990s.[25] This study is also not reflective of current UK practice and is therefore outdated. It is likely to overestimate cardiac mortality, based on recent evidence.[26] This is because of the impact of both the aforementioned introduction of oral chelation therapies and the introduction (in 1999 in the UK) of T2* cardiovascular magnetic resonance (CMR) for identifying myocardial siderosis. T2* CMR was applied rapidly in clinical management from 2000 as the benefits of direct visualisation of cardiac siderosis as a guide to the need for intensified iron chelation therapy, and a means of assessing response became clear.[27] The ERG's clinical adviser also stated that patients picked up as having an iron problem via T2* CMR would subsequently be managed by a cardiologist, which should improve their cardiac outcomes. The company's own review also reported that "adults aged 20 to 40 years old between 2000 and 2009 had a lower risk of cardiac mortality compared to similar adults in 1990 to 1999".[17] An assumed SMR of 1.25 was used to model for transfusion independent patients. This was based on the potential impact of myeloablative conditioning chemotherapy. In summary, the model inputs for mortality risk in patients who are transfusion-dependent is likely to have been overestimated and the risk in patients who achieve TI is uncertain since there is little robust evidence to support it.

Iron overload in TDT patients

In the company's systematic review 56 publications were identified which evaluated the burden of illness of iron overload in TDT.[17]

Cardiac complications of iron overload

The CS stated that 17 studies were identified which reported clinical measurements and outcomes relating to cardiac disease. A study by Pepe et al was used to inform annual rates of complications based on it having a large sample size (n=481), a good duration of follow-up (mean of 58 months), and the explicit provision of hazard ratios by myocardial T2*.[28] The ERG considers this to be a reasonable source of data to use, although notes that the study was conducted in a white population. There is therefore some uncertainty about the applicability of its results to a UK TDT population since in the UK only around 10-15% of TDT patients are white.[8].

Liver complications of iron overload

The CS stated that 18 studies of liver-related complications were identified, but none provided relationships between liver iron levels and complication rates. Therefore, a further 'targeted literature review' was conducted but no further details were given about this. The study selected was published in 2002 and was acknowledged in the CS as being outdated, though it did give separate results for patients with or without hepatitis C.[29] Given the previously discussed improvements in TDT patient care since 2002, the data from this study are likely to overestimate the rate of liver complications for patients with high iron levels. However, in addition to reporting by iron levels, the study reported liver complications by presence of hepatitis C infection. Many liver complications developed in patients in the past are a result of hepatitis C infections from historical blood transfusions carrying the virus. The use of these data was thought to mitigate the fact that this study is somewhat outdated, since it can be assumed that future rates of liver complications will be closer to those of patients without hepatitis C virus due to current blood donation screening practices. The study found that HCV negative patients with low or moderate iron levels remained fibrosis progression-free, but HCV negative patients with high iron had a median time to fibrosis progression of 100 days.

Other complications of iron overload

One study was used to predict diabetes and hypogonadism in adults using myocardial and serum iron levels.[30] The study was retrospective with case note and electronic data collated for the period 1999 to 2010. It reported a diabetes prevalence rate of 41% and a 67% rate for hypogonadism. These are notably higher than the rates reported in the company's Chart Review of UK patients (see Section 4.3.5).

Adverse events of chelation therapies

Although the company undertook a systematic review of the safety of iron chelation therapies it did not use the results to inform Table 51 of the CS which presented the probability of adverse events with iron chelation therapy. Instead, data were used from the prescribing information for deferasirox[31] and deferiprone[32] and from a Cochrane review for desferrioxamine.[33] The CS did not state why it did not use data from its own systematic review of adverse events and instead used alternative sources, including the Cochrane review (reviews appeared to be excluded from the company's systematic review, SLR 1).

4.3.5 Observational 'Chart Review' of UK TDT patients

The manufacturer also conducted and submitted a report of an observational study to understand the current real-world routine management of patients with TDT in the UK.[18] It aimed to describe: transfusion requirements, patient demographics and baseline clinical characteristics, routine management, clinical outcomes, impact of TDT on quality of life and complications related to iron overload and iron chelation therapy.

The study included 165 patients, a third of which were over 40 years old, whereas the oldest patient treated with Zynteglo in the trials was 34 years old. Patients had a mean of 13.5 transfusion episodes (20% of patients had 16 or more transfusions per year) and a median of 32.4 units of blood transfused per year. It is noteworthy that although several patients were excluded from the Zynteglo trials for having comorbidities – advanced liver disease or cardiac disease – such patients were not excluded from this chart review study. This was reflected in the proportion of patients who had high liver iron concentrations (29%). The prevalence of diabetes in the Chart Review was 13%, hypogonadism prevalence was 7%, and hypogonadotropic hypogonadism prevalence was 20%. These are much lower prevalences than those reported in the study identified in the company's systematic review (see Section 4.3.4) which were used to derive risks of developing these conditions in the model.

Another difference between the Chart Review and the Zynteglo trials is that [redacted] Pistoia et al (2019), in a study of 671 regularly transfused β-thalassaemia-major patients, found that the homozygous β^+/β^+ patients showed less myocardial iron overload and a concordant better global heart function when compared to the more severe groups (β^+/β^0 and β^0/β^0) and that the β^+/β^0 patients showed significantly higher global heart T2* values than the β^0/β^0 patients ($p < 0.05$).[34]

4.3.6 Zynteglo proxy data

The company also stated that they undertook reviews to identify proxy data for expected longer-term outcomes on Zynteglo. Studies of allogeneic post-transplant patients were used to identify proxy data for:

- Infertility and gonadal function, and
- Time to iron normalisation

The CS reported that three studies were identified using a "targeted review" on infertility and gonadal function (p171). Although it was unclear whether these were identified systematically, the CS stated that they had generally consistent findings on fertility rates. The company justified the use of one particular study based on it being the only study specifically in stem-cell transplanted thalassaemic survivors with infertility measured by gonadal dysfunction.[35] Based on this study, and on UK HES data, the company assumed that the conditioning chemotherapy associated with Zynteglo therapy would increase infertility by 24% in men and 57% in women (compared to SoC TDT patients).

Another 'targeted literature review' was used to identify two papers on iron store changes post allogeneic HSCT in thalassaemia patients. The company stated that they 'conservatively' used the Chaudhury et al 2017 study to support an assumption of a 4-year iron normalisation period following Zynteglo therapy.[36] However, this study (of 176 patients) reported that at ≥4 years post-transplant median ferritin levels were 870 ng/mL (range, 52 to 6847). Based on upper ranges of 'normal' levels being 200ng/mL in females and 300ng/mL in males the ERG does not consider this to be a conservative estimate.

4.3.7 Summary

The company's systematic reviews were restricted to studies published from 2007 onwards and review articles appeared to have been excluded. These criteria proved to be too restrictive since, in subject areas where suitable studies were not identified, the company had to undertake additional "targeted reviews" to identify studies. There was a lack of transparency about how these additional studies were identified and selected, meaning it was not possible for the ERG to make a judgement on whether the most appropriate evidence was used. This was exacerbated by the limited, or absent, critiques of the strengths and weaknesses of these studies. The ERG understands that it is often impractical to use systematic review methods to identify all sources of data for an economic evaluation, but transparency on the methods used to identify and select studies is nevertheless very important. It was also unclear why the company sometimes did not make use of their own systematic review results (e.g. for adverse events of chelation therapy). Consequently, the ERG has concerns that some model inputs for TDT patients receiving routine care – such as mortality risk and the rate of liver complications in patients with high iron levels – are likely to be overestimates.

A difference between the comparator studies and the population eligible for Zynteglo therapy is the genotype restriction (with Zynteglo). The comparator studies did not restrict by genotype and will have included some β^0/β^0 patients. It is possible that comparator study cohorts may have achieved better outcomes if patients with β^0/β^0 genotypes had been excluded.

4.4 Conclusions of the clinical effectiveness section

The Zynteglo trial results have somewhat limited applicability to the population likely to receive Zynteglo in the NHS as the trial population might under-represent certain genotypes which are prevalent in the UK. This is important because while most patients appear to respond well to Zynteglo, some patients tend not to respond as well as others. In particular, patients with a genotype deemed very similar or equivalent to a β^0/β^0 genotype (i.e. "severe" non-β^0/β^0 genotypes, which are covered by the marketing authorisation) and patients with a β^0/β^0 genotype (who are not covered by the marketing authorisation) appear less likely to achieve transfusion independence status than patients with other genotypes.

The Zynteglo manufacturing processes have evolved during the trial programme with the aim of maximising response rates. It is possible that [redacted] may increase the probability of achieving TI in patients with severe non-β^0/β^0 genotypes (compared to the previous processes used in the trial programme) but only results from the ongoing study HGB-212 and further data from the HGB-207 study (also ongoing) can resolve this uncertainty. The trials results are still quite immature, and the number of patients treated is small, so uncertainty exists regarding the longevity of Zynteglo and regarding the possibility of adverse events in the medium-to-long term.

A limitation of the company's systematic reviews to identify comparator group data was a lack of transparency about how studies were identified and selected, meaning it was not possible for the ERG to make a judgement on whether the most appropriate studies were used. The ERG also has concerns about the applicability of many of the studies which were selected as being appropriate (for providing model parameter data). Many studies are out of date and do not reflect the improvements in TDT patient treatment and monitoring achieved over the last 10-20 years. The company's own 'Chart Review' study of UK TDT patients also had limitations in how well it reflected the Zynteglo trial population. Specifically, the Chart Review study did not exclude patients with a β^0/β^0 genotype nor patients with important comorbidities (such as advanced liver disease or cardiac disease). Evidence identified from a study of thalassaemia patients who successfully underwent allogeneic stem cell transplants suggests that the conditioning chemotherapy associated with Zynteglo therapy would increase infertility when compared to TDT patients: by 24% in men and 57% in women.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided in response to the ERG's clarification questions. The submission was subject to a critical review on the basis of the company's report and by direct examination of the executable model. The critical appraisal was conducted with the aid of a checklist to assess the quality of the economic evaluation and a narrative review to highlight key assumptions and uncertainties (Appendix 1: Drummond Checklist).

5.1 ERG comment on company's review of cost-effectiveness evidence

The CS describes a systematic literature review that was conducted to identify economic studies (Section B.3.1, p. 148). One overall search was used to identify studies on the cost-effectiveness of treatments, HRQoL, and cost and resource utilisation in patients with TDT.

5.1.1 Searches

Searches were initially undertaken in 2017 and updated in 2019.[17, 19] The databases and other sources searched were appropriate to locate both published and unpublished studies of cost-effectiveness, HRQoL, and cost and resource use relating to transfusion-dependent beta-thalassaemia. The search strategies for all databases (MEDLINE, Embase, PsycINFO, and EconLit) were structured appropriately. Some minor reporting errors were found by the ERG relating to the searches. Full details of the search strategy used are provided in Appendix G of the CS. Further critique of the company's searches are provided in Appendix 2: Critique of the company's search strategies for cost-effectiveness evidence

5.1.2 Inclusion/exclusion criteria used for study selection

The company did not describe the eligibility criteria for study selection in their systematic review of cost-effectiveness studies. The search was described as a 'collective search strategy', which sought to identify cost-effectiveness studies, health related quality of life studies, and cost and resource use studies. The company stated that only studies evaluating blood transfusions and chelating agents were included, and that the 'geography' was limited to the US, France, Italy, Germany, Greece, and the UK. It is unclear why the company only considered these locations, and whether studies that drew efficacy data from outside these countries were also included.

The CS also discusses the results of a targeted search of cost-effectiveness studies evaluating allogeneic HSCT in any country; however, the methods are not described.

5.1.3 Studies included and excluded in the cost effectiveness review

According to the PRISMA diagrams presented in Appendix G of the company submission, the original review conducted by the company in May 2017 identified a total of 3,161 potentially relevant

studies, of which 2,920 were excluded at the primary screening stage. The remaining 241 studies underwent full-text assessment for eligibility. Seventy-two of these studies were excluded for a number of reasons reported in Figure 1 of CS Appendix G, and a further 154 studies were excluded as 'non-economic articles', producing a total of 15 studies. The company updated this review in April 2019, screening a total of 1,298 records for inclusion, none of which were found to be relevant.

The review identified five cost-effectiveness models and one cost-of-illness model. The remaining nine publications were resource use/cost studies. The company provided a brief description of the structures and assumptions of three cost-effectiveness studies conducted in the UK, one in the US, and one in Italy, and presents a summary of each in CS Table 43. The two cost-effectiveness studies identified through the 'targeted review' of included allogeneic HSCT for patients with thalassaemia major were undertaken in India[37] and Thailand[38], and were described in detail. Two of the identified cost-effectiveness analyses[21, 39] were used to inform clinical parameters in the company model.

5.1.4 Conclusions of the cost effectiveness review

The company makes no overall assessment of the appropriateness of inputs and assumptions adopted in the five cost-effectiveness studies identified in the initial review. They notably exclude some key assumptions and inputs considered in previous UK models from their own model, e.g. the development of osteoporosis. The company state that while the two studies from India and Thailand were unlikely to inform the parameters for the present evaluation as the intervention was allo-HSCT, the control arm comprising transfusion and chelation therapy could be useful for model validation. However, these studies were considered by the company to be particularly relevant to the Zynteglo model, and were used to guide their model structure and the selection of complications associated with iron overload.

The ERG considers the company's aggregation of the results of the systematic reviews of cost-effectiveness studies, costs and resource use, to be inappropriate and contrary to the principles of the PRISMA statement for transparency in reporting. Because the review methods were not reported, it is unclear whether all relevant literature was identified and included in the review.

However, as there are unlikely to be any studies which assess the cost-effectiveness of Zynteglo in a TDT population, the ERG consider the *de novo* cost-effectiveness analysis reported in the CS to be the most relevant source of evidence to address the present decision problem.

5.2 ERG's summary and critique of company's submitted economic evaluation

The company presented a *de novo* economic analysis of Zynteglo compared with standard care, consisting of blood transfusions and iron chelation therapy, in TDT. Effectiveness of treatment was

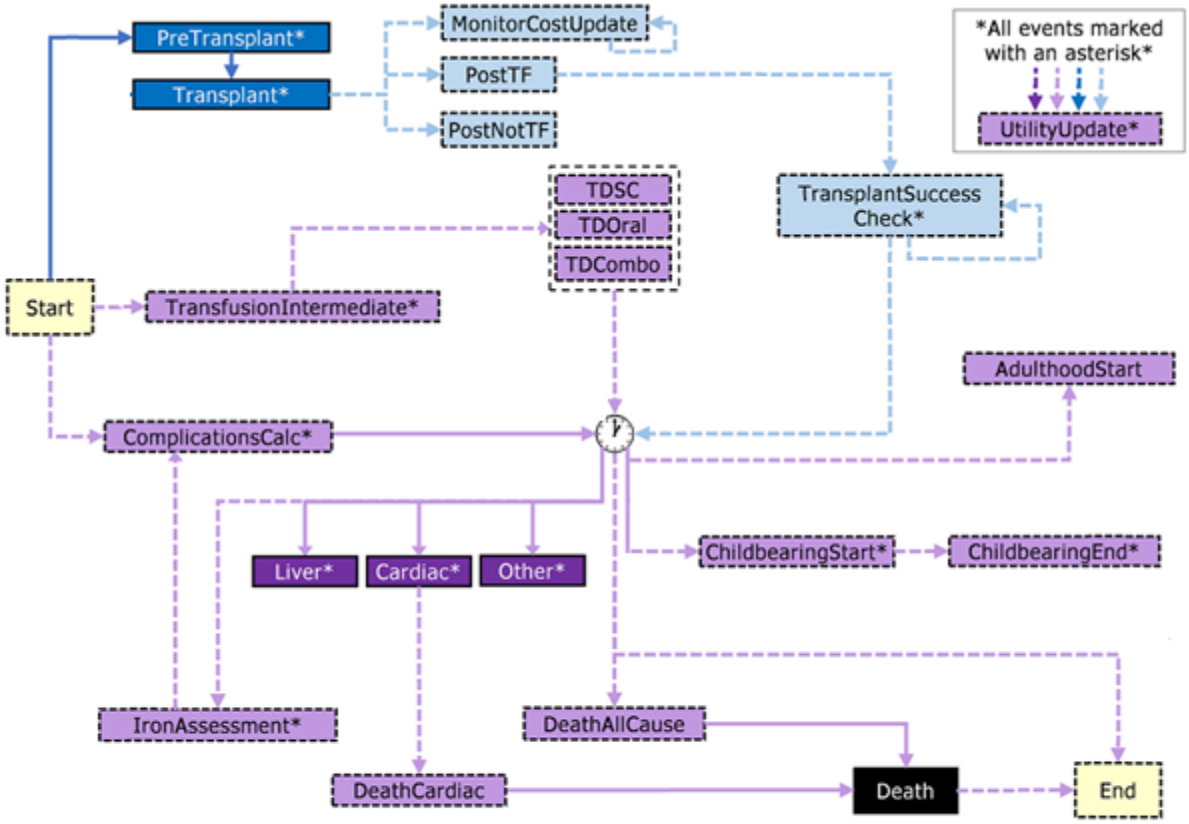
assessed through the achievement of transfusion-independence. Total costs and QALYs were assessed for each arm over a lifetime time horizon, and discounted at a rate of 1.5%.

The company submitted two economic models: one at the start of the appraisal, and an updated and corrected model following the clarification stage. The updated model included changes made by the company to some of the base case assumptions, as a result of clarification questions from the ERG. The ERG also identified modelling errors throughout the appraisal process, resulting in the company providing a number of iterations of the model containing various model corrections. All results presented in this section reflect the final, corrected version of the model provided appear less likely to achieve transfusion independence status than patients with other genotypes, and will not reflect the results presented in the original company submission or PFC.

5.2.1 Model structure

The company developed a *de novo* Excel-based model using a discrete event simulation structure, implemented through the discretely integrated condition event (DICE) simulation framework[40]. The basis of the model structure was driven by the transfusion status of patients, which determined their tissue-specific iron levels. A patient's iron level drives their risk of developing complications attributable to iron overload, and also influences mortality risk, quality of life and chelation requirements. Complications were assumed to be associated with the cardiac, liver and endocrine systems, as these were considered to be the organs most affected by iron overload. The presence of any of these complications was associated with an additional impact on quality of life, management costs and, in the case of cardiac disease, excess mortality risk.

Figure 2 Model schematic (Fig 2, clarification response)



Transfusion status

Patients enter the model as transfusion dependent, receiving a mean of 13.5 transfusions per year. In the Zynteglo arm, after infusion of transduced cells, patients are partitioned based on treatment success: they may become transfusion independent, have a clinically meaningful reduction in transfusion frequency (i.e. 'transfusion-reduced') or continue to receive the same number of transfusions as they did prior to receiving Zynteglo. Transfusion independence is defined as being free from transfusions for 12 months and having sustained haemoglobin levels above 9 g/dL. The rates at

which these outcomes occurred were based on Zynteglo trial data (HGB-204, HGB-205, and HGB-207) for non-β^0/β^0 patients, discussed in Section 4.2.2 and Section 5.2.6. In the model, TI patients were considered to be independent from transfusions (if achieved) beginning at 12 months post-transplant. In the standard of care arm, i.e. transfusions and iron chelation therapy, patients were assumed to remain transfusion dependent for the duration of the model time horizon.

While the model contains the functionality for patients to experience engraftment failure, or loss of graft and relapse after initially successful treatment with Zynteglo (i.e. losing their TI status), the company assumed that this would not occur in any patient.

Iron levels

Baseline iron levels, applied to patients in both treatment arms in the model, were estimated from a Chart Review of TDT patients in the UK, which was funded by the company (Section 4.3.5).[18] The baseline iron overload risk category for each simulated patient was randomly selected from the starting distribution (for details of this distribution see Section 5.2.6.3). Iron levels in the cardiac, liver and endocrine systems were based on the myocardial T2*, LIC and serum ferritin assessments respectively, and patients were classed as being either in a low, moderate or high risk category.

If transfusion independence was achieved after Zynteglo treatment, patients were assumed to achieve normalised iron levels after four years. Patients with substantially reduced transfusions (defined as at least a 60% reduction) were assumed to achieve reduced, but not normalised, levels of iron relative to their baseline levels. A distribution of lower iron levels was assumed by the company and applied in the model from one year onwards.

For patients receiving standard care, the baseline levels of iron were applied for the duration of the patients' lifetime; that is, iron levels in these patients did not increase or decrease over time, with the company justification that they represented the population mean iron levels for a TDT population and would be representative throughout their lifetime. These patients do not achieve a reduction or independence from transfusions at any time.

Risk of complications

The times to each complication event (cardiac, liver, and endocrine) were estimated at baseline, and were determined by the patient's assigned iron overload risk category. If patients achieved a reduction or independence from transfusions after treatment with Zynteglo, their risk of complications was reduced in line with their reduced iron overload category. Patients who were transfusion dependent maintained their risk throughout the model time horizon. After the iron normalisation period, TI patients were assumed to have no risk of additional iron overload or new iron-related complications: if the model estimated their time to developing a complication would occur after the date when iron normalisation would occur (4 years), then the risk was assumed to no longer apply and the

complication would not occur. If the time to developing a complication were to be reached before the end of the iron normalisation period, then the complication would occur. A similar method was applied for transfusion-reduced patients, although instead of patients facing no risk after four years, their time to the complication was re-estimated at one year, taking into account time already elapsed since the start of the model, based on the lower levels of iron.

Transfusion and chelation

In the standard care arm, patients received regular transfusions and chelation therapy to remove excess iron. Each patient was randomly allocated to receive either oral, subcutaneous, or a combination of oral and subcutaneous iron chelation therapy, using a distribution that was estimated from the Chart Review (Section 5.2.4).

Since excess iron can persist for several years after Zynteglo infusion and engraftment, iron chelation therapy and/or phlebotomy was continued following treatment. Transfusion independent patients continued to receive ongoing chelation and/or phlebotomy up until the end of the iron normalisation period, and experience the costs and the HRQoL impact associated with the mode of iron normalisation therapy received. Patients who became "transfusion reduced" following Zynteglo infusion were assumed to continue blood transfusions and iron chelation therapy, but with fewer transfusions and lower chelation therapy exposure, compared to the period before transplant.

Patient profiles

The discrete event simulation structure employed in the model is evaluated stochastically on a patient-level basis to produce estimates of the expected costs and benefits across the specified patient population. The model runs a number of 'profiles', which are hypothetical patients defined by age and gender, with each profile weighted to reflect the distribution of patients in the eligible treatment population (Section 3.1).

The model originally submitted by the company was based on [redacted] unique profiles reflecting the distribution of age and gender combinations between [redacted], and estimated results generated from 100 random samples of these profiles. Profiles in an updated company model were based on gender and three age bands of child, young adult, and adult, and the model estimated results generated from 600 samples. Patient age was used to determine the mortality rate (i.e. the time to death), quality of life, and some treatment related costs.

Time-to-event values are sampled for individual patients from probability distributions. Events that occurred stochastically were: time to development of complications due to iron overload in the cardiac, liver and endocrine systems, and time to death. Zynteglo treatment success and subsequent transfusion status was also assigned stochastically for patients in the Zynteglo arm. Baseline patient characteristics that were assigned randomly included organ-specific iron levels and type of chelation

agent. Generally, each stochastically-generated input was estimated independently of each other; for example, the risk of a patient having high cardiac iron was not linked to the likelihood that they would also have high liver iron, although the same random seed was used to estimate baseline and future iron levels for a given organ system, which enforced a degree of correlation between the two.

5.2.1.1 ERG comment

Omission of key elements of the condition

The company model, reflecting iron overload complications only in the liver, cardiac and endocrine organ systems, may have omitted some other important complications of beta thalassaemia, such as splenectomy and the development of osteoporosis. These have been present in other cost-effectiveness analyses for this condition, and the clinical advisor to the ERG suggested that, since TDT patients were living longer at present due to improvements in overall patient care, the management of osteoporosis is of increasing importance to older TDT patients. However, osteoporosis is associated with a low cost impact, and is considered to be a late developing complication with a more heavily discounted impact.

Diabetes and hypogonadism were modelled together within one category, both being complications associated with the endocrine system. However, in the model, it is not possible to develop both conditions concurrently. While the risk of developing each condition is estimated separately, the model considers only the one that occurs first. The unit cost of "endocrine complications" is a weighted average cost of treating each condition for each patient rather than a sum of each cost. The ERG requested that the company amend the model so that they are considered individually; however, the company did not do this as they considered that adding this complexity into the model would not result in significantly different results but would add to the level of uncertainty.

As it is likely that a successful transplant will lower the risk of complications, the omission of these aspects from the patient pathway is conservative, as it may underestimate the impact of these conditions upon costs and quality of life in transfusion dependent patients, i.e. those on the standard of care.

Timing of TI status after Zynteglo

In the model, patients who achieved transfusion independence were assumed to do so beginning at 12 months. As illustrated in Table 24 in the CS, TI-evaluable patients in the trials became transfusion independent from 12 to 24 months (time to reach TI ranged from [redacted] months), with a mean time to TI of [redacted]. While the timing of achievement of TI status has little impact in the company's base case model, where the cost of Zynteglo is subject to a simple discount applied at the time of treatment, it could be problematic should an outcomes-based payment scheme for

Zynteglo be introduced, when the timing of the assessment for the first outcome-based payment would be important.

Lack of correlation between patient characteristics and key outcomes

Although the model generated a range of patient characteristics to define the population, only age and gender were correlated with one another, and their interaction with other outcomes was limited. These limitations undermine the face validity of the model.

For example, in the company's base-case analysis, age was not linked to patient weight or iron level in each organ system, with the model taking the mean cohort value for all patients (Section 5.2.6). Patient weight in particular is strongly associated with age, although it is less clear how iron levels change over time.

There was also a lack of interaction between patient characteristics and event risk, and between the events themselves. Iron levels and the development of complications in each of the three organ systems were modelled independently of each other, and did not account for patient history to determine the rate of future events (e.g. time with iron levels to determine complications rate, or mortality). The time to iron normalisation was always modelled as being four years in TI patients, regardless of the patient's prior iron levels. The company justified this assumption as their trial data did not indicate a noticeable trend in length of time to move from higher iron levels to lower or normal iron levels post Zynteglo.

Overly complicated model structure

The company justified the use of an individual patient modelling approach as it has the possibility to allow the timing and order to vary between the various organ-specific iron overload events that could occur. They also considered that if the model took a cohort approach, an unfeasible number of health states would be required to model the range of iron levels in the three organ systems. A patient-level approach allows for interactions between variables to be captured, and patient history to be accounted for. The ERG considers that the model developed by the company adopted an overly complex structure but modelled outcomes in a simplistic manner. The model did not fully exploit the benefits of the patient-level approach, since outcomes in each organ system were modelled independently, and patient history was not always accounted for e.g. in the estimation of iron overload related complications. However, in order to benefit from the additional level of complexity that the patient-level model structure allows, it is necessary to be able to quantify the complex processes and relationships between patient characteristics and outcomes to inform the model. In many cases, contemporary data do not exist and it not possible to undertake these more realistic analyses.

Development of iron overload related complications

The risk of developing iron overload-related complications was based on a simplistic approach, which depended only on the iron load category, and did not consider the history or duration of iron overload or the patient's age.

It is possible that the model underestimates the risk of developing cardiac complications in the Zynteglo arm. Since the model did not take into account the patient's historic iron levels, very few patients in the Zynteglo arm developed cardiac complications (10% in the Zynteglo arm, compared to 41% for standard care). Patients who achieve transfusion independence experience normalised iron levels after four years in the model, at which point their complication risk is reassessed and fixed to zero. Therefore, transfusion independent patients are only at risk of such complications during the first four years of the model. However, some iron damage to the cardiac system is irreversible, and so patients who have developed some degree of damage before iron levels return to normal may continue to be at risk of complications, albeit to a lesser extent (discussed in more detail in Section 5.2.6.4).

Since the model did not take patients' age into account when estimating the time to development of complications, the actual age of onset varied considerably between patients, and lacked clinical plausibility. For example, cardiac complications typically present when a patient is in their 20s to 30s.[41] However, inspection of the sampled results for each patient for the company base case analysis showed that the age of onset of cardiac complications occurred equally at any age. This means that the modelled patient disease trajectory lacked face validity in this respect.

However, changing the model to account for patient history would require a fundamental change to the structure, and incorporation of data that does not presently exist. The company performed an SLR and search of real-world data sources to identify evidence of the relationship between iron levels at Time X and subsequent clinical events (i.e. complications) at Time Y, and it was not deemed possible to generate the required evidence in time for the appraisal.

5.2.2 The company's economic evaluation compared with the NICE reference case checklist

Table 6 summarises the ERG's assessment of whether the company's economic evaluation meets NICE's reference case and other methodological recommendations.

Table 6 Comparison of company's economic evaluation with NICE reference case

Attribute	Reference Case	Included in CS	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Defining the decision problem	The scope developed by NICE	Yes	
Comparator(s)	As listed in the scope developed by NICE	Yes	
Perspective on costs	NHS and PSS	Partly	Only NHS costs have been considered.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes	The model considered QALY benefits to treated individuals.
Type of economic evaluation	Cost-utility analysis	Yes	
Time horizon	Sufficient to capture important differences in costs and outcomes between the technologies being compared.	Yes	The economic model uses a lifetime horizon, which caps survival at age 100.
Synthesis of evidence on health effects	Systematic review	Yes	
Source of data for measurement of health-related quality of life	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Partly	Utilities were populated using a combination of sources, including the Chart Review study which used EQ-5D-3L. These values were used to estimate QALYs for untreated patients. Utilities derived from time trade-off interviews with the general public were used to estimate post-treatment utility scores. For some utility decrements, HUI-2 values were treated as equivalent to EQ-5D.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Partly	Estimates of post-treatment HRQoL elicited from unaffected members of the public in TTO interviews. Utility of untreated patients based on EQ-5D. Disutilities associated with treatment and complications derived from TTO interviews with the US/UK public. Some estimated by healthcare professionals.

Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Partly	Value set used was based only on healthy members of the UK general public.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	No special weighting undertaken.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	Partly	Costs under control of personal and social services not considered. eMIT prices were not used.
Discounting	3.5% on costs and health benefits	No	Costs and benefits were discounted at 1.5% per annum.

5.2.3 Population

The patient population included in the cost-effectiveness analysis was patients 12 years and older with TDT who do not have a β^0/β^0 genotype. Section 3.1 provides further details on the population described in the licensed indication for Zynteglo.

The age and gender distribution of patients considered in the company's economic model were based on the [redacted] patients evaluable for transfusion independence from the clinical studies, HGB-204, HGB-205, and HGB-207. Clinical evidence on the effectiveness of Zynteglo is drawn from this analysis, see Section 3.1 for details. Age and gender were used to estimate mortality rates and baseline utility values, and some cost inputs.

The license for Zynteglo further describes that patients should be suitable for HSC transplantation. This specifically excludes patients with evidence of liver disease and patients with severely elevated cardiac iron (T2* <10 msec). This was also the exclusion criteria in the Zynteglo trials. The economic model, therefore, omitted patients with any iron overload-related complications at baseline (although these may develop at a later stage).

Other patient characteristics, such as weight and baseline iron levels, were based on the company's Chart Review (Section 4.3.5). The company considered the Chart Review to be a robust source reflecting current UK practice, and preferred its usage for these parameters over those of patients in their trials. Patient weight was specified in the model in order to calculate the costs of chelating agents which involve weight-based dosing. Mean patient weight was estimated [redacted], and this value was applied to all patients in the model. The baseline distribution of iron levels, presented in Table 7,

categorised patients as normal, low, moderate, or high iron based on serum ferritin, LIC, and myocardial T2* . Since patients with high cardiac iron loading would not be eligible for Zynteglo therapy, the distribution of Myocardial T2* was adjusted so no patients had high iron.

Table 7 Distribution of iron loading for transfusion-dependent patients (Table 48, CS)

Iron damage at baseline	Serum ferritin	LIC)	Myocardial T2*
Low iron	[redacted]	61%	88%
Moderate iron	[redacted]	23%	12%
High iron	[redacted]	16%	0%
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 (LIC): 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			

5.2.3.1 ERG comment

Several inconsistences between the populations in the Chart Review and the trial populations are described in Section 4.3.5. This impacts upon the estimation of baseline iron load and patient age. This also has implications for the estimation of HRQoL for standard care patients (Section 5.2.7) and the distribution of chelation therapy (Section 5.2.4), which were also based on the analyses of the Chart Review data.

Additionally, the ERG has a number of concerns around the modelled patient weight, comorbidities, and genotype distribution at baseline.

Age

The ERG considered that the most appropriate age range of patients was that of the patients in the Zynteglo trials, which were used to define the patient profiles in the model. However, a number of model inputs were derived from the company's Chart Review study, which included patients aged up to [redacted], whereas the trial populations from which Zynteglo data were derived was limited to patients aged 12-35 (see Section 5.2.4 for further detail). Table 8 illustrates the differences in the age distribution of the trial population whose efficacy data was used in the model, and the Chart Review. Most notably, [redacted] of the Chart Review population were over the age of 30 [redacted], whereas only 8.3% of the trial population were aged over 30 (all of whom were aged <35).

The characteristics, outcomes and HRQoL of patients in the older age ranges may not be reflective of patients under current clinical practice, due to changes in how patients have been managed over the last decade. They are also less likely to be eligible for Zynteglo treatment. However, the Chart Review analysis was not adjusted to account for this.

Table 8 Age distribution of patients in included trials vs Chart Review

Patient Age Distribution (Years)	Company base-case (clinical studies HGB-204, 205, 207) (n=[redacted])	Chart Review population (n = 165)
<12	[redacted]	[redacted]
12<18	[redacted]	[redacted]
18<30	[redacted]	[redacted]
30<40	[redacted]	[redacted]
40<50	[redacted]	[redacted]
50<60	[redacted]	[redacted]
≥60	[redacted]	[redacted]

Iron loading at baseline

The ERG considers the distribution of iron loading, derived from the Chart Review, to be broadly in line with the population based on estimates provided in the literature.[42] However, there were some differences between iron levels of the Chart Review population and the trial population; for example, more patients in the Zynteglo trials had low levels of cardiac iron (Table 32 of CS). As discussed in Section 4.3.5, this may due to the inclusion of a [redacted], who have been shown to be associated with higher levels of iron overload.[34] It may also be attributable to the patients in the Chart Review population who are older than those in the Zynteglo trials, who began management of iron overload before chelation and monitoring practices improved.

Baseline iron levels determine the rate at which patients develop complications, and so an overestimation of iron levels at baseline will, in turn, overestimate the rate at which complications develop. This will impact the standard of care arm more so than the Zynteglo arm, as the patients who achieve reduced levels of transfusions will develop lower rates of iron overload and, therefore, experience fewer complications (Section 5.2.6.4).

Patient weight

In the economic model, patient weight was used to calculate the dosage, and thus the cost of chelating agents. The company's base-case model fails to account for any interaction between age and weight, and assumes a constant weight of [redacted] throughout the patient's lifetime, which is likely to overestimate the weight of paediatric patients, placing a modelled 12 year old in the 98th percentile in the UK.[43, 44] Furthermore, the mean weight of patients included in the Zynteglo trials was [redacted]. An overestimation of patient weight in certain patient profiles will inflate the costs of standard of care and subsequently underestimate the ICER of Zynteglo. The company provided a scenario analysis which reduced the average weight of paediatric profiles in response to a request by the ERG. The scenario

adopted a weight of [redacted] for paediatric patients and [redacted] for adult patients, and the results can be seen in Section 5.2.10.3.

Iron overload-related complications

The modelled population excludes patients with the presence of iron overload-related complications at baseline. However, the company response to the ERG's clarification questions stated that "*individuals with TDT would not specifically be excluded from eligibility for Zynteglo due to either diabetes or hypogonadotrophic hypogonadism*." The Chart Review population included 20% of patients with hypogonadotrophic hypogonadism, [redacted] with diabetes and [redacted] with hypogonadism. The ERG believes patients with these complications should be included in the model to reflect baseline comorbidities in the population receiving Zynteglo. However, the number that would have endocrine disorders at baseline is difficult to determine. It is possible that the patients with these endocrine complications in the Chart Review also have other complications that preclude them from treatment with Zynteglo, but neither the CS nor the draft publication provided to the ERG provides this level of detail. These data are also not available from the Zynteglo trials, to provide a comparison with the Chart Review data.

The Chart Review population included patients with complications and high cardiac iron levels that would contraindicate treatment with Zynteglo. A number of important model parameters used in the model were based on the analysis of the Chart Review. This discrepancy in populations had a greater impact on the standard care arm, where the HRQoL throughout the modelled time period was based upon these analyses. This is discussed further in Section 5.2.7.

Representativeness of the distribution of genotypes

It is important to consider the heterogeneity of mutations covered by the marketing authorisation and whether the modelled population represents the distribution of genotypes that are present in the UK TDT population. As is described in Section 3.1, the trial population potentially underrepresents the severe non-β^0/β^0 mutations which are covered by the marketing authorisation and are prevalent in the UK. The underrepresentation of these difficult to treat genotypes with a potentially poorer prognosis may result in overestimated transfusion-related benefits for the Zynteglo-treated population, and underestimation of uncertainty in the cost-effectiveness results.

The Chart Review population does not exclude patients with β^0/β^0 mutations; however, clinical advice to the ERG suggested that other characteristics of TDT, such as HRQoL and transfusion and chelation requirements, are not influenced by genotype. Therefore, the analyses conducted by the company on their Chart Review data may not need to be adjusted for this characteristic.

5.2.4 Interventions and comparators

Zynteglo treatment

The intervention, as implemented in the model, consists of three stages, each of which comprises distinct processes and treatment costs. Further detail on the Zynteglo treatment process can be found in Section 3.2. In brief, these include mobilisation and apheresis of the patient's stem cells, hypertransfusion, pre-treatment and myeloablative conditioning. After these steps have been completed, the transduced cells (the Zynteglo product) are infused into the patient. This is followed by an inpatient stay of 21-42 days until engraftment of the infused cells has occurred.

The minimum recommended dose of Zynteglo is 5.0×10^6 CD34+ cells/kg (proportion of successfully transduced LVV+ cells varied between [redacted] in the HGB-207 study). In cases where multiple rounds of mobilisations were required, patients would receive more than one product lot of Zynteglo, and these were administrated in succession and considered one dose. Other drugs and dosages used in the executable model during steps 1 and 2 of the Zynteglo process are as follows:

- Filgrastim (Zarzio®) 1.0 million units/kg/day for 7 days;
- Plerixafor (Mozobil®), 0.24 mg/kg/day for 2 days;
- Busulfan, 0.8 mg/kg every 6 hours for 4 days;
- Ursodeoxycholic acid, 10mg/kg/day for 21 days;
- Clonazepam, 1mg/kg every 6 hours for 5.5 days.

Current standard of care

The comparator considered in the company's model was 'current care' for patients without an available HLA-matched related HSC donor. The current standard of care, therefore, consists of regular transfusions and iron chelation therapy, as detailed in Section 3.3. The company used the Chart Review described in Section 4.3.5 to define the management of standard of care (SoC) patients in their economic model. To determine the cost of chelation therapy in the model, patients were allocated to either oral (deferasirox, deferiprone), subcutaneous (desferrioxamine) or a combination of oral and subcutaneous chelation therapies, and incurred a weighted acquisition and monitoring cost for the iron chelating agents according to the proportion of patients on each therapy in the Chart Review (see Table 9), where [redacted] of patients received a combination of oral and subcutaneous chelation therapies.

The ERG requested that the company provide a reanalysis of the distribution of iron chelating agents excluding patients who would not have been eligible for enrolment in the Zynteglo trials. The results of this analysis are presented in Table 9. This appeared to show that

[redacted]

[redacted]. These younger patients also represented [redacted] of those on two different oral chelation therapies in combination.

Table 9 Distribution of chelating agents in the company model (Table 44, CS)

Iron chelator	Mode of Administration	Distribution in full Chart Review population n (%)	Distribution in age 12-35 Chart Review reanalysis n (%)
Deferasirox	Oral	[redacted]	[redacted]
Deferiprone	Oral	[redacted]	[redacted]
Desferrioxamine	Subcutaneous	[redacted]	[redacted]
Deferiprone and Desferrioxamine	Oral and Subcutaneous	[redacted]	[redacted]
Deferiprone and Deferasirox	Oral	[redacted]	[redacted]
Deferasirox and Desferrioxamine	Oral and Subcutaneous	[redacted]	[redacted]

Standard of care patients were modelled to receive 13.5 transfusions per year, with those aged ≤18 years assumed to receive one pRBC unit per transfusion, while those aged >18 receive two units per infusion.

5.2.4.1 ERG comment

The ERG considers the intervention as implemented in the economic model to be in line with the licence. The comparator, i.e. blood transfusions and iron chelation therapy, is appropriate and in line with current practice in this population.

The ERG were concerned that the distribution of chelating agents may not be representative of those used in this population in practice. The relatively recent development of the evidence base around oral chelators and the safety and efficacy of combination therapy has resulted in uncertainty and inconsistency in clinical practice.

Clinical advice suggested that the iron load of older patients may no longer be adequately controlled by a single chelating agent, and thus these patients may be more likely to receive combination therapy. However, this did not appear to be reflected in the reanalysed Chart Review population, where a greater proportion of patients aged 12-35 were receiving combination therapy than the unrestricted population overall. It may be that the distributions in recent medical records are unstable and progressing towards combination therapy as clinical understanding and confidence with these drugs improves. This remains an area of uncertainty in the model.

It appears that in the model it is not possible for patients to receive two oral chelation therapies. These patients accounted for [redacted] in the company's analysis and [redacted] in the re-analysis of the Chart Review data. Therefore, the company model may underestimate the cost of chelation in a small proportion of patients.

5.2.5 Perspective, time horizon and discounting

The company's analysis adopted an NHS perspective only, and did not consider any costs incurred by Personal Social Services (PSS), which is not the perspective preferred in the NICE Methods guide.[7]

A lifetime horizon of 100 years was chosen as it was considered sufficient to capture all relevant differences in costs and benefits between the comparators. The ERG considers this an appropriate time horizon, as it is very unlikely that any patients would remain alive beyond this time period.

The economic model presented in the CS used a non-reference case discount rate of 1.5% for both cost and outcomes.

5.2.5.1 ERG comment

The ERG has a number of substantive concerns regarding the company's justification for the use of the non-reference case discount rate of 1.5% in the economic evaluation. The company's arguments are discussed in turn in the sections below, with specific focus on the implications for the economic analysis presented.

Zynteglo restores people who would otherwise die or have a very severely impaired life to full or near full health

The ERG has concerns with the company's position that the eligible population would otherwise die or have a very severely impaired life, and that Zynteglo restores these people to near or full health.

The ERG disputes the notion that without Zynteglo patients would otherwise die, given the uncertainty in the long term mortality of patients treated with transfusions and chelation. Estimates of life expectancy must be based upon current clinical management, and mortality figures cited by the company are based on up to 50-year old data. It is the ERG's understanding that evidence on projected life expectancy for patients treated optimally with current management strategies and therapies do not exist (see Section 5.2.6). Existing studies present limited follow-up data and enrol patients managed with different techniques and chelators increasing the uncertainty in the external validity of these results.[41] The lack of long term and generalisable survival data raises concerns regarding the statement that patients would "otherwise die". Furthermore, in the most recent edition of *Standards* published by the UK Thalassaemia Society,[45] it is stated that "the expectation is that well monitored and chelated patients will have a near normal life expectancy", which casts further doubt on the claim that conventionally treated patient would die.

The company's assertion that patients undergoing transfusion and chelation would otherwise have a severely impaired quality of life (HRQoL) is also not supported by existing evidence. As the company state in their CS, two studies in the literature derived utilities using EQ-5D and reported values of 0.86 and 0.87 for those with TDT on chelation therapy.[46, 47] These values suggest that TDT is associated with only a modest reduction in quality of life, and are supported by the analysis of 16-35 year olds with TDT in the Chart Review, whose HRQoL was reported as [redacted] (see Section 5.2.7). Data included in the UK Patient Preference Report provided by the company also seem not to support the assertion that patients on transfusions and chelation have a very severely impaired HRQoL.[48] Results showed 61% of TDT patients disagreed that beta thalassaemia significantly impacted upon their quality of life. Patients recruited to the Zynteglo trials also generally rated their HRQoL as similar to that of the general population prior to treatment.

Furthermore, in the most recent edition of *Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK,*[45] it is stated that "discussion with the family must stress the usually excellent outcomes for children and adults managed conventionally with transfusion and chelation, now that monitoring for iron overload is more accurate and chelation choices are wider." The ERG would argue that it is, therefore, not likely that patients not treated with Zynteglo would otherwise have a "severely impaired" HRQoL, which is argued by the company to be comparable to patients with advanced stage cancer.

Finally, the ERG has concerns about the statement that Zynteglo restores the health of those treated to full or near full health. The ERG considers there to be insufficient evidence to conclude that Zynteglo restores individuals' health to full or near full, both in terms of length and quality. The trial data captured in HGB-204, HGB-205 and HGB-207 and provided in the CS does not provide sufficiently mature follow-up data to support this assumption. The company considered the HRQoL data captured in the trials was uncertain and potentially subject to bias and as a result, a vignette study was instead used. This evidence was based upon the UK general population's views on the descriptions of a pre- and post-Zynteglo health state, rather than from patients with beta-thalassaemia in the trial, as is recommended in the NICE reference case. As such, this evidence cannot be used to support the statement that Zynteglo restores people to full or near-full health.

Benefits are long term

As described in Section 5.2.6 and above, the ERG believes there is insufficient evidence to conclude with certainty that benefits of treatment will be truly life-long. Durable clinical efficacy has been demonstrated to 61.3 months in a small number of patients; however, with no data beyond this, the necessarily lifelong benefits of Zynteglo have not yet been demonstrated. This uncertainty applies to both persistence of transduced cells, and ongoing sufficient haemoglobin production of the graft, i.e. patients remaining transfusion-independent. On the subject of persistence of transduced CD34 cells vs

non-transduced cells, the company stated that peripheral blood vector copy number (PB VCN) serves as a surrogate marker for persistence of transduced HSCs and there had been no significant changes in PB VCN from Month 6 to last follow-up (Section 4.2.1). The ERG accepts that these results are promising but the evidence to suggest the life-long persistence of the graft in all patients is as yet unavailable.

Zynteglo will not commit the NHS to significant irrecoverable costs

The ERG contests the company's assertion that Zynteglo will not commit the NHS to significant irrecoverable costs. The ERG considers the [redacted] acquisition cost of Zynteglo to be significant, and one which could not be recovered by the NHS if the engraftment fails at any point, with patients reverting to transfusion and chelation therapy. As outlined in Section 5.2.4, there is limited long-term evidence of graft durability or transfusion independence, or reduction in iron loading. Should patients become transfusion-dependent at some point after Zynteglo, then not only would the full cost of Zynteglo have been incurred as well as any potential adverse events, such as infertility, leukaemia, and lymphoma, these costs would then be additional to the ongoing costs of transfusions and chelation. The ERG appreciates that such a scenario may be pessimistic; but the potential cost to the NHS associated with anything but an indefinite treatment effect in all patients could be large.

It is the ERG's understanding that the company have submitted a complex PAS to the Patient Access Scheme Liaison Unit (PASLU). The details of this PAS have not been finalised, however, the ERG understands the PAS consists of outcomes-based payments over time conditional on patients remaining transfusion-independent. The ERG has concerns over a PAS based on patient outcomes and length of time over which these outcomes will be judged. If payments are to be staggered over a time period [redacted], evidence from the clinical trials will not be able to address the uncertainty that there may be significant irrecoverable costs should patients become transfusion-dependent after the end of the payment period. In this case, the NHS will have paid the full acquisition cost and not received the lifetime benefits required to plausibly make Zynteglo a cost-effective treatment option. The timing and magnitude of the first payment must also be considered, when the complex PAS has been finalised.

Precedent

The company cite precedent as justification for the use of a 1.5% discount rate in the appraisal of gene therapies. The company submission states that as the lower discount rate of 1.5% was used in the appraisal of Strimvelis,[49] this should also apply to Zynteglo. Strimvelis, used for the treatment of adenosine deaminase deficiency–severe combined immunodeficiency, was evaluated under the highly specialised technology (HST) programme.[49] Within the NICE methods process guide for HSTs, the use of a non-reference case discount of 1.5% for both costs and health effects is permitted. In addition

to this, the HST guidance states that the use of the lower discount rate is for cases in which treatment has a very high likelihood of restoring people who would otherwise die or have a very severely impaired life to full or near full health, over a period of 30 years or more. In the appraisal of Strimvelis, overall survival data was available for up to 13 years. However, the NICE committee concluded that it was uncertain whether Strimvelis met the criteria to use a discount rate of 1.5% given uncertainties in whether the long-term benefits of treatment would be achieved.

As a result, the ERG believes there is little justification for the use of the non-reference case discount rate of 1.5%, and disputes all arguments put forward by the company in support of this assumption. The impact of using the reference case discount of 3.5% for costs and outcomes rather than 1.5% is explored in scenario analysis in Section 6.3.8.

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Transfusion dependence

The clinical effectiveness of Zynteglo in the model is measured by the proportion of patients achieving transfusion independence. Transfusion independence is defined as being free from transfusions for 12 months and having sustained haemoglobin levels of above 9 g/dL. This was estimated from pooled results in all non-β^0/β^0 genotype subjects from studies HGB -204, HGB-205 and HGB-207 (see Section 4.2.2 for further details of the trials and the clinical data). A significant reduction in transfusions was stated as being a 60% reduction.

Of the 24 patients evaluable for TI status at the time of the submission, a total of 20 patients achieved TI (83.3%). Of the [redacted] patients who did not achieve TI, [redacted] ([redacted]) experienced significantly reduced transfusions. Of the remaining [redacted] ([redacted]) patients modelled as being transfusion-dependent, [redacted] remained transfusion-dependent following treatment with Zynteglo, and [redacted], and was modelled as being transfusion-dependent. In the original economic model, the company had assumed that the [redacted] patients who did not achieve TI were transfusion-reduced, but this was updated to the assumptions above following a clarification question from the ERG.

ERG comment

The ERG has some concerns regarding the applicability of these results to UK clinical practice, which were highlighted in Section 3.1. These pertained to the representation of the more severe genotypes in the trial population, and the refinement of the manufacturing process over time.

The trial population may not be generalizable to the UK, where patients with the IVS-I-110 or IVS-I-5 mutations, who are quite prevalent in the UK (Section 3.1), may be underrepresented. This will

potentially have an impact on the estimation of the rate of achieving transfusion independence. As these genotypes are known to be associated with reduced β-globin production, they may be less likely to achieve transfusion independence. The ERG has implemented an exploratory scenario in Section 6.3.2 whereby the proportion of patients who are transfusion independent has been re-estimated in accordance with the expected prevalence of IVS-I genotypes in the UK population.

These issues may be resolved upon further data collection, with the publication of the results from the HGB-212 trial enrolling the IVS-1-110 patients and using the optimised manufacturing process. At this point, it is difficult to predict the direction in which any future effectiveness estimates may go: as the procedure is optimised going forward, outcomes after Zynteglo treatment may be more optimistic than is currently estimated; however, the inclusion of the patients with more severe genotypes may imply less optimistic outcomes. The rate of transplant success was demonstrated to be a key driver of the model in the company's deterministic sensitivity analysis (Section 5.2.9.3), and so it is imperative that this uncertainty is considered during the decision making process.

5.2.6.2 Engraftment success and graft durability

The engraftment procedure was assumed to be successful in all patients, as there were no engraftment rejections (failures) in the trials. However, the need to collect back-up cells for rescue treatment, acknowledges that such a risk exists. It is possible that it occurs in such a small number of patients that it has not yet occurred during the limited data collection to date. It is also possible that moving from the trial setting to general practice, the risk will become more apparent.

In the long-term, it was assumed that there would be no loss of graft, that is, no patients would lose their transfusion independence status either by experiencing reduced haemoglobin levels or a return to transfusion, and that transfusion-reduced patients would not experience an increase in the need for transfusions or return to transfusion dependency over time.

ERG comment

There is currently insufficient available follow-up data for patients in the trials to determine whether permanent long-term engraftment occurs. The duration of transfusion independence was censored at the last Hb assessment and no events for loss of transfusion independence have yet been recorded (page 92 of CS). The clinical advisor to the ERG considered that the assumption of permanent engraftment among all patients was potentially over-optimistic.

[redacted] (page 89 of CS, discussed in Section 4.2.1). The company claim that the integrated transgene is stable in the HSCs, as no significant changes have been observed in PB VCN (peripheral blood vector copy number, used as a surrogate

marker for persistence of transfused cells) from month 6 to last follow up. The ERG considers that it is reasonable to assume the transgene is stable as long as TI status persists; follow-up data collected in LTF-303 will provide more evidence to support this assumption.

However, there is concern around the consequences of returning the patient's original cells (i.e. those that are not gene-corrected) in the Zynteglo product back to the patient, and that it may lead to decreased haemoglobin production and a return to a need for transfusions.

[redacted]

5.2.6.3 Organ-specific iron overload

Baseline levels of iron overload (discussed in Section 4.3.5), were based on the mean of the population studied in the Chart Review, with each simulated patient randomly assigned to an overload risk category (low, medium, high risk) for the cardiac, liver and endocrine systems. As mentioned in Section 5.2, these were assigned independently to each other and to the patient's age. Post-baseline, iron levels were dependent on the patient's transfusion status.

Transfusion-dependent patients
Iron levels in patients who are transfusion dependent were assumed to remain at their baseline levels throughout the time horizon of the model. These included all patients in the standard care arm, and the proportion of patients receiving Zynteglo who remained transfusion dependent.

Transfusion-independent patients
Transfusion-independent patients were assumed to achieve normalised iron levels in all organ systems by four years from initial treatment with Zynteglo.

Since the current evidence for long-term changes in iron levels following an auto-HSCT procedure such as Zynteglo is limited, the company searched for data on iron levels in patients that have received allogeneic-HSCT to inform the model. The company identified two papers that described the time course of iron store changes post-transplant specific to patients with TDT; however, the data provided by these studies was limited. An RCT comparing patients on deferasirox (n=12) to those receiving phlebotomy (n=14) at one year after HSCT, found reductions in LIC after one year; however these remained within the "moderate risk" category after one year [50]. One retrospective study with a longer follow-up period followed a small number of paediatric patients for four years, and found a 47% reduction in median ferritin levels after four years [36]. The company stated that the results

of this study supported an assumption of a 4-year iron normalisation period following Zynteglo therapy (p172 of CS).

Reduced transfusions

Patients who achieved meaningful transfusion reduction were assumed to also achieve reduced levels of iron, on the basis that ongoing chelation can "'catch up' on the existing iron stores and start reducing iron" (page 172 of CS).

In the model, reduced levels of iron were assumed to be achieved one year after initial Zynteglo treatment. Patients were assigned to either the low or medium overload risk categories, with relatively more patients having low iron levels compared to moderate iron levels (Table 10). It was assumed that no patient would achieve normalised iron levels, given the ongoing need for transfusions, and there would be no patients in the high iron categories. However, it was not clear how the proportions of patients in the low and moderate categories were derived.

Table 10 Distribution of iron loading for transfusion reduced patients (adapted from Table 49, CS)

Iron Normalisation at 4 Years Post-transplant	Distribution of Iron Loading			
	Serum Ferritin	LIC	Myocardial T2*	
			LIC ≥15 mg/g (High)	LIC <15 mg/g (Moderate/ Low)
Transfusion-reduced patients				
Normalised Iron	0%	0%	0%	0%
Low Iron	48%	74.5%	92.5%	92.5%
Moderate Iron	53%	25.5%	7.5%	7.5%
High Iron	0%	0%	0%	0%
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				

ERG comment

The ERG considers that the studies identified and described by the company did not support their assumption of iron normalisation in all patients,[36, 50] and that an assumed four year time to normalisation may be too optimistic. While both studies demonstrate that iron levels do reduce following an allo-HSCT, neither study demonstrates a time point by which all patients achieve normalised levels of iron. The authors of one study quoted that "only ≥4 years did ferritin levels begin to trend downward with a median 870 ng/mL".[36] The studies themselves are associated with a number of limitations, namely that they do not report on iron levels in all organ systems included in the model and they include only small patient numbers. In Chaudhury (2017), there was large variation in iron levels post-transplant, as observed by the wide confidence intervals reported for each data point.[36]

However, the studies are of limited generalizability to Zynteglo, since they included patients of a younger age and there is some evidence to suggest that age is significantly associated with post-transplant iron levels.[51] Therefore, older patients eligible for auto-HSCT may take even longer to achieve normalised iron levels.

However, the data collected to date for iron normalisation in patients who achieve transfusion independence following Zynteglo are too limited to determine the rate at which it occurs (Section 4.2.2.2). At the 48 month follow up, there remained a number of patients with moderate to high levels of serum ferritin and LIC (Table 11).

Table 11 Iron distribution (adapted from Table 22, clarification response)

Iron level	Serum Ferritin	Liver Iron	Cardiac T2*
Baseline iron levels (trial population, n=[redacted])			
Low	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]
Iron levels at 48 months (trial population, status of transfusion independence, n=[redacted])			
Low	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
High	[redacted]	[redacted]	[redacted]
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			

The model also does not contain a function of iron decline over time for those who experience transfusion independence or reduction. Post-transplant iron levels are not linked to patient characteristics or pre-transplant iron levels. There is no modelled gradual decline in iron throughout the normalisation period, as iron levels are allocated at baseline and then re-assigned to post-transplant (normalised or otherwise) levels at the end of the normalisation period. This method overestimates exposure to iron overload during the duration of the normalisation period, which results in greater exposure to risk of iron-related complications, resulting in a conservative estimate of cost-effectiveness.

5.2.6.4 Complications from iron overload

To predict the complications of iron overload, the model uses literature-based rates and risk equations to estimate the rate of developing complications based on distribution of iron levels in the heart, liver, and serum (ferritin), provided in Table 12. The company undertook a systematic literature review to identify complication rates (Section 4.1.5). Cardiac disease outcomes were reported in 17 studies,

liver-related complications in 18 studies, and a single study was identified for diabetes and hypogonadism.

The study selected to provide the rate of developing cardiac complications reported that 2.2% of patients with low iron had heart failure, compared to 3.9% with moderate iron and 12.5% with high iron.[52] The mean time to heart failure onset was reported as 24.81 months (appearing at a mean age of 32.11 years), and this was used to estimate an annualised rate for each iron overload risk category. The study also reported the proportion of patients who developed arrhythmias and pulmonary hypertension, although only the rates for heart failure were used in the model.

Angelucci (2002) was the only study identified by the company that reported liver-related complications by iron level.[29] These data were used to estimate an annual rate of liver complications for high iron. Patients with medium and low risk from iron overload were assumed not to have a risk of developing liver complications.

The systematic review identified a single source which followed up 92 patients in the UK for signs of endocrinopathies.[30] The study reported a prevalence rate for diabetes of 41% and a rate of 67% for hypogonadism, the two most common endocrinopathies. Historic iron levels, including the patients' worst myocardial T2 and LIC levels and their mean serum ferritin levels, were analysed for associations with endocrinopathies. The rate of the development of these conditions was found to be significantly associated with cardiac iron (myocardial T2) as well as age. The company extracted odds ratios for variables included in their multivariate analyses, and estimated a risk equation to predict diabetes and hypogonadism based on age, myocardial and serum iron levels. As noted in Section 5.2.1.1, patients could develop diabetes or hypogonadism but not both concurrently.

Table 12 Predicting complications of iron overload (Table 50, CS)

	Annual Rate to Develop Complication		
Iron Loading	**Cardiac Complications**	**Liver Complications**	**Source:**
Low Iron	0.011	0.000	Pepe *et al.*, Angelucci *et al.*[28, 53]
Moderate Iron	0.019	0.000	
High Iron	0.065	0.083	
	Risk Equation for Other Complications		
Coefficient Names	**Diabetes Mellitus**	**Hypogonadism**	**Source:**
Intercept	-6.642	-2.921	Ang *et al.*[30]
Myocardial T2	2.960	1.361	
Age	0.095	0.095	
Ferritin	2.695	1.065	
Duration of Follow-up	8 years	8 years	

ERG comment

The ERG was concerned that the total impact of developing cardiac complications is not accounted for, and that there is an inconsistency with how cardiac complications are modelled. Only the rate of heart failure from the study was applied in the model; however, the costs of managing cardiac complications reflected a range of conditions including those with arrhythmia, which accounted for almost half of cardiac complications identified in the study.[21, 52] However, it is possible that the use of data from this study means that the model overestimates the proportion of cardiac complications that result in excess mortality. The study is considered to be outdated, with patients first scanned between 2008 and 2012. As discussed in Section 4.3.4, improved monitoring of cardiac symptoms may result in increased detection of abnormalities, but these patients are able to be managed early and optimally, resulting in fewer of the more severe complications and ultimately improved survival.

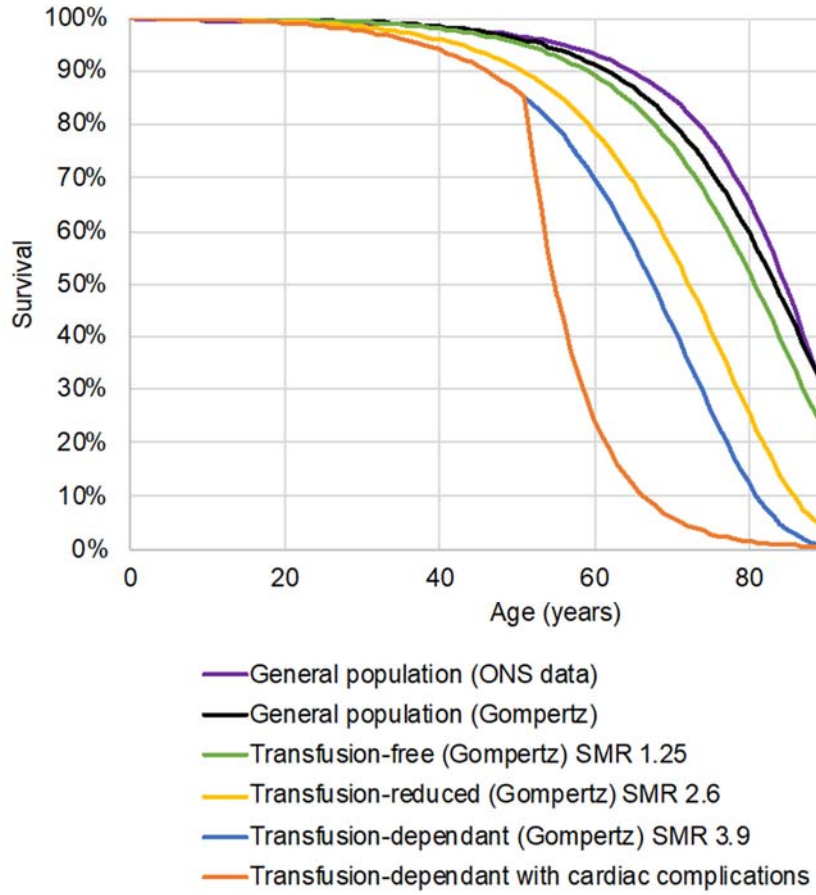
There was additional concern regarding the assumption that transfusion independent patients who achieve normalised iron levels are no longer at risk of developing iron overload-related complications. However, current evidence is limited and often contradictory. There may be a degree of pre-existing irreversible damage before treatment with Zynteglo, albeit sufficiently small to allow for eligibility for treatment, which could theoretically result in a long-term risk of developing complications. Looking to experience from the allo-HSCT population, occurrence of late hepatic, endocrine and cardiovascular complications, related to past and residual iron overload, have been acknowledged.[54] This is considered particularly relevant when transplant is performed in older children, adolescents or adults, and in patients who have received inadequate chelation therapy before HSCT. However, a French retrospective study of 99 patients found that very few patients developed a cardiac insufficiency, although no cardiac MRI was available at the onset of cardiac symptoms to allow investigation of a possible cardiac iron overload.[51, 55]

The long-term consequences of iron damage in patients who achieve transfusion independence remains an uncertainty in this analysis, and it is possible that the elevated risk of mortality modelled for these patients (Section 5.2.6.5) captures some of the impact of any complications that occur.

5.2.6.5 Mortality

In the absence of direct long-term survival data for a TDT population after treatment with Zynteglo, it was necessary to use a range of external sources to predict long-term survival. To model mortality in each treatment arm, the company applied an SMR based on transfusion-dependency status to the general population mortality. Mortality following the development of cardiac complications was modelled separately, to account for the specific impact of this aspect of the condition.

Figure 3 Illustration of SMRs applied to the general population of England and Wales (Fig 32, CS)



Age-related mortality

Age-related mortality was modelled using a Gompertz curve fit to life tables for England and Wales.[56] The purpose of fitting a curve rather than applying the survival data directly in the model is that it allows the application of a modifier, or a mortality hazard ratio, to adjust the survival for patients with TDT. Figure 3 allows for a visual inspection of fit between the fitted and observed survival estimates: the Gompertz provides an underestimate of survival between ages 60 and 85 and an overestimate thereafter, although both tend to zero at approximately the same time. No other survival models were explored.

Transfusion-independent mortality

Transfusion-independent patients in the model were assumed to have survival that is slightly worse than that of patients in the general population, with an SMR assumed to be 1.25. The company justified the use of an assumed rather than a literature-derived value due to insufficient evidence of the natural history following transplant in patients with thalassaemia, as no adult transplants have been endorsed or funded in the UK to date. The SMR was assumed to capture the potential mortality impact of myeloablative conditioning associated with the Zynteglo procedure.

Transfusion-dependent mortality

To estimate mortality in patients with cardiac complications and transfusion-dependent patients (without cardiac complications), two cost-effectiveness analyses identified by the company (described in Section 5.1 and Section 4.3.4) provided information for survival in TDT patients. An SMR of 3.9 was reported in a cost-effectiveness analysis of deferasirox and desferrioxamine in TDT, for patients who did not experience any cardiac complications.[21] This used data reported by a US study, which estimated mortality from 257 TDT patients on desferrioxamine followed between 1965 and 1994.[22] The SMR was estimated from the mortality of these patients relative to US 1998 mortality data.

In the absence of a specific SMR for patients with reduced transfusions, it was assumed that the mortality ratio was the mid-point of transition-dependent (3.9) and transfusion-independent patients (1.25), resulting in an assumed SMR of 2.6.

Cardiac mortality

The company states that cardiac dysfunction is considered to be the leading life-limiting complication in patients with TDT, due to cardiac iron accumulation. To capture the importance of cardiac mortality for patients with thalassaemia, mortality associated with the development of cardiac complications was modelled separately. All patients who acquire cardiac disease (regardless of transfusion status) were modelled as experiencing an annual mortality rate of 13%, based on a study which reported 48% survival after heart failure at 5 years.[25] The two cost-effectiveness analyses identified by the company both applied this rate in their analyses.[21, 39]

ERG comment

Mortality in transfusion-independent patients

The ERG considers that it is appropriate to model an elevated mortality for these patients compared to the general population, to capture the potential mortality impact of myeloablative conditioning associated with the Zynteglo procedure. While they will have had no iron-related complications to date (otherwise they would not be eligible for Zynteglo), they may have iron overload-related damage to a certain extent that might occur prior to transplant, which may be associated with an additional mortality risk. While there is no data available to determine the extent of this, the ERG considers that the SMR used by the company appears plausible.

Mortality in transfusion-dependent patients

The approach taken to model mortality was linked to transfusion status rather than the patients' iron levels. With greater clinician experience, alongside improved monitoring and iron chelation practices observed over the last decade, iron levels in TDT are more likely to be well controlled, and transfusion-dependent patients will have better mortality than is predicted by the older studies.

The study used to model transfusion-dependent mortality in this appraisal was outdated and of limited generalisability to the present decision problem, being based on a sample of subcutaneous chelation patients.[22] Further still, patients in the current decision problem would have lower iron levels and fewer iron overload-related complications than an unrestricted TDT population, with eligibility for Zynteglo requiring patients to be sufficiently fit to undergo the procedure.

There is some additional uncertainty regarding the estimation of the SMR value for transfusion-dependent patients. The SMR value for TDT, estimated by Delea from survival data reported by Gabutti, was "consistent with the range of parameters identified in Karnon et al (2012)" who also based their mortality rates on the Gabutti study.[21, 22, 39] Though the Karnon study did not provide a preferred point estimate, the range of RRs was between 1.1 and 3.91: the SMR applied by the company falls at the more pessimistic end of this range.[39] In the absence of a more contemporary source, the ERG has explored the impact of assuming lower SMRs in Section 6.3.6.

The same SMR was applied to patients in the standard care arm and the patients who remained transfusion-dependent after treatment with Zynteglo. Since patients are exposed to additional mortality risks due to the myeloablative conditioning procedure that occurs prior to Zynteglo, it is possible that transfusion-dependent patients after Zynteglo treatment may have an excess mortality that is higher than transfusion-dependent patients in the standard care arm.

The ERG noted that in the company's economic model, the majority of patients who developed cardiac complications died from said complications. The ERG considers that mortality related to cardiac disease is likely overestimated. As described in Section 4.3.4, improvements in monitoring of cardiac symptoms have led to improved patient outcomes after developing cardiac complications.

5.2.6.6 Adverse events of treatment

Associated with Zynteglo treatment

Patients face a risk of becoming infertile due to the use of myeloablative conditioning with transplantation. Data on infertility and sub-fertility following allogeneic HSCT is used as a proxy for possible infertility and sub-fertility following Zynteglo therapy. A study in Thailand[35] in stem-cell-transplanted, thalassaemic survivors, with infertility measured by gonadal dysfunction, reported 48% of men and 77% of women are infertile in a population receiving a mixture of standard and reduced intensity conditioning regimens. The company's UK HES analysis has indicated that 23.9% of male patients with TDT have testicular dysfunction and 19.5% of female patients have ovarian dysfunction.[57] The difference between these rates with TDT and the rates of infertility following myeloablative conditioning are applied in the model, to represent the incremental impact of infertility following myeloablative conditioning on TDT patients who receive Zynteglo. Thus, it is assumed that Zynteglo increases infertility by 24% in men and 57% in women.

Other adverse events specifically associated with Zynteglo (Section 4.2.3), are not explicitly modelled as it is assumed that the cost impact of the adverse events is captured by administration, hospitalisation and ongoing monitoring costs, and that the quality of life impact is reflected in the utility decrement associated with transplantation.

Associated with iron chelation

AEs associated with chelation therapy were included in the model if they occurred with an annual incidence of >5%. For deferiprone and deferasirox, AE data was taken from the respective prescribing information for each drug.[31, 32] For desferrioxamine, AE data were obtained from a published systematic literature review.[33] Rates are provided in Table 51 in the CS.

As with the adverse events of Zynteglo treatment, the model assumes that each adverse event disutility is captured in the health state utility. Costs of managing AEs are described in Section 5.2.8.

ERG comment

Treatment with Zynteglo is theoretically associated with the risk of insertional mutagenesis, potentially leading to development of malignancy. As per the SmPC for Zynteglo, patients are required to be monitored annually for signs of leukaemia or lymphoma.[58] The risk of developing leukaemia has not been included in the economic analysis, presumably due to a lack of sufficiently long-term data in sufficient numbers of patients to allow the estimation of malignancy risk to be estimated.

It was unclear what grade of adverse events were modelled for chelation therapy. Typically, only events of grade 3 and above are included in an economic analysis, because these have significant consequences on costs and HRQoL, and typically require hospitalisation. The wording of the description of the events in the publication suggests that the rates presented are for events of all grades, and the costs applied to these AEs are very low.

5.2.7 Health related quality of life

The company considered three main sources of evidence on HRQoL in the parameterisation of the economic model. These comprised the Zynteglo trials; a vignette study, in which time trade-off interviews were conducted with members of the general public to elicit utilities associated with TDT and its treatment; and a review of the medical records of UK TDT patients commissioned by the company (referred to as the Chart Review).[18, 59] Utility values estimated from the vignette study and the Chart Review were applied in the economic model, and were supplemented by values sourced from a number of published studies. For each health state and event, the company estimated the associated utility decrement, which was applied to general population utility norms in order to capture the impact of ageing.

Modelled patients incur a HRQoL decrement based on their transfusion status. Transfusion reduced patients incurred a disutility of 0.13, which was based on an assumption of a linear improvement in HRQoL between transfusion dependence and independence. In the company's model, transfusion reduced patients achieve a mean reduction of [redacted] in the number of transfusions per year. The company therefore assume the TD decrement of 0.27 is also reduced by [redacted] for TR patients.

A summary of the utility decrements applied in the model are provided in Table 13.

Table 13 Utility decrements used in the company base-case model (Table 56, CS)

Health state	Company base-case decrement	Assumption source
Zynteglo treatment	0.31	Vignette study
Up to one year post-Zynteglo	0.31	Vignette study
Transfusion-independent	0.02	Vignette study
Transfusion-reduced	0.13	Assumption
Transfusion-dependent	0.27	Chart Review [18]
Infertility	0.07	Busnelli *et al*., 2015; Scotland *et al*., 2011 [60, 61]
Cardiac Complications	0.11	Karnon *et al*., 2012 [39]
Liver Complications	0.067	Assumption
Endocrine Complications	0.074	Karnon *et al*., 2012 [39]

5.2.7.1 Trial-based utility values

HRQoL evidence was collected in the HGB-204, HGB-205, and HGB-207 studies (see Section 4.2.2). The company reported that for many patients in HGB-204 and HGB-205, baseline assessments were not performed. High baseline utility values were observed, and the general trend in change over time was of an initial reduction in HRQoL and a [redacted] by 12 months following receipt of Zynteglo. The company considered the baseline values to be "artificially high", which may be due to an "adjustment bias", making it difficult to detect a treatment benefit following Zynteglo. As such, the company elected not to apply the utility values estimated from EQ-5D data collected in their trials in the economic model.

5.2.7.2 Health state utility values

HRQoL associated with Zynteglo

The company conducted a vignette study to inform a number of important assumptions on quality of life of patients with TDT, including HRQoL in the time following treatment with gene therapy (Zynteglo) and of those achieving transfusion independence (following treatment with Zynteglo).[59] This study consisted of time trade-off interviews with members of the general public who were unaffected by TDT (n=207). Participants were asked to value eight TDT-related health state vignettes

which described disease and treatment scenarios in terms of a series of health events (symptoms, treatment, adverse events etc.).

The vignette study indicated a utility of 0.93 for transfusion independent patients, which the company concluded to be 0.02 lower than the general population value for this age group (40 to 45 years) using a set of population utility norms that were reported for individuals without comorbidities and no history of any health condition.[62]

The vignette study also estimated that patients would have a utility value of [redacted] in the year after treatment with Zynteglo. The public rated a vignette which describes the transplant and recovery process after gene therapy. The ERG consider this value to be appropriate and largely in line with the magnitude of disutility applied in previous appraisals for HSCT, given that Zynteglo would not be associated with GvHD.

HRQoL associated with TDT

The company commissioned a review of the medical records of 165 patients with TDT in the UK (the Chart Review), in response to the perceived lack of appropriate HRQoL data (see Section 4.3.5).[18] Utility scores were generated using the EQ-5D-3L questionnaire scores for [redacted] adult (≥16 years) patients, and the EQ-5D-Y for [redacted] patients aged 7-15 years. The mean of all patients aged ≥16 included in the Chart Review was estimated as 0.69, resulting in a utility decrement estimated by the company and applied to transfusion-dependent patients in the model of 0.27. Similarly to the transfusion independent utility value estimated from the vignette study, the decrement was estimated using a set of population utility norms that were reported for individuals without comorbidities (0.96). The company concluded that due to the similarity of this figure with that generated in the vignette study, this utility was appropriate and robust. Using the general population utility which is preferred by the ERG (0.93), the company's preferred disutility would be [redacted].[62]

The vignette study also provided an estimate for TDT, although the company considered that patient-elicited utility values were more appropriate for inclusion in the model. The public valued a health state describing life with TDT treated with transfusions and oral chelation agents with a utility score of 0.73; for those on transfusions and subcutaneous chelation agents this was 0.63. While the utilities associated with oral and subcutaneous chelation in TDT were not used directly in the company's base-case, they provided important support for their argument that patients with TDT have a 'very severely impaired life'.

ERG comment

Adjustment of HRQoL for age

Age-related decrements in quality of life were not appropriately captured in the company's model in

two fundamental ways. Firstly, an inappropriate value set was selected as the basis of the general population utility estimates. The company used age-stratified EQ-5D scores derived from a large population study by Ara and Brazier,[62] which has extensive precedent in previous NICE technology appraisals. However, they selected a subset of this population, which excludes all individuals with a history of a health condition, and with any ongoing health conditions. This is clearly inappropriate; by selecting out only individuals in perfect health in each age group, the company implicitly assume that patients with thalassaemia will never develop any other unrelated health condition during their lifetime. These patients will essentially remain in perfect health until death, excepting any previously incurred treatment related decrements associated with their TDT. This had an important effect upon the HRQoL of modelled patients, meaning that the baseline utility of a patient aged 75 would be higher than someone aged 30 in the general population. Compared to the correct general population value set, (i.e. inclusive of all individuals irrespective of health status), the modelled age-based utilities were 0.08 higher at age 40, 0.11 at age 60, and 0.19 at age 80.

Secondly, a modelling error meant that utilities were not regularly adjusted for age beyond the end of the first year of the model. This error was corrected by the company upon request by the ERG (Section 5.2.10).

HRQoL of transfusion dependent patients

The company's submission acknowledged that there is considerable existing evidence on the quality of life of patients with thalassaemia. One study elicited utilities from 196 TDT patients using the EQ-5D questionnaire.[46] These patients had a utility of 0.86 (95% CI 0.83 – 0.89), which, along with the other literature-derived estimates, the company described as 'unexpectedly high', and that they didn't appear to reflect the 'considerable burden' of the disease and its treatment. The relatively high HRQoL estimates derived from TDT patients were dismissed as being due to 'adaptation to life with a chronic condition', and therefore the company deem them not to truly represent the burden of the disease. However, the ERG disagrees that these values are too high, and that the HRQoL of TDT patients has been underestimated by the company. A patient preference report submitted by the company found that it is anticipated that only [redacted] of patients would be willing to accept treatment with Zynteglo, and only [redacted] said that beta thalassaemia significantly impacted upon their quality of life.[48] This may support the idea that current management is acceptable to most patients – rather than TDT resulting in a 'very severely impaired life', as argued by the company (Section 5.2.5).

In the clarification questions submitted to the company, the ERG questioned the use of the utility derived from the whole Chart Review population (0.69) for a number of reasons. Firstly, the demographics of the patients whose data were collected in the Chart Review appeared to differ substantively from those included in the Zynteglo trials. Table 8 in Section 5.2.3 illustrates the differences in the age distribution of the trial population whose efficacy data was used in the model,

and the Chart Review from which the modelled HRQoL values were derived. As utilities were adjusted over time to reflect the natural decline in HRQoL associated with age, the model would also have double counted the effects of aging due to the HRQoL having originally been derived from an older population.

Due to the long-term effects of transfusions and chelation therapy, and historic differences in disease management, it might be expected that the HRQoL of older patients to be lower than that of optimally managed younger patients. Therefore, the use of a mean HRQoL based on an older population for transfusion dependent patients in the model may be inappropriate. The ERG requested that the company re-analyse the HRQoL data in the Chart Review, limiting the population to only those aged from 12-35 years, and by matching to the age distribution in the three Zynteglo trials, i.e. the base-case model distribution.

The ERG also requested that, for this analysis, the company exclude patients with 'high' cardiac T2*, and patients whose existing co-morbidities were already accounted for separately in the model (to avoid double counting), or would otherwise be precluded from enrolling in the Zynteglo trials. Results were only available for TDT patients aged 16-35 who completed the EQ-5D-3L questionnaire, in whom the mean utility was [redacted] Thus, the most appropriate decrement applied in the model for TDT patients would be [redacted], i.e. the general population utility for people aged <30, 0.9383, minus the mean utility of patients aged 16-35 from the Chart Review, [redacted]. This value may be an underestimate, as at least one participant in this group rated their HRQoL as [redacted] which may be a reporting error and could have had an effect on the mean estimate.

Treatment-related utility decrements

The model assumes that only the frequency of transfusions has an effect on the disutility incurred, and a constant decrement is applied regardless of the type of chelation therapy received. This appears to be inconsistent with the results of the company's vignette study, in which the utility of TDT patients treated with oral chelation was rated 0.10 higher than for those on subcutaneous chelation (0.73 vs 0.63).

Zynteglo patients continue to receive iron chelation therapy during the 'iron normalisation' period, which, in the company's model, lasts for four years from Zynteglo infusion. However, utility decrements associated with the chelation therapies themselves were not applied in this period. It may therefore be plausible that transfusion independent patients treated with subcutaneous iron chelation therapy should incur a disutility for the duration of the iron normalisation period. A scenario applying a disutility to TI patients still on subcutaneous chelation therapy is presented in Section 6.3.9.3.

5.2.7.3 Complications and adverse event-related disutilities

While the model justifiably assumed that disutilities associated with individual adverse events would be captured in the utilities, the company separately applied decrements for broad groups of co-morbidities: infertility due to myeloablative conditioning, and for complications that develop due to iron overload including cardiac complications, liver complications, and endocrine complications (see Table 13 for a summary of utility decrements).

A disutility of 0.11 for cardiac complications was sourced from Karnon *et al*. (2012), a cost-utility analysis of deferasirox in TDT, which reported a decrement of 0.114 based on a 1993 study by Fryback *et al*.[39, 63] This study comprised time trade-off interviews with 1,356 people from a single US town between 1988 and 1990. The company also cite this cost-effectiveness study as the source of disutility estimates for endocrine complications, which again are originally from Fryback *et al.* In the company's model, the onset of a first endocrine complication (diabetes, hypogonadism etc.) is associated with a life-long utility decrement of 0.074. In the model presented by Karnon *et al*., diabetes was associated with a life-long utility decrement of 0.133, and all other endocrine disorders considered were each assumed to incur an additional decrement of 0.074, based on an assumption that each was worth half the disutility of diabetes.

A utility decrement of 0.07 associated with infertility was applied during 'childbearing years' – classed by the company as being between the ages of 15 and 45. This value was ultimately derived from a US study in which a committee used the HUI-2 scale to rate the quality of life of a female made infertile by gonorrhoea infection who wanted to have children.[64, 65]

ERG comment

Disutility associated with endocrine complications

Given more recent studies in which the EQ-5D was administered directly to patients with diabetes, a disutility of 0.133 for diabetes may be too large, particularly given advances in management of the condition over the 30 years since this value was elicited.[66, 67] The ERG therefore considers the company's preferred value of 0.074 to be reasonable for diabetes, but that other important endocrine disorders should have been associated with a separate disutility.

Disutility associated with infertility

While the value applied for infertility has precedent in previous cost-effectiveness models of fertility treatment, the ERG questions the appropriateness of its use in this disease area. The impact of infertility upon HRQoL is poorly understood and not typically well captured using EQ-5D. There is also a lack of reliable literature appropriately disentangling the effect of infertility itself from its most common causes and associated co-morbidities (e.g. endometriosis). As such, the ERG explores the

impact of removing the infertility-related decrement from the cost-effectiveness analysis in Section 6.3.9.4.

The ERG also questions the time frame within which the infertility decrement is applied; this appears to have been selected arbitrarily, and it is uncertain whether patients aged 15 would consider their lives to be adversely affected by an inability to have children. The studies cited in support of this value sought to capture the impact of infertility in individuals actively seeking fertility treatment, most of whom were around the age of 40. There may therefore be many patients aged >45 whose lives were adversely affected by an inability to have children. Equally, it cannot be assumed that all individuals of childbearing age necessarily incur the same disutility based on people seeking to address their infertility through assisted reproductive technology.

5.2.8 Resources and costs

The company's model adopted an NHS cost perspective. The costs included in the model comprised:

- Zynteglo acquisition, work-up and administration costs,
- Post-transplant monitoring costs,
- Blood transfusions,
- Iron chelation treatment and their associated administration costs,
- Monitoring costs for transfusion and chelation therapy,
- Management of chelation-related AEs,
- Management of iron overload-related complications.

Unit costs were sourced from a number of national sources, including NHS Reference Costs, the British National Formulary (BNF) and from the Personal Social Services Research Unit (PSSRU).[68-70] The key costs included in the model are summarised in Table 14, and a detailed description is provided in Section B.3.5 of the CS.

The required tests prior to Zynteglo treatment were based on the protocol for Study HGB-207. The company noted that a cost has been assigned to each test, despite not all being required. The costs associated with mobilisation and apheresis were sourced from a French budget impact analysis,[71] since the collection of relevant costs by bluebird bio were still ongoing at the time of the submission. A proportion of patients required multiple rounds of mobilisation, based on data from HGB-204, -205 and -207. Post-transplant monitoring was informed by the protocol for a bluebird bio registry, REG-501.

A micro-costing approach for transfusions was based on the costing statement for NICE guideline on blood transfusion.[72] Dosing of the iron chelation therapies was estimated from their respective

SmPCs. The cost of managing AEs associated with oral chelation was estimated at £16.33 per year, with £3.26 for subcutaneous chelation.

Table 14 Summary of the costs included in the economic model

Description of cost	Patients ≤18 years	Patients >18 years	Source
Zynteglo			
Zynteglo acquisition cost	[redacted]	[redacted]	bluebird bio, includes PAS
Pre-transplant cost	£27,057	£27,130	
Transplant-related costs	£34,539	£18,529	NHS Reference Costs[68]
Post-transplant monitoring costs – Years 1 & 2	£1,128	£1,128	NHS Reference Costs[68]
Post-transplant monitoring costs – Years 3 & 4	£927	£927	NHS Reference Costs[68]
Blood transfusions and chelation			
Annual treatment of blood transfusions and subcutaneous chelation therapy (transfusion-dependent)	£18,168	£23,287	NHS Reference Costs,[68] Agrawal *et al.,*[73] NICE guideline on blood transfusions,[72] PSSRU 2018,[70] BNF,[69] Bentley et al.,[74] Karnon *et al.*[75]
Annual treatment of blood transfusions and oral chelation therapy (transfusion-dependent)	£22,538	£24,772	
Annual treatment of blood transfusions and subcutaneous chelation therapy (transfusion-reduced)	£15,362	£16,290	
Annual treatment of blood transfusions and oral chelation therapy (transfusion-reduced)	£14,532	£15,460	
Health state costs			
Cardiac complications – Year 1	£6,871		Karnon *et al.*[39]
Cardiac complications – Year 2+	£3,534		Karnon *et al.*[39]
Liver complications	£1,754		NHS Reference Costs[68]
Endocrine complications (diabetes or hypogonadism)	£1,557		Karnon *et al.*[39]

5.2.8.1 ERG comment

The ERG has a number of concerns regarding the costs used in the economic model. These include the a number of minor costs associated with Zynteglo treatment that may have been omitted from the analysis, the use of BNF drug acquisition costs rather than eMIT costs, and the uncertainty in the cost of managing iron overload-related complications.

Underestimation of some of the costs of Zynteglo treatment

The ERG believes there may be costs associated with Zynteglo that have not been captured in the economic model. However, the ERG believes the impact of this on the company's base-case ICER to be limited, as they account for a small proportion of the total costs.

The model only estimates the cost of Zynteglo treatment for those patients who are successfully infused. There may be patients who initiate pre-transplant testing but are found not to be eligible for treatment with Zynteglo, or who experience failure of mobilisation, whose costs are not account for.

The revised CONSORT flow diagram presented in the company's response to clarification questions shows that one patient from the ITT population in HGB-204 discontinued Zynteglo due to inadequate stem cell mobilisation (Section 4.2.1). The costs that this patient incurred would include those associated with hypertransfusion, pre-treatment tests, and the costs of mobilisation and apheresis. In the company's base case, the pre-transplant costs in the Zynteglo arm are [redacted], and so a failure during the pre-transplant stage could result in irrecoverable costs for which there are no associated benefits. The CONSORT flow diagrams also show that, upon screening, patients in HGB-204 and 207 were found not to be eligible for Zynteglo and did not progress to gene therapy treatment (Section 4.2.1). The total cost of pre-treatment stage tests for such patients ≤18 and >18 are £2,629 and £2,539, respectively.

The CS includes thalassaemia genotyping in the listed pre-transplant tests, and states that the cost of genotyping is to be incurred by bluebird bio. As a result, the economic model assumes no cost of genomic testing. In the NHS, the recording of genotype appears to be already undertaken in some centres but practice is varied. (Section 3.1) In the company's Chart Review of medical records, [redacted] of patients had a recorded genotype, although no details were provided as to how genotype was determined. The clinical advisor to the ERG noted that it was not routinely undertaken at their centre.[76] The ERG also has concerns about the practicalities of the costs of genomic testing being incurred by the company, as testing is moving towards a new centralised system and it might be challenging for bluebird bio to incur the costs. As a result, the ERG notes that the company's model could result in underestimated associated costs to the NHS of Zynteglo treatment.

Additional resource use that may be associated with Zynteglo treatment and has been omitted from the model includes: the cost of repeating all childhood vaccinations 6 months post-transplant; and the long-term annual monitoring of transfusion independent patients for signs of leukaemia and lymphoma.[1, 59] The appropriate length of hypertransfusion prior to Zynteglo infusion is unclear, as the source study reported a duration of 3 months compared to one month applied in the company model, although the ERG noted that this study was based in France and may not be generalizable to UK practice.[71]

eMIT drug costs

The company sourced the unit costs of drugs in the model from the BNF.[69] The costs for a number of these, including the subcutaneous iron chelating agent desferrioxamine and two drugs used during the pre-transplant stage of Zynteglo treatment, can also be obtained from the electronic market information tool (eMIT).[77] This provides information on the average price paid by the NHS for pharmaceuticals, which can differ from the list prices listed in the BNF, and is seen as a more accurate and up to date indicator of costs. The difference between the BNF and the eMIT unit costs are presented in Table 15.

Despite a small difference in the BNF and eMIT drug acquisition costs of desferrioxamine, the ERG believes the overestimation of the costs could be important, given patients treated with chelation therapy remain on this treatment for life. The ERG considers eMIT to be a more appropriate source of drug acquisition costs, where available, and presents a scenario analysis in Section 6.3.10 using these values.

Table 15 Pre-transplant drug acquisition costs

Drug	Source in CS	BNF	eMIT
Busulfan	Assuming recommended daily dose 0.8mg/kg for 4 days (SmPC). Busulfan 60mg/10ml concentrate for solution for infusion vials (Accord Healthcare Ltd)	£1529.50	£386.14
Ursodeoxycholic acid	Assuming recommended dose of 10 mg/kg/day for 21 days (SmPC); unit cost of Ursofalk (Dr. Falk Pharma UK Ltd) 150mg tablets (60 tablets per package)	£19.02	£8.46
Desferrioxamine	Assuming 6 times per week, dose 40 mg/kg.	£46.63	£34.06

Cost of managing iron overload-related complications

There were some minor limitations associated with the estimation of the costs of managing iron overload-related complications. The company obtained the cost of cardiac complications from a cost-effectiveness study of chelation therapy and inflated to 2018 prices.[39] This study used a value reported by an older cost-effectiveness analysis,[21] where the costs of managing cardiac complications were estimated from US health insurance and pharmacy claims for patients with a diagnosis of cardiomyopathy, conduction disorders, cardiac dysrhythmias, or heart failure. It is unclear how the US health insurance costs were converted to UK-specific costs, and the ERG has concerns regarding how generalisable these costs are to current NHS practice. They are also inconsistent with how cardiac complications are modelled, where only the time to heart failure is captured.

As noted previously (Section 5.2.1), the endocrine complication was modelled as the first occurrence of either diabetes or hypogonadism and these conditions could not occur concurrently. In this respect, the total cost of endocrine complications will be underestimated in the model, as only one condition is accounted for. However, the total endocrine cost may be overestimated due to differences in prevalence rates between diabetes and hypogonadism. Given the range in the costs of managing endocrine complications (annual costs: diabetes (£4,497), hypogonadism (£487), hypoparathyroidism (£233) and hypothyroidism (£30)), the (unweighted) average endocrine cost will underestimate the cost of managing diabetes and overestimate the cost of hypogonadism in the model. Since hypogonadism is associated with a higher prevalence rate than diabetes in the model (41% and 67%, respectively), it is more likely to be the first (and therefore, only) occurring event.[30] As a result, if a

patient only develops hypogonadism, their total cost will be overestimated. Additionally, the use of hypo- and hypoparathyroidism costs in the average cost means that it is inconsistent with the rate of endocrine complications, where only the time to hypogonadism and diabetes are captured.

5.2.9 Cost effectiveness results

Zynteglo has a confidential patient access scheme (PAS), comprising a simple discounted price per patient of [redacted]. This is a discount of approximately [redacted] on the list price. The original company submission considered a complex PAS, but this had not been included in the cost-effectiveness results reported below as it is still under development and has not yet been approved at the time of the submission. The results of the original and uncorrected company base-case ICER cannot be reproduced in this report due to the inclusion of currently unconfirmed commercial agreements. No interventions that comprise the Zynteglo workup, administration and monitoring costs or those used in transfusions and iron chelation therapy have an associated PAS.

The cost effectiveness results outlined in this section are provided from a corrected and updated company analysis following the ERG's clarification questions and subsequent model corrections. The results presented below include the simple PAS discount for Zynteglo.

5.2.9.1 Base case results

Table 16 presents the base-case deterministic analysis of Zynteglo. These results are based on the mean costs and QALYs of 600 patient profiles generated by the model.

It shows that Zynteglo was associated with increased costs (cost difference of [redacted]) and was more effective (gain of 13.14 QALYs), compared with standard care (transfusions and iron chelation therapy). The company's base-case ICER was [redacted] per QALY.

In the Zynteglo arm, treatment costs of Zynteglo accounted for 88% of total costs, of which 84% were Zynteglo acquisition costs. Of the remaining costs, the item that accounted for the largest proportion of costs were the transfusion and iron chelation.

In the SoC arm, the costs of transfusion and iron chelation therapy accounted for 95% of the total costs. Oral chelation therapy plus transfusions accounted for the largest proportion of this, making up 65% of the total SoC costs. Of the remaining costs, iron overloading complications accounted for the largest proportion.

Table 16 Company model base-case results (Table 2, clarification response)

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	37.79	17.20			
Zynteglo	[redacted]	53.63	30.34	[redacted]	13.14	[redacted]

CS, company submission; ICER, incremental cost-effectiveness ratio; LYs, life-years (undiscounted); QALYs, quality-adjusted life-years (discounted); PAS, patient access scheme; SoC, standard of care (consisting of transfusions and iron chelation therapy)
These results were provided by the company on 20th December 2019

5.2.9.2 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) by running 1,000 iterations of the 600 profiles produced in the economic model. In each iteration, the model drew inputs from defined distributions for selected parameters. The mean probabilistic ICER of Zynteglo was [redacted] per QALY gained versus standard care. The cost-effectiveness plane showing the results of the PSA can be seen in Figure 4.

The company attributed the small differences between the results of the deterministic and the probabilistic analyses to the difference in the age distribution sampled in each analysis. The PSA allowed ages of up to 50 years, whereas only patients up to the age of 34 are included in the efficacy population.

The ERG has concerns regarding the 1,000 iterations used in the PSA and whether this accurately characterises decision uncertainty. Running 1,000 iterations required considerable computation time and due to time constraints and the nature of the company's model structure, the ERG was unable to re-run the model with an increased number of iterations.

Table 17 Company model probabilistic cost-effectiveness results (adapted from Table 3, clarification response)

Technologies	Total costs [95% CI]	Total LYs [95% CI]	Total QALYs [95% CI]	Incremental costs	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	39.03 [31.41 ; 46.63]	17.51 [14.10 ; 20.69]			
Zynteglo	[redacted]	53.82 [52.52 ; 55.01]	30.39 [29.63 ; 31.11]	[redacted]	12.89	[redacted]

CS, company submission; ICER, incremental cost-effectiveness ratio; LYs, life-years (undiscounted); QALYs, quality-adjusted life-years (discounted); PAS, patient access scheme; SoC, standard of care (consisting of transfusions and iron chelation therapy)
These results were provided by the company on 20th December 2019

Figure 4 Cost-effectiveness plane for Zynteglo (generated from the company model)

The probability that Zynteglo is the most cost-effective treatment option at WTP threshold of £30,000 is [redacted]. The cost-effectiveness acceptability curve for both comparators is provided in Figure 5.

Figure 5 Cost-effectiveness acceptability curve for Zynteglo and transfusions and chelation therapy (Fig 9, clarification response)

The results show that there is a difference of [redacted] per QALY between the deterministic and probabilistic ICERs. The average incremental QALYs gained with Zynteglo compared to transfusions and chelation therapy was [redacted], which was [redacted] QALYs less than in the deterministic analysis.

5.2.9.3 Deterministic sensitivity analysis

The company presented a series of deterministic sensitivity analyses (DSA) in the form of univariate sensitivity analyses to assess the impact of varying key model input parameters upon the ICER. The DSA inputs can be seen in the company's economic model.

A tornado diagram summarising the most influential parameters as reported by the company is presented in Figure 6. The results indicate that varying the rate of transplant success, the acquisition cost of the chelation therapy and the distribution of oral chelation therapies have the greatest impact on the ICER. The age distribution used in the model was also a driver of the model's results. In the base case, transplant success is 83.3%, however reducing the transplant success to 66% results in an increase of [redacted] in the ICER.

Due to an error in the implementation of the DSA in the company's model, the results provided in Figure 6 are based on an ERG corrected version of the model. For more detail see Section 5.2.10.

Figure 6 Univariate sensitivity analysis for Zynteglo vs standard care (generated from the company model, containing ERG corrections)

5.2.9.4 Scenario analyses

Following amendments made to the original base-case at the request of the ERG, the company provided resubmissions of original scenario analyses in their response to clarification questions. The scenarios assessed the robustness of the model results and the impact of the assumptions included in the base-case analysis. The results of the scenario analyses performed on the company's updated base case are presented in Table 18.

Table 18 Company scenario analysis results

Parameter	Value	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Baseline age and gender	Demographic characteristics taken from HES data	[redacted]	12.00	[redacted]
Mortality	No impairment of survival due to myeloablative conditioning (SMR = 1)	[redacted]	13.85	[redacted]
Utility	Values from vignette study only	[redacted]	12.10	[redacted]
These results were provided by the company on 20th December 2019				

The results of the company's scenario analyses show the result were sensitive to a change in the baseline demographics.

5.2.9.5 Additional scenarios requested by the ERG at points for clarification

Additional scenarios were requested by the ERG and were provided by the company at the clarification questions stage. The scenarios requested were:

i) Using age- and gender-appropriate distributions of baseline iron load and patient weight i.e. for each age and gender profile, Chart Review data to be analysed to provide the mean patient weight and baseline iron levels,

ii) Recalculate the baseline iron distribution data from the subset of patients aged 12-35 without comorbidities that would preclude treatment with Zynteglo,

iii) Recalculate baseline iron distribution data from the subset of all patients aged ≤ 18 without comorbidities that would preclude treatment,

iv) Proportion of patients receiving each type of chelation therapy and mean number of transfusions for the transfusion-dependent population (both of which are sourced from the Chart Review) to be re-analysed limited to patients aged 12-35 years,

v) Proportion of patients receiving each type of chelation therapy and mean number of transfusions for the transfusion-dependent population to be re-analysed limited to patients aged ≤18 years,

vi) Reanalyse the HRQoL data from the Chart Review to limit the included patients strictly to those who would be eligible for Zynteglo, i.e. exclude patients with 'high' T2* iron (≥15 mg/g),

vii) Limit the HRQoL data to those included in scenario (vi) and in addition only include those patients aged 12-35 years,

viii) Limit the HRQoL data to those included in scenario (vi) and in addition only include all patients aged ≤ 18,

ix) Limit the HRQoL data to those included in scenario (vi) and average the HRQoL weighted according to the age distribution in the three Zynteglo trials.

Table 19 ERG requested scenario analyses

Parameter		Value	Incremental Costs	Incremental QALYs	ICER (£/QALY)
(i)	Baseline iron and weight	Reanalysed Chart Review data	[redacted]	13.14	[redacted]
(ii)	Baseline iron	Limited to age 12-35 years	[redacted]	13.16	[redacted]
(iii)	Baseline iron	Limited to age ≤ 18 years	[redacted]	13.18	[redacted]
(iv)	Chelation therapy	Limited to age 12-35 years	[redacted]	13.14	[redacted]
(v)	Chelation therapy	Limited to age ≤ 18 years	[redacted]	13.14	[redacted]
(vi)	HRQoL	Limited to eligible patients i.e. removal of patients with T2* iron ≥15 mg/g	[redacted]	11.16	[redacted]
(vii)	HRQoL	Scenario (vi) and limited to age 12-35 years	[redacted]	8.93	[redacted]
(viii)	HRQoL	Scenario (vi) and limited to age ≤ 18 years	[redacted]	9.42	[redacted]
(ix)	HRQoL	Scenario (vi) and reweight Chart Review according to trial age distribution	[redacted]	10.41	[redacted]

For further details of the ERG's description of the limitations of the baseline characteristics, chelation therapy and the HRQoL see Sections 5.2.3, 5.2.4 and 5.2.7, respectively.

The scenario analysis with the largest impact on the results is the reanalysis of the HRQoL data to match patients included in the Zynteglo trials, i.e. through exclusion of patients with high T2* and limiting the age to 12-35 years. This reanalysis resulted in an increase in the company's base case ICER to [redacted] per QALY.

5.2.10 Model validation and face validity check

5.2.10.1 Use of the DICE framework

Transparency is one of the key benefits that has been ascribed to the DICE method. The DICE model can be implemented in a spreadsheet, containing a set of tables that specify the conditions with their values and the events with their consequences. However, the transparency of the model relies upon accurate and thorough reporting of how assumptions are implemented and outcomes are modelled. If the modeller uses inconsistent labelling and does not adhere to the prescribed table and reporting structure, the model can very quickly lose transparency. The ERG found that the model originally submitted by the company did not contain sufficient annotation, which made it challenging to understand and validate. It was also not accompanied by the model technical report, user guide and model blueprint, all of which are of key importance for understanding a DICE model. Given that this is an emerging and evolving method, the ERG would like to strongly emphasise the importance of providing the supporting documentation to review groups, and reporting standards should be formalised for NICE submissions.

Since the DICE model is a relatively recent development compared to other model structures that have traditionally been applied within the context of HTA, there are few applications of the method published to date. The ability of the DICE model to predict and replicate the results of a non-DICE model in a NICE context have been published in two analyses (although there may be others that the ERG is not aware of).[78, 79] In both examples, the double-programmed model performed very similarly to the DICE model; however, these were based on model structures that are a lot simpler (containing fewer events) than that implemented in the current appraisal of Zynteglo. The company also stated that an independent health economics agency produced a simplified cohort (Markov) version of the DICE model; however, specific details were not provided.

The company stated that the panel of independent health economists that were consulted throughout the model development process were initially sceptical regarding the use of a DICE model, given previous challenges in NICE appraisals, but were reassured by the company stating that NICE and ERGs have been provided extensive training. However, to our knowledge it is mostly the NICE guideline group and not the technology appraisal groups that have experience with using DICE models prior to this appraisal and no specific ERG training has been implemented.

The ERG also noted the significant run time of the model. To run the PSA took between 18 and 23 hours, depending on the machine used.

5.2.10.2 Model errors

The ERG conducted a validation of the functions and input parameters contained in the executable model. A validation of the underlying code that implements the DICE framework was not undertaken, since this has been reported on by prior groups.

The ERG identified an error in how age-related utilities were estimated in the originally submitted model. This was corrected in an updated version of the model provided by the company at the clarification stage. In the original model, the age characteristic used to calculate the age-related HRQoL of a patient was not updated at regular intervals beyond the first year of the modelled time-horizon. Therefore, when a patient's utility was drawn to calculate accrued QALYs, the model used the utility associated with the last time this age characteristic had been updated, which was often several decades prior, thus the health state utilities were not appropriately adjusted for age.

The impact of this correction was to reduce the number of QALYs gained across both the Zynteglo and SoC arms. As Zynteglo patients lived to a greater age in the model, and thereby incurred larger age-related utility decrements, the magnitude of the effect of the correction was greatest in these patients. The ICER of Zynteglo versus SoC, therefore, increased.

The updated model contained a number of inconsistencies regarding the input values when compared to the original model; these were also amended by the company in a subsequent version of the model.

In the final version of the model submitted by the company, the ERG noted that the estimation of the 95% confidence interval around the proportion of patients achieving transfusion independence differed to that of the original model. The 95% CI in the updated model was narrower, which had the impact of making the value appear to be less influential in the DSA. The ERG considered that the original model contained the correct calculations, and updated the analysis accordingly.

5.2.10.3 Stability of results

The model, a discrete event simulation (DES), estimated the mean cost-effectiveness results from the total costs and QALYs generated by a number of simulated patients. Stochastic models, such as DES, typically require a large number of iterations to generate stable results, as some variation will appear as a result of 'random noise', or first-order uncertainty.[80] The ERG noted that the company model used a total number of 600 patient profiles to estimate their base case deterministic results. To assess

the stability of results using different numbers of iterations, the ERG re-ran the deterministic model with up to 20,000 profiles.

Table 20 Results of the company base case analysis based on different numbers of patients profiles

Number of profiles in the model	ICER	Difference from company model
100	[redacted]	[redacted]
500	[redacted]	[redacted]
600 (company model)	[redacted]	-
1,000	[redacted]	[redacted]
5,000	[redacted]	[redacted]
10,000	[redacted]	[redacted]
20,000	[redacted]	[redacted]
50,000	[redacted]	[redacted]

As illustrated in Table 20, there is a large amount of variation in the ICER, particularly when small numbers of patient profiles were generated. Results appeared to stabilise when higher number of patient profiles were generated. To determine the driver of the differences of the results, the ERG examined the outcomes in the models of 600 and 5000 patient profiles (Table 21). With a greater number of patient profiles, Zynteglo total costs increased while SoC total costs decreased, and the number of QALYs in each arm decreased. From inspection of the breakdown of results in both models, it appears that the difference in costs was mostly due to iron chelation. The difference in life years between the two versions of the models was small, but potentially contributed towards the difference in lifetime chelation costs.

The ERG remained unclear on why the model estimated a higher ICER with a greater number of profiles, and which was the most appropriate method to generate results.

Table 21 Comparison of results of the model run with 600 and 5,000 patient profiles

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case (with 600 patient profiles)					
SoC	[redacted]	17.20			
Zynteglo	[redacted]	30.34	[redacted]	13.14	[redacted]
Model with 5,000 patient profiles					
SoC	[redacted]	17.01			
Zynteglo	[redacted]	29.90	[redacted]	12.90	[redacted]

5.2.10.4 Consistency of results with published economic models

To validate the prediction of life years in the standard care arm of the model, the company provided a comparison to those estimated by Weidlich,[41] a recent UK-based analysis estimating the total costs, QALYs and life years for patients on blood transfusions and iron chelation therapy with TDT.[41] Survival was predicted in this study using a meta-analysis, with a focus on patients born after 1970 and European-based studies, as thalassaemia management was considered to be most similar to the UK. Their model predicted a similar number of QALYs to the company model (11.5 in the Weidlich analysis compared with 12.55 in the company model using an equal discount rate). Higher costs predicted by the company model were due to a greater proportion of patients on the more expensive chelation agent deferasirox. However, this study was subject to the same limitations that are present within this appraisal. The survival data used in this analysis were based on patients born between 1970 and the early 2000s, and not those born more recently who will probably achieve a better life expectancy due to advancements in clinical management. The clinicians interviewed by the study authors expected disease patterns to change in the future and patients' life expectancy to improve.

5.3 Conclusions of the cost effectiveness section

The ERG considered the company's economic submission to meet the requirements of the NICE reference case with a few notable exceptions, which may have a significant impact upon the cost-effectiveness results. Additionally, the ERG identified a number of uncertainties regarding key model inputs. The main concerns identified by the ERG include:

1. The complexity of the modelling approach

The ERG considers that the modelling approach employed introduced unnecessary complexity and reduced transparency, and the key benefits of a DICE modelling framework were not fully exploited. Despite this model complexity, a number of simplifying assumptions were made that undermined its face validity. A limited number of baseline characteristics were used to define individual patients, and their interaction with other outcomes was limited. Also, iron overload-related impacts to the three organ systems included in the analysis were modelled independently with no interaction between them, and the model did not account for patient history to determine the rate of future events. The ERG accepts that in many cases, this was due to limited data to inform these structural assumptions, but as a result, the model complexity created significant challenges for the ERG in terms of identifying and following key assumptions without much benefit.

2. The use of iron chelation agents in current practice is subject to uncertainty

Clinical practice regarding the use of iron chelation agents is evolving, due to improvements in evidence and confidence around the use of newer chelation agents. This is particularly true regarding to the use of chelation therapies used in combination, an option which may be becoming more common. The company's review and analysis of medical records of TDT patients in the UK showed that combination therapy was more common in those aged 12-35 than in the older age groups.

3. Differences between the modelled and the eligible population

The mean body weight used in the model was based on an average for the population. Considering that the model fails to account for an interaction between weight and age, the value was thought to be too high for younger patients. This has implications for the cost of chelating agents, as dose is calculated by patient weight.

Presence of cardiac and liver complications preclude patients from eligibility with Zynteglo. However, the model also excludes patients with endocrine complications such as hypogonadism when they would, in fact, be eligible for Zynteglo.

Patients with certain genotypes may be underrepresented in the Zynteglo trials. This limits the generalisability of the modelled population to the eligible population in the UK, and has a potential impact on the estimation of the treatment effect of Zynteglo since the underrepresented mutations are generally associated with poorer outcomes.

4. Long-term benefits of Zynteglo are uncertain

While late graft rejections are generally considered to be rare events in HSCT, the long-term benefits of Zynteglo remain uncertain. There is currently insufficient available follow-up data in the trials to determine whether there is a permanent treatment effect, although a loss of transfusion independence has not yet been recorded in any patients.

[redacted], so there is a concern regarding the consequences of a low transduction percentage upon the long-term persistence of a sufficient proportion of cells capable of producing healthy haemoglobin.

5. The iron normalisation period is potentially too short

There is a lack of representative data on how long it takes for iron levels to normalise in patients who achieve transfusion independence. The ERG considers the Zynteglo trials and the studies identified by

the company to provide insufficient support for their assumption of iron normalisation in all patients achieving transfusion independence, and that the assumed four year time to normalisation may be too optimistic. No evidence source appears to identify a time point by which all patients achieve normalised levels of iron. The studies themselves are associated with a number of limitations, and are of limited generalisability to Zynteglo since they included much younger patients who received allogeneic HSCT.

6. Mortality of transfusion-dependent patients is likely to be over-estimated

The mortality of transfusion dependent patients was likely to be over-estimated. Survival rates were estimated from an outdated study of patients performed when standard practice comprised subcutaneous chelation agents. With greater clinician experience alongside improved monitoring and iron chelation practices observed over the last decade, iron levels in TDT are more likely to be well controlled, and survival in well-chelated patients is thought to be approaching a normal pattern. Further still, patients in the current decision problem would have lower iron levels and fewer iron overload-related complications than the unrestricted TDT population followed in the study, with eligibility for Zynteglo requiring patients to be sufficiently fit to undergo the procedure.

7. The use of a discount rate of 1.5% is unjustified

The company applied a discount rate of 1.5% to costs and benefits, which is inconsistent with the NICE reference case. This significantly impacts the results of the analysis, since the costs of Zynteglo are incurred upfront while the potential benefits are generated over the patient's lifetime. The ERG believes there to be little justification for the use of the non-reference case discount rate of 1.5%, and disputes all arguments put forward by the company in support of this assumption.

The company asserted that Zynteglo restores people who would otherwise die or have a very severely impaired life to full or near full health. While HRQoL and survival of patients who are successfully treated with Zynteglo could reasonably be expected to approach that of the general population, the ERG consider that the impact of TDT on the survival and HRQoL of optimally managed patients has been overstated, particularly using modern monitoring and treatment strategies. The ERG considers that the evidence collected to date is insufficient to determine whether the benefits of Zynteglo persist into the long term. Finally, the company stated that Zynteglo will not commit the NHS to significant irrecoverable costs. However, this was on the basis of a proposed outcomes-based commercial agreement, which remained under negotiation at the time of the submission. Under most pricing scenarios, the potential cost to the NHS associated with anything but an indefinite treatment effect in all patients could be very large.

8. HRQoL of patients on standard care was underestimated

The HRQoL for patients who are transfusion dependent was estimated from a review and analysis of medical records of UK TDT patients. However, this Chart Review population is older than the modelled patients. Due to the long-term effects of transfusions and chelation therapy, age related decline in HRQoL, and historic differences in disease management, it might be expected that the HRQoL of older patients to be lower than that of optimally managed younger patients.

The population in the Chart Review also included patients with existing complications who incurred separate decrements in the model (i.e. the impact of these was double counted). The ERG was concerned that due to both of these issues the utility value used by the company was underestimated, as it is much lower than reported in other studies.[46, 47]

A re-analysis of the medical records, limiting the population to those aged from 12-35 years and without iron overload-related complications that were already accounted for in the model, produced a much higher utility estimate. This may support the idea that current management is acceptable to most patients, rather than resulting in a 'very severely impaired life'.

9. Inappropriate source of age-based HRQoL values was used

An inappropriate value set was selected as the basis for the general population utility estimates. The company used a subset of the general population, which excludes all individuals with a history of a health condition, and with any ongoing health conditions. This is inappropriate because it means that patients in the model will essentially remain in perfect health until death, excepting any treatment- or complication-related decrements associated with their TDT explicitly accounted for in the model. As a result, age-based utilities were much higher than genuine general population values, leading to an overestimation of QALYs.

The utility decrement associated with transfusion dependence, estimated from the difference between the mean value observed in the Chart Review and the "perfect health" population utility value, was subsequently estimated to be greater than it should have been. This undermines the company's argument that patients on standard care experience a 'very severely impaired life', comparable to patients with advanced cancer, which was used to justify the lower discount rate.

10. Disutility for patients who become infertile following Zynteglo is uncertain

The impact of infertility upon HRQoL is poorly understood and not typically well captured using EQ-5D, and the value was estimated from a source that was not generalisable to the present context. It

may not be appropriate to capture this impact within this appraisal, as it has previously only been used in models of assisted reproductive technologies for patients actively seeking fertility treatment. It was also uncertain whether the duration for which the decrement was applied was appropriate.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

The following sections provide details of the additional analyses undertaken by the ERG to explore the key issues and uncertainties raised in the review and critique of the cost-effectiveness evidence submitted by the company. Section 6.2 describes the impact of errors identified in the ERG's validation of the company's executable model.

Section 6.3 presents the results of a series of exploratory analyses based upon uncertainties identified by the ERG. These scenario analyses examine the impact of a number of alternative assumptions upon the robustness of the cost-effectiveness results, focusing on the following:

- Baseline population characteristics and presence of co-morbidities adjusted to better reflect the eligible population,
- Distribution of chelation agents adjusted to better reflect the eligible population, using a re-analysis of the Chart Review data,
- Clinical effectiveness data adjusted for the underrepresentation of the IVS-I-5 and IVS-I-110 genotypes,
- Alternative assumptions around the rate of early engraftment failure and the long-term persistence of transfusion independence,
- Alternative assumptions on the mortality of transfusion dependent patients,
- Alternative assumptions around iron normalisation and the development of iron overload-related complications,
- Impact of using a 3.5% discount rate on costs and effects,
- Use of a number of different sources and assumptions around health-related quality of life,
- Drug acquisition costs from eMIT.

In Section 6.4, the ERG presents an alternative base-case which combines a number of the exploratory analyses presented in Section 6.3, which the ERG considers to better reflect the cost-effectiveness of Zynteglo were this technology to be approved for use on the NHS. A number of scenario analyses on the ERG alternative base-case analysis are also presented.

The results in this section are presented inclusive of the confidential PAS discount for Zynteglo. At the time of the submission, this comprised [redacted]. For brevity, the comparator of transfusions and iron chelation

is referred to as standard of care, or SoC, throughout. Life years presented are undiscounted. Deterministic results are based on 600 patient profiles, to be consistent with the company base-case analysis: results of the ERG alternative base-case analysis, based on 5,000 patient profiles, are also presented. Due to time constraints and the nature of MS Excel-based DICE models, it was not possible to produce probabilistic results for each of the following scenarios, therefore all results in the following section are deterministic unless otherwise stated.

6.2 ERG corrections and adjustments to the company's base case model

The correct and latest iteration of the company base-case results are presented in Table 22, and all additional ERG analyses that follow use this model as a basis. An error in the company's executable model was identified by the ERG, which was highlighted in the ERG's clarification letter to the company, who later provided a corrected version of the model. Further details of the error are provided in Section 5.2.10.

Table 22 Deterministic results of the corrected company base-case analysis (Table 2, clarification response)

Intervention	Total			Incremental		
	Costs	LYs	QALYs	Costs	QALYs	ICER
Company base-case analysis						
SoC	[redacted]	37.79	17.20			
Zynteglo	[redacted]	53.63	30.34	[redacted]	13.13	[redacted]

* undiscounted life years

6.3 Additional ERG analyses

6.3.1 Changes to baseline population characteristics

As discussed in Section 5.2.3, the ERG did not consider the baseline characteristics of the modelled population to adequately represent those of the population eligible to receive Zynteglo in practice. Firstly, the mean patient weight ([redacted]), based on the average weight of patients in the Chart Review, is likely to be higher than that of much of the eligible population at baseline, many of whom are aged <18.

The ERG requested that the company add into the model the functionality to link patient weight to their age at baseline. In this scenario, patients aged 12 to 17 had a mean body weight of [redacted], and the weight of those aged over 18 was [redacted]. When paediatric patients reach the age of 18, any weight-based drug costs are thereafter based on the adult weight. The results of this scenario are presented in Table 23, which show a small increase in the ICER of Zynteglo versus SoC (transfusions and iron chelation). This is attributable to the reduction in accrued costs of the chelation agents.

Table 23 ERG Scenario 1: Age category-specific body weight (paediatric and adult)

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	53.63	30.34	[redacted]	13.13	[redacted]	[redacted]

* undiscounted life years

Section 5.2.3 also details the ERG's concern that the company's model did not account for presence of endocrine disorders at baseline. The company stated in response to a clarification question from the ERG that individuals with TDT would not be precluded from receiving Zynteglo due to hypogonadotrophic hypogonadism or diabetes. The ERG therefore presents a scenario in which 20% of patients have hypogonadism at baseline (per the Chart Review population), and thus incur additional costs of treatment and the effects upon HRQoL (Table 24). The impact on the ICER is relatively small, since this assumption applies to patients in both treatment arms.

Table 24 ERG Scenario 2: Hypogonadism present in 20% of patients at baseline

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	17.10				
Zynteglo	[redacted]	53.63	30.08	[redacted]	12.98	[redacted]	[redacted]

* undiscounted life years

6.3.2 Clinical effectiveness data adjusted for the underrepresentation of the IVS-I-5 and IVS-I-110 genotypes

As discussed in Section 5.2.3, the ERG considers the modelled population to underrepresent the proportion of severe non-β^0/β^0 mutations covered by the marketing authorisation, such as IVS-I-5 and IVS-I-110. The base case modelled population includes [redacted] patients with severe non-β^0/β^0 mutations; however, evidence suggest this could be as high as 28% of UK patients (see Section 3.1). Limited data collected to date suggests that patients with these mutations may be less likely to achieve transfusion independence, due to their reduced ability to produce haemoglobin.

To reflect this, the ERG presents an exploratory scenario in which the proportion of patients with severe non-β^0/β^0 mutations is increased from [redacted] to 28%, which decreases the modelled probability of transplant success from 83.3% to [redacted]

The results of this scenario are presented in Table 25 which shows an increase in the ICER of Zynteglo versus SoC.

Table 25 ERG Scenario 3: Adjusting clinical effectiveness data for underrepresented genotypes

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	52.71	29.65	[redacted]	12.45	[redacted]	[redacted]

* undiscounted life years

6.3.3 Adjustment to distribution of chelating agents

In Section 5.2.4, the ERG discussed the appropriateness of the distribution of different chelating agents used in the model. This was originally based upon the whole Chart Review population, but the ERG received advice that chelation practices have evolved over the years, and that the regimens used in patients treated currently may not reflect historic practices. The ERG requested that the company provide the distribution of iron chelation agents in patients aged 12-35, to better reflect the current standard of care in patients who would be eligible to receive Zynteglo (Table 9). The results of this scenario are presented in Table 26 below, which show a reduction of [redacted] (-2.3%) per QALY gained in the ICER of Zynteglo versus SoC. The re-analysis of the Chart Review data showed that there was a greater proportion of patients in this age category who received combination therapy, which increased the accrued cost of chelation agents.

Table 26 ERG Scenario 4: Distribution of chelating agents based on 12-35s in Chart Review

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	53.63	30.34	[redacted]	13.13	[redacted]	[redacted]

* undiscounted life years

6.3.4 Early engraftment failure

The ERG also identified early engraftment failure as a potential issue in Sections 4.2.1 and 5.2.6.2. While engraftment failure has not yet occurred to date, it is possible that engraftment may not be achieved in a small number of patients. As only 42 patients have received Zynteglo as per the product license, (Section 4.2) the rate of engraftment failure may not have yet been captured in existing trial data if it occurred in sufficiently small patient numbers (e.g. less than 1 in 42 patients, or lower than 2.3%).

Table 27 illustrates the effect upon the ICER of 1% and 5% of patients failing to successfully achieve engraftment, and thus requiring rescue therapy, i.e. the reserve of the patient's non-transduced cells are re-infused, with a 54% chance of mortality, as per the company's assumptions around this

scenario. When engraftment failure occurs in only 1% of patients, the impact to the ICER remains relatively small.

Table 27 ERG Scenarios 5 and 6: Engraftment failure following Zynteglo treatment

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs	QALYs	Costs	QALYs	ICER	
ERG Scenario 5: Engraftment failure occurs in 1% of Zynteglo patients							
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	53.45	30.23	[redacted]	13.03	[redacted]	[redacted]
ERG Scenario 6: Engraftment failure occurs in 5% of Zynteglo patients							
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	51.39	29.01	[redacted]	11.81	[redacted]	[redacted]

* undiscounted life years

6.3.5 The persistence of treatment effect

Section 5.2.6.2 highlights a number of reasons why the ERG believe that the therapeutic effect of Zynteglo may not be life-long in all patients. To explore the impact of late graft failure in a small proportion of patients upon the ICER, the ERG present two exploratory scenarios to highlight the relative importance of this assumption. Note that these scenarios are not based upon clinical data, and these are intended to be illustrative and exploratory only. They assume that all patients who relapse undergo graft failure sufficient to return them to a transfusion dependent state, regardless of their starting point. Figure 7 represents the long-term persistence of the treatment effect in ERG Scenarios 7 and 8 compared to the base case, assuming that the time at which graft rejections can occur is capped at 50 years.

In the first of these, it is assumed that every 10 years, 5% of transfusion independent and transfusion-reduced patients 'relapse' and once again become dependent upon transfusions and iron chelation. This increases the ICER by [redacted] (+26.9%) per QALY gained on Zynteglo. The second scenario assumes that 10% of patients relapse every 10 years. This results in an increase of [redacted] (+62.1%) to the ICER, illustrating the potentially significant effect uncertainty around the long-term persistence of treatment effect could have on the cost-effectiveness of Zynteglo.

Figure 7 Persistence of Zynteglo treatment effect over time in ERG Scenarios

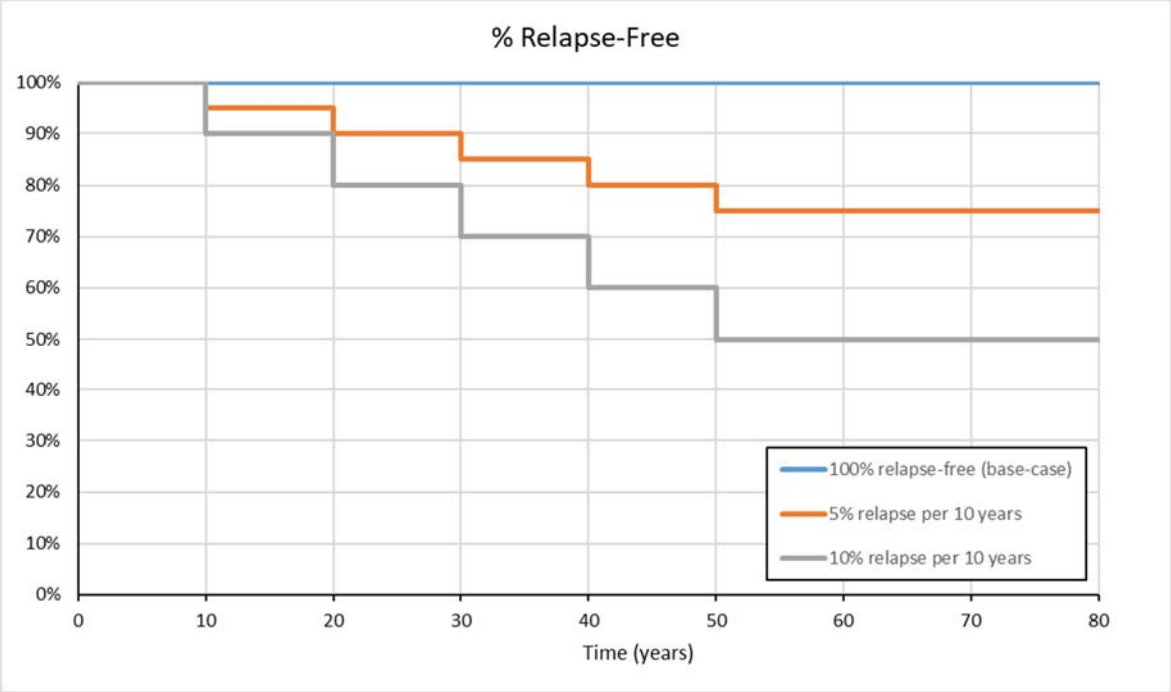


Table 28 ERG Scenarios 7 and 8: Alternative assumptions around long-term loss of treatment effect

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
ERG Scenario 7: 5% of patients relapse every 10 years							
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	50.69	28.46	[redacted]	11.26	[redacted]	[redacted]
ERG Scenario 8: 10% of patients relapse every 10 years							
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	48.10	26.71	[redacted]	9.51	[redacted]	[redacted]

* undiscounted life years

6.3.6 Mortality of transfusion dependent patients

The ERG questioned the appropriateness of the SMR the company applied to transfusion dependent patients in Section 5.2.6.5. The ERG considers the source that it was derived from to be obsolete in terms of its relevance to current NHS practice, due to improvements in iron chelation and patient monitoring which have led to more favourable mortality rates in TDT patients. The patients in the study of TDT survival are likely to have less favourable baseline characteristics: in order to be eligible for Zynteglo treatment, the patient must be sufficiently fit to undergo the procedure. Additionally, the ERG was particularly concerned that the company had selected the most pessimistic estimate from the literature for these patients.

Scenario 6 explores the impact of using an alternative assumption for the mortality rate associated with the transfusion dependent health state. Note that mortality due to cardiac complications is still separately accounted for in these patients: this specifically models the survival of TDT patients who have not developed cardiac complications.

In ERG Scenario 9 (Table 29), a lower SMR value of 2.0 was assumed for transfusion dependent patients. This results in a small decrease in the ICER of Zynteglo versus SoC. This is driven by the increased cost of SoC due to more of these patients remaining alive and requiring treatment, which outweighs the increase in QALYs due to a reduction in mortality.

Table 29 ERG Scenario 9: SMR of 2.0 applied to transfusion-dependent patients

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	42.41	18.50				
Zynteglo	[redacted]	54.09	30.49	[redacted]	11.99	[redacted]	[redacted]

* undiscounted life years

6.3.7 Iron normalisation and iron-related complications

The ERG identified a number of issues with the company's assumptions regarding the time to iron normalisation, and the risk of complications faced by patients who achieve normalised levels of iron after achieving transfusion independence. The following subsections address each of the issues raised in Section 5.2.7.

6.3.7.1 Iron normalisation period

As discussed in Section 5.2.6.3, the ERG did not concur with the company's conclusion that identified evidence supported an assumption of normalised iron levels in all patients after four years. Indeed, the limited data available from the Zynteglo trials was not sufficient to support this assumption; the iron levels of some TI patients remained elevated after 48 months of follow-up, and many trial patients remained on iron removal therapy (chelation or therapeutic phlebotomy) at the latest follow-up. It, therefore, appears that the assumption that all patients have normal iron levels four years after treatment may be not be accurate.

The ERG therefore presents scenarios in which the effect of an iron normalisation period of 5, 7, and 10 years is explored. During this time, patients incur the additional costs of iron chelation therapy, and are at a higher risk of certain complications associated with their elevated iron levels.

The results of ERG Scenarios 10, 11 and 12 are shown in Table 30, illustrating the potentially significant increase in the ICER of Zynteglo if iron levels are not normalised at 4 years, as assumed in the company's analysis. If iron levels were to take 7 years to normalise following treatment with Zynteglo, the resulting ICER would be [redacted] (17.4%) higher per QALY gained.

Table 30 ERG Scenarios 10-12: Alternative time to iron normalisation in transfusion independent patients

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
ERG Scenario 10: 5 year iron normalisation period							
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	53.40	30.05	[redacted]	12.85	[redacted]	[redacted]
ERG Scenario 11: 7 year iron normalisation period							
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	52.28	29.21	[redacted]	12.01	[redacted]	[redacted]
ERG Scenario 12: 10 year iron normalisation period							
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	51.26	28.49	[redacted]	11.28	[redacted]	[redacted]

* undiscounted life years

6.3.7.2 Complications due to iron overload in transfusion independent patient

The long-term consequences of iron damage in patients who achieve transfusion independence is an uncertainty in this analysis, since current evidence is limited and often contradictory. The company assumed that patients who have normalised iron levels are no longer at risk of developing complications. However, clinical advice to the ERG suggested that there may be a degree of pre-existing irreversible damage in many patients prior to treatment, albeit sufficiently small to allow for eligibility, which could theoretically result in a long-term risk of developing complications. In Scenario 13, the ERG applied the rates of developing cardiac complications associated with low iron overload, to patients with normalised iron levels (as described in Section 5.2.6.4).

The results of this analysis are presented in Table 31. The ERG highlight that this scenario is illustrative and represents the most conservative scenario regarding this assumption. However, given the large increase to the ICER, this scenario demonstrates that this source of uncertainty is important and shows that the development of long-term complications has consequences to the cost-effectiveness of Zynteglo.

Table 31 ERG Scenario 13: Patients with normalised levels of iron face a residual risk of developing iron overload-related complications

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	45.06	26.33	[redacted]	9.13	[redacted]	[redacted]

* undiscounted life years

6.3.8 Application of a 3.5% discount rate on costs and effects

The ERG's position is that Zynteglo does not meet the criteria for a 1.5% discount rate for costs and outcomes, as was used in the economic evaluation provided by the company. Section 5.2.5 provides a detailed description of the reasons for this. The results of the company's corrected base-case analysis are presented using a 3.5% discount rate for costs and outcomes in Table 32. This has the effect of more than doubling the ICER of Zynteglo versus SoC to [redacted] (+130.5%) per QALY gained.

The reasons for this are twofold; firstly, the majority of the hypothetical QALY gains associated with Zynteglo are received long into the future. Secondly, SoC is associated with much higher long-term costs, which are now subject to a higher discount rate, while almost all of the costs associated with Zynteglo are incurred upfront and thus have no discounting. This has the effect of substantially reducing the total cost of SoC but not of Zynteglo. This is appropriate, as there may be potentially substantial irrecoverable costs to the NHS, given the uncertainties around the long-term therapeutic effect of Zynteglo, which is better understood for transfusions and iron chelation therapy.

Table 32 ERG Scenario 14: 3.5% discount rate on costs and effects

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	12.55				
Zynteglo	[redacted]	53.63	19.84	[redacted]	7.29	[redacted]	[redacted]

* undiscounted life years

6.3.9 Health related quality of life scenarios

The ERG identified a number of issues with the company's preferred utility values and the way in which they had been implemented in the economic model. The following subsections address each of the issues raised in Section 5.2.7.

6.3.9.1 Age decrements based on Ara and Brazier general population values

As discussed in Section 5.2.7, the company's base case analysis used an inappropriate value set as the basis of general population utility by age. The subgroup from Ara and Brazier[62] selected by the

company included only those individuals in perfect health with no history of health problems in each age group. The company's base-case therefore assumes that patients would remain in otherwise perfect health until death, and never develop any health condition not explicitly included in the model.

The use of the whole-population dataset from Ara and Brazier[62] has extensive precedent in cost-utility analyses, and was therefore used in Scenario 15 in Table 33 below. The resulting ICER for Zynteglo is increased by [redacted] (+16.1%) per QALY gained versus SoC.

Table 33 ERG Scenario 15: Age-related disutilities taken from full Ara and Brazier population

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	16.43				
Zynteglo	[redacted]	53.63	27.74	[redacted]	11.32	[redacted]	[redacted]

* undiscounted life years

6.3.9.2 Utility for TDT based on adjusted Chart Review population

The utility describing the HRQoL of transfusion dependent patients used in the company's economic model was 0.69. This was the mean of all patients aged ≥16 in the Chart Review, but the ERG highlighted this population was substantially older than the patients included in the trial, and had no restrictions on co-morbidities, iron load, or general baseline health. The ERG, therefore, requested that the company provide a re-analysis of HRQoL in the Chart Review dataset, limiting the population to those aged 12-35, and excluding patients with a 'high' cardiac T2* and those whose existing co-morbidities were already separately accounted for in the model (such as diabetes and hypogonadism) to avoid double counting these decrements. The mean utility of this population was [redacted] which the ERG considered to be more comparable to that of the baseline value for patients included in the Zynteglo trials, and to the population who might be eligible for treatment in practice. By removing older patients from this analysis, it also means that we are no longer adjusting down an already age-adjusted utility value for age, which resulted in an overly low utility for older patients in the company's analysis.

The use of the age-appropriate Chart Review population utility increased the ICER of Zynteglo by [redacted] (+47.2%) per QALY gained versus SoC, from the corrected company base-case analysis (Table 34). The impact upon the ICER is so significant because the majority of QALY gains on Zynteglo in the company's analysis are generated through improvement in the modelled HRQoL of patients over a long period of time, rather than by an extension to life. By aligning the HRQoL of TDT patients to be consistent with the trial population and avoiding double counting the impact of

iron-related complications and age, Zynteglo generates fewer incremental QALYs compared with the company base case analysis.

Table 34 ERG Scenario 16: Transfusion dependence utility from adjusted Chart Review population

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	21.95				
Zynteglo	[redacted]	53.63	30.87	[redacted]	8.92	[redacted]	[redacted]

* undiscounted life years

The ERG also considered the combined impact of the two scenarios explored above: use of the age-related disutilities taken from the full Ara and Brazier population, and the analysis of the adjusted Chart Review population to estimate the health state utility value for transfusion dependent patients. As presented in Table 35, the impact to the ICER is substantial, as both analyses result in a higher HRQoL for standard care patients, leading to fewer incremental QALYs for Zynteglo.

Table 35 ERG Scenario 17: Combination of Scenario 14 and 15

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	21.17				
Zynteglo	[redacted]	53.63	28.28	[redacted]	7.11	[redacted]	[redacted]

* undiscounted life years

6.3.9.3 Transfusion independent patients incur a disutility for subcutaneous chelation during iron normalisation period

The ERG did not consider it appropriate to disregard the disutilities associated with subcutaneous iron chelation therapy in transfusion independent patients who continued to receive this treatment during the iron normalisation period. In the Zynteglo trials, a proportion of patients remained on, or returned to, iron chelation therapies following their treatment with Zynteglo. The company applied utilities derived from the vignette study for SoC patients, and specifically referenced the disadvantages of using subcutaneous iron chelators throughout their submission.

The ERG examined the impact of including a utility decrement relative to the patient's baseline utility, equivalent to that captured in the vignette study, for those treated using subcutaneous iron chelators during the iron normalisation period, thus capturing the additional burden of administration and adverse effects associated with this treatment. The results of this scenario are presented in Table 36 below.

Table 36 ERG Scenario 18: Disutility for TI patients on subcutaneous chelation therapy

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	53.63	30.26	[redacted]	13.06	[redacted]	[redacted]

* undiscounted life years

6.3.9.4 Removal of the disutility for infertility

The ERG questioned the appropriateness of including the impact of infertility upon HRQoL as a result of the myeloablative conditioning procure given prior to Zynteglo treatment. Its impact is poorly understood and not typically well captured using EQ-5D, and the value was estimated from a source that was not generalizable to the present context. It may not be appropriate to capture this impact within the present appraisal, and it has previously only been used in models of assisted reproductive technologies for patients actively seeking fertility treatment.

The ERG examined the impact of removing this disutility from the analysis. The results of this scenario are presented in Table 37 below. A modest decrease in the ICER was observed.

Table 37 ERG Scenario 19: Removal of the disutility for infertility

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	53.63	30.91	[redacted]	13.71	[redacted]	[redacted]

* undiscounted life years

6.3.10 Drug acquisition costs from eMIT

Drug acquisition costs for a number of therapies used in the treatment process were obtained from the BNF. However, some of the therapies, including the subcutaneous chelation agent desferrioxamine and two of the therapies used in the Zynteglo treatment process, are generic products that are widely available to the NHS at discounted prices. The ERG considers eMIT to be a more representative estimate of drug expenditure (costs presented in Table 15 in Section 5.2.8). Unit costs from eMIT are generally considerably lower than those in the BNF, and the use of the BNF costs will overestimate drug expenditure.

Results of this scenario are presented in Table 38. The inclusion of eMIT unit costs results in a small increase to the ICER. While using eMIT unit costs impacts the total costs accrued in both arms, the

effect is more pronounced in the SoC arm where desferrioxamine is applied over a lifetime, while the two treatments associated with Zynteglo are one-off.

Table 38 ERG Scenario 20: Drug unit costs acquisition costs from eMIT

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	53.63	30.34	[redacted]	13.13	[redacted]	[redacted]

* undiscounted life years

6.4 ERG's alternative base-case analysis

The ERG's alternative base-case analysis combines a number of the above scenario analyses. The ERG considers this new analysis to better reflect the uncertainties around the clinical data, and to address the ERG's concerns surrounding the assumptions and data sources used company's base-case analysis.

This analysis includes the following changes from the company's base-case:

- Age category-specific body weight used in chelation dosage calculations (Scenario 1),
- 20% of the population have hypogonadism at baseline (Scenario 2),
- Distribution of iron chelation therapies based on 12-35s in Chart Review (Scenario 3),
- Iron normalisation period of 5 years (Scenario 10),
- Costs and outcomes discounted at 3.5% (Scenario 14),
- Age-adjustment of utilities based on Ara and Brazier general population values (Scenario 15),
- Age- and comorbidity-adjusted Chart Review utility values (Scenario 16),
- eMIT drug acquisition costs used (Scenario 20).

The results of the probabilistic and deterministic base-case analyses are presented in Table 39. The deterministic ICER generated using this set of assumptions is [redacted] and the probabilistic ICER is [redacted] per QALY for Zynteglo compared with standard care. These results include the confidential PAS discount available for Zynteglo.

Table 39 Results of the ERG's alternative base-case analysis

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
Company's corrected base-case results (deterministic)							
SoC	[redacted]	37.79	17.20				
Zynteglo	[redacted]	53.63	30.34	[redacted]	13.13	[redacted]	-
ERG deterministic base-case							
SoC	[redacted]	37.79	15.48				
Zynteglo	[redacted]	53.40	18.53	[redacted]	3.05	[redacted]	[redacted]
ERG probabilistic base-case							
SoC	[redacted]	39.03	15.62				
Zynteglo	[redacted]	53.54	18.55	[redacted]	2.93	[redacted]	[redacted] **

* undiscounted life years, ** relative to the base-case probabilistic ICER

6.4.1 Scenarios on the ERG alternative base case analysis

The selection of changes made to the ERG base-case analysis were driven by the available evidence; however, a number of important uncertainties remain. To address the remaining uncertainty, the ERG conducted a number of scenarios on their alternative base-case analysis.

The first of these scenarios included the use of a 1.5% discount rate for costs and benefits, which was originally applied by the company in their base-case analysis. The company cited the example of Strimvelis, the only other gene therapy considered by NICE, which was appraised using the NICE HST process. The NICE committee discussing the evidence for Strimvelis stated that "it was uncertain about whether Strimvelis fully met the criteria to use a discounting rate of 1.5%, and that both discount rates should be considered by the committee during its decision-making".[49] As such, the ERG hereby presents the results of their analysis using the 1.5% discount rate to enable a comparison of results, but considers that the discount rate of 3.5% remains the most appropriate for reasons discussed extensively in Section 5.2.5.

In a second scenario, the ERG considers the impact of assuming a less severe impact to the survival of transfusion dependent patients, and applies an SMR of 2 in their alternative base case analysis. This value is not driven by published evidence but rather a clinically justified assumption that current transfusion-dependent patients, who do not have any cardiac complications, would have much improved survival than that observed in previous decades (Section 5.2.6.5). Since it is subject to a high degree of uncertainty, the ERG did not consider it appropriate to use this value in their

alternative base case scenario, but considers it an important assumption to explore, as the alternative base-case almost certainly underestimates the number of LYs generated by standard care patients.

Table 40 presents the results of these additional scenarios. Notably, with the application of the company's preferred discount rate of 1.5%, Zynteglo cannot be considered cost-effective, with an ICER of [redacted]. As demonstrated in the second scenario, the application of a lower value for the SMR for transfusion dependent patients had a much greater impact to the ICER than when it was applied to the company's base-case analysis (a decrease of [redacted] to the ICER when applied to the company analysis, versus an increase of [redacted] when applied to the ERG analysis). In the company model, the increased cost of SoC due to more of these patients remaining alive and requiring treatment outweighs the increase in QALYs due to a reduction in mortality. However, in the ERG analysis, greater QALYs are generated by patients on SoC due to higher utility estimates being estimated and applied by the ERG for transfusion dependent patients.

Table 40 Results of scenario analyses on the ERG alternative base case analysis

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
Scenario: 1.5% discount rate							
SoC	[redacted]	37.79	21.07				
Zynteglo	[redacted]	53.40	27.78	[redacted]	6.71	[redacted]	[redacted]
Scenario: SMR of 2 for transfusion dependent patients							
SoC	[redacted]	42.41	16.14				
Zynteglo	[redacted]	53.89	18.62	[redacted]	2.48	[redacted]	[redacted]
Scenario: 1.5% discount rate and SMR of 2 for transfusion dependent patients							
SoC	[redacted]	42.41	22.54				
Zynteglo	[redacted]	53.89	27.96	[redacted]	5.42	[redacted]	[redacted]

* undiscounted life years

Due to the uncertainty in the modelling sampling procedure and its impact on the ICER, the results of the ERG base case are presented in Table 41, in which results are based on 5,000 modelled profiles, rather than 600 as in the company base-case analysis.

The results show a considerable increase in the ICERs of all three scenarios compared to the same scenarios based on 600 profiles (presented in Table 40). The change from the company base-case ICER was estimated using the company ICER based on 5,000 patient profiles. Notably, increasing the number of 5,000 profiles increases the ICER of the ERG base case to [redacted], from [redacted] per QALY.

Table 41 Results of scenario analyses on the ERG alternative base case analysis, using 5,000 profiles

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
ERG base case analysis, based on 5,000 model profiles							
SOC	[redacted]	37.34	15.32				
Zynteglo	[redacted]	52.60	18.25	[redacted]	2.93	[redacted]	[redacted]
Scenario: ERG base-case analysis with 1.5% discount rate, based on 5,000 model profiles							
SoC	[redacted]	37.34	20.81				
Zynteglo	[redacted]	52.60	27.28	[redacted]	6.47	[redacted]	[redacted]
Scenario: ERG base-case analysis with SMR of 2 for transfusion dependent patients, based on 5,000 model profiles							
SoC	[redacted]	41.97	15.99				
Zynteglo	[redacted]	53.13	18.35	[redacted]	2.35	[redacted]	[redacted]
Scenario: ERG base-case analysis with 1.5% discount rate and SMR of 2 for transfusion dependent patients, based on 5,000 model profiles							
SoC	[redacted]	41.97	22.30				
Zynteglo	[redacted]	53.13	27.47	[redacted]	5.17	[redacted]	[redacted]

* undiscounted life years

6.5 Conclusions from the ERG analyses

The ERG has presented a number of additional analyses carried out in stages. These exploratory analyses were undertaken on a model provided by the company at the clarification stage, which addressed an error identified by the ERG, and included updates to a number of modelling assumptions. The impact of these changes resulted in a company base-case ICER of £[redacted] per QALY.

Using the corrected and updated model, the ERG then presented a number of "single-change" analyses considering a range of issues raised in Section 5.2. These scenario analyses addressed the following issues:

- Baseline population characteristics and presence of co-morbidities adjusted to reflect the eligible population,
- Distribution of iron chelation agents adjusted to reflect the eligible population, using a re-analysis of the Chart Review data,
- Clinical effectiveness data adjusted for the underrepresentation of the IVS-I-5 and IVS-I-110 genotypes,

- Alternative assumptions around the rate of early engraftment failure and the long-term persistence of transfusion independence,
- Alternative assumptions on the upon mortality of transfusion dependent patients,
- Alternative assumptions around iron normalisation and the development of iron overload-related complications,
- Impact of using a 3.5% discount rate on costs and effects,
- Use of a number of different sources and assumptions around health-related quality of life,
- Alternative drug acquisition unit costs.

The scenarios associated with the greatest impact on cost-effectiveness outcomes involved the use of a 3.5% discount rate for costs and benefits, as per the NICE reference case. The discount rate significantly impacts the analysis due to the difference in the way Zynteglo and standard care patients accrue costs and QALYs. With Zynteglo, the majority of costs are allocated upfront while benefits are generated over the lifetime. Aligning the discount rate in the model to that specified in the reference case resulted in the ICER increasing from £[redacted] to £[redacted]. Scenario analyses that explored the impact of an alternative source of general population age-related utility values and a re-estimate of the utility values for transfusion dependent patients demonstrated that the results of the model are sensitive to these assumptions, as the majority of the benefit attributed to Zynteglo was assumed to be due to reductions in morbidity as well as mortality. The company's original assumptions over-estimated HRQoL following Zynteglo treatment and under-estimated HRQoL on standard care.

The ERG alternative base-case implemented a number of the assumptions that were included in the company exploratory analyses. This analysis estimated Zynteglo to be more costly (cost difference [redacted]) and more effective (3.05 QALY gain) compared with standard care, and suggests that the ICER for Zynteglo compared with standard care is £[redacted] per QALY. Further analyses undertaken by the ERG on their alternative base-case suggested that the mortality rate for transfusion-dependent patients was also an influential parameter in the analysis.

7 End of life

This intervention does not meet the end of life criteria published by NICE.

8 Overall conclusions

Results from the three Zynteglo trials demonstrate that most patients respond well to Zynteglo and achieve transfusion independence. However, the Zynteglo trial population appears not to be a particularly good representation of the UK TDT population and consequently there is uncertainty about how effective Zynteglo is in the subgroup of patients with severe non-β^0/β^0 genotypes. It is possible that [redacted] may increase the probability of achieving TI in patients with severe non-β^0/β^0 genotypes (compared to the previous processes used in the trial programme) but only results from the study HGB-212 and further data from HGB-207 can resolve this uncertainty. The trials results are still quite immature, and the number of patients treated is small, so uncertainty exists regarding the longevity of Zynteglo and the possibility of adverse events in the medium-to-long term.

The applicability of the comparator data selected by the company is not optimal since some studies did not reflect the improvements in TDT patient treatment and management achieved over the last 10-20 years. This was exacerbated by the lack of transparency regarding the methods used to identify many studies and the limited consideration of the implication of study limitations.

[redacted]

The ERG's critique of the economic evaluation presented by the company focused upon a number of key challenges, and performed a range of scenarios to explore the impact of alternative assumptions upon the cost-effectiveness of Zynteglo.

The ERG proposed an alternative base-case analysis to address several of the key uncertainties identified. The main changes implemented by the ERG include adjustment of the baseline characteristics of the modelled population based on a reanalysis of the Chart Review data, increasing the iron normalisation period to 5 years, discounting of costs and outcomes at 3.5% per annum, use of a more appropriate value set to calculate age-related decline in HRQoL, and using utility estimates for TDT patients based on reanalysis of the Chart Review population adjusted for age and co-morbidities. The probabilistic ICER estimated using the ERG's preferred assumptions was [redacted], which was [redacted] higher than the company's base-case probabilistic ICER. The single most significant reason for this increase was the use of a 3.5% discount rate over the company's 1.5% rate, since for Zynteglo the majority of costs are incurred upfront and are therefore mostly unaffected by the higher discount rate, while benefits are generated over the patient's lifetime and are thus subject to more discounting.

A number of uncertainties remain unexplored in the absence of more appropriate evidence. This could mean that the results of the ERG's preferred base-case analysis may underestimate the true ICER for Zynteglo. Firstly, the long-term benefits of Zynteglo are uncertain due to the immaturity of the evidence base. The ERG is concerned that anything other than an indefinite treatment effect across all patients could have a substantial impact upon the cost-effectiveness of Zynteglo, and may subject the NHS to large irrecoverable costs. Heterogeneity of treatment effect also remains an area of uncertainty, as heterogeneity based on genotype and manufacturing process is not addressed in the evidence. Further uncertainty also surrounds the resolution of elevated iron levels following successful treatment with Zynteglo, and the associated reduction in risk of iron-related complications.

8.1 Implications for research

As Zynteglo has a conditional license via the EMA's adaptive pathways programme, further follow-up data on efficacy and safety will continue to be routinely collected for all the Zynteglo trials. Of particular interest would be data on the iron normalisation period following Zynteglo treatment, and persistence of the therapeutic effect in the long term.

More contemporary evidence on survival and HRQoL of TDT patients on current therapies, including the use of combination chelation therapy, would be beneficial.

9 References

1. Zynteglo SmPC. bluebird bio, Zynteglo 1.2 20 × 106 cells/mL dispersion for infusion. Draft Summary of Product Characteristics. 2019.
2. Henderson S, Timbs A, McCarthy J, Gallienne A, Van Mourik M, Masters G, et al. Incidence of haemoglobinopathies in various populations - the impact of immigration. *Clin Biochem* 2009;**42**:1745-56.
3. Kulozik AE, Locatelli F, Yannaki E, Porter JB, Thuret I, Sauer MG, et al. *Results from the phase 3 Northstar-3 study evaluating lentiglobin gene therapy in patients with transfusion-dependent β-thalassaemia and a β0 or IVS-I-110 mutation at both alleles of the HBB gene*. In: 24th European Hematology Association Congress. Amsterdam, June 13-16; 2019.
4. Lal A, Locatelli F, Kwiatkowski JL, Kulozik AE, Yannaki E, Porter JB, et al. Northstar-3: Interim results from a phase 3 study evaluating lentiglobin gene therapy in patients with transfusion-dependent β-thalassemia and either a β0 or IVS-I-110 mutation at both alleles of the HBB gene. *Blood* 2019;**134**:815.
5. Hongeng S, Thompson AA, Kwiatkowski JL, Rasko JE, Schiller GJ, Deary B, et al. *Clinical outcomes following lentiglobin gene therapy for transfusion-dependent β-thalassemia in the northstar HGB-204 study*. In: 23rd Annual Congress of 2018 Asia-Pacific Blood and Marrow Transplantation Group (APBMT). Taipei, Taiwan, 2-4 Nov; 2018.
6. Jackson R, Ameratunga S, Broad J, Connor J, Lethaby A, Robb G, et al. The GATE frame: critical appraisal with pictures. *Evid Based Med* 2006;**11**:35-8.
7. National Institute for Health and Care Excellence (NICE). *Methods for the development of NICE public health guidance (third edition)*. London: NICE; 2012.
8. Foster M. *National Haemoglobinopathy Registry annual report - 2018/19*. Manchester: Medical Data Solutions and Services (MDSAS); 2019.
9. bluebird bio Inc. *Clinical Study Report HGB 205: A phase 1/2 open label study evaluating the safety and efficacy of gene therapy of the β-hemoglobinopathies (sickle cell anemia and β-thalassemia major) by transplantation of autologous CD34+ stem cells transduced ex vivo with a lentiviral β^{A-T87Q}- globin vector (Lentiglobin BB305 drug product). [Unpublished, confidential document]*. Cambridge, MA: bluebird bio Inc; 2018.
10. bluebird bio Inc. *Clinical Study Report HGB-204. A phase 1/2, open label study evaluating the safety and efficacy of gene therapy in subjects with β-thalassemia major by transplantation of autologous CD34+ stem cells transduced ex vivo with a lentiviral $\beta^{A\ T87Q}$-globin vector (LentiGlobin BB305 drug product). [Draft, unpublished confidential document]*. . Cambridge, MA: bluebird bio Inc; 2018.
11. Thompson AA, Walters MC, Kwiatkowski J, Rasko JEJ, Ribeil J-A, Hongeng S, et al. Gene therapy in patients with transfusion-dependent β-thalassemia. *N Engl J Med* 2018;**378**:1479-93.
12. bluebird bio Inc. *Interim Clinical Study Report HGB-207. A phase 3 single arm study evaluating the efficacy and safety of gene therapy in subjects with transfusion-dependent β-thalassemia, who do not have a β^0/β^0 genotype, by transplantation of autologous CD34+ stem cells transduced ex vivo with a lentiviral $\beta^{a\text{-}t87q}$-globin vector in subjects ≤50 years of age. [Unpublished, confidential document]*. Cambridge, MA: bluebird bio Inc; 2018.
13. bluebird bio Inc. *June 2019 integrated TLFs for HGB-204, HGB-205, HGB-207 and LTF-303*. In: bluebird bio Inc; 2019.
14. Locatelli F, Wlater MC, Kwiatkowski JL, Porter JB, Sauer MG, Thuret I, et al. LentiGlobin gene therapy for patients with transfusion-dependent β-thalassemia (TDT): results from the phase 3 Northstar-2 and Northstar-3 studies. In: *American Society of Hematology*; 2018; San Diego, CA. 2018.
15. Rasko JE, Thompson AA, Kwiatkowski JL, Hongeng S, Schiller GJ, Anurathapan U, et al. *Clinical outcomes of LentiGlobin gene therapy for transfusion-dependent β-thalassemia following completion of the Northstar HGB-204 study*. In: American Society of Hematology. San Diego, CA; 2018.

16. *Summary of product characterstics for Busilvex 6mg/ml concentrate for solution for infusion*: European Medicines Agency; 2017.
17. Evidera, bluebird bio Inc. *Systematic literature review to support lentiglobin® in transfusion-dependent β-thalassemia for NICE submission. Study Report. EVA-20726-04 (version 1.0) [confidential]*: Evidera; 2019.
18. bluebird bio Inc. *An observational study to evaluate the routine management, healthcare resource use and outcomes for patients with transfusion-dependent β-thalassaemia treated in the United Kingdom (TDT Chart Review) [draft manuscript, confidential]*. In: Open Vie; 2019.
19. Evidera, bluebird bio Inc. *Systematic review of the burden of disease and treatment for transfusion dependent β-thalassemia EVA-20726 (version 3.0) [confidential]*: Evidera; 2018.
20. Higgins JPT, Sterne JAC, Savovic J, Page MJ, Hróbjartsson A, Boutron I, et al. A revised tool for assessing risk of bias in randomized trials. *Cochrane Database of Systematic Reviews* 2016;**10**:29-31.
21. Delea TE, Sofrygin O, Thomas SK, Baladi JF, Phatak PD, Coates TD. Cost effectiveness of once-daily oral chelation therapy with deferasirox versus infusional deferoxamine in transfusion-dependent thalassaemia patients: US healthcare system perspective. *Pharmacoeconomics* 2007;**25**:329-42.
22. Gabutti V, Piga A. Results of long-term iron-chelating therapy. *Acta Haematol* 1996;**95**:26-36.
23. Piga A, Gaglioti C, Fogliacco E, Tricta F. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. *Haematologica* 2003;**88**:489-96.
24. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J* 2001;**22**:2171-9.
25. Kremastinos DT, Tsetsos GA, Tsiapras DP, Karavolias GK, Ladis VA, Kattamis CA. Heart failure in beta thalassemia: a 5-year follow-up study. *Am J Med* 2001;**111**:349-54.
26. Casale M, Filosa A, Ragozzino A, Amendola G, Roberti D, Tartaglione I, et al. Long-term improvement in cardiac magnetic resonance in beta-thalassemia major patients treated with deferasirox extends to patients with abnormal baseline cardiac function. *Am J Hematol* 2019;**94**:312-8.
27. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2008;**10**:42.
28. Pepe A, Rossi G, Bentley A, Putti MC, Frizziero L, D'Ascola DG, et al. Cost-utility analysis of three iron chelators used in monotherapy for the treatment of chronic iron overload in beta-thalassaemia major patients: an Italian perspective. *Clin Drug Investig* 2017;**37**:453-64.
29. Angelucci E, Muretto P, Nicolucci A, Baronciani D, Erer B, Gaziev J, et al. Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation. *Blood* 2002;**100**:17-21.
30. Ang AL, Tzoulis P, Prescott E, Davis BA, Barnard M, Shah FT. History of myocardial iron loading is a strong risk factor for diabetes mellitus and hypogonadism in adults with beta thalassemia major. *Eur J Haematol* 2014;**92**:229-36.
31. Novartis Pharmaceuticals Corporation. *Prescribing information for JADENU® (deferasirox) tablets, for oral use and JADENU® Sprinkle (deferasirox) granules, for oral use*. 2019. Available from: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/jadenu.pdf. [accessed 14th January 2020].
32. Apotex. *Prescribing information for FERRIPROX® (deferiprone) tablets, for oral use*. 2011. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021825lbl.pdf. [accessed 14th January 2020].
33. Fisher SA, Brunskill SJ, Doree C, Gooding S, Chowdhury O, Roberts DJ. Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia. *Cochrane Database Syst Rev* 2013:CD004450.
34. Pistoia L, Meloni A, Salvadori S, Spasiano A, Lisi R, Rosso R, et al. Cardiac involvement by CMR in different genotypic groups of thalassemia major patients. *Blood Cells Mol Dis* 2019;**77**:1-7.

35. Poomthavorn P, Chawalitdamrong P, Hongeng S, Mahachoklertwattana P, Pakakasama S, Khlairit P, et al. Gonadal function of beta-thalassemics following stem cell transplantation conditioned with myeloablative and reduced intensity regimens. *J Pediatr Endocrinol Metab* 2013;**26**:925-32.
36. Chaudhury S, Ayas M, Rosen C, Ma M, Viqaruddin M, Parikh S, et al. A multicenter retrospective analysis stressing the importance of long-term follow-up after hematopoietic cell transplantation for beta-thalassemia. *Biol Blood Marrow Transplant* 2017;**23**:1695-700.
37. John MJ, Jyani G, Jindal A, Mashon RS, Mathew A, Kakkar S, et al. Cost Effectiveness of Hematopoietic Stem Cell Transplantation Compared with Transfusion Chelation for Treatment of Thalassemia Major. *Biol Blood Marrow Transplant* 2018;**24**:2119-26.
38. Leelahavarong P, Chaikledkaew U, Hongeng S, Kasemsup V, Lubell Y, Teerawattananon Y. A cost-utility and budget impact analysis of allogeneic hematopoietic stem cell transplantation for severe thalassemic patients in Thailand. *BMC Health Serv Res* 2010;**10**:209.
39. Karnon J, Tolley K, Vieira J, Chandiwana D. Lifetime cost-utility analyses of deferasirox in beta-thalassaemia patients with chronic iron overload: a UK perspective. *Clin Drug Investig* 2012;**32**:805-15.
40. Caro JJ. Discretely Integrated Condition Event (DICE) Simulation for Pharmacoeconomics. *Pharmacoeconomics* 2016;**34**:665-72.
41. Weidlich D, Kefalas P, Guest JF. Healthcare costs and outcomes of managing β-thalassemia major over 50 years in the United Kingdom. *Transfusion* 2016;**56**:1038-45.
42. Kwiatkowski JL, Kim HY, Thompson AA, Quinn CT, Mueller BU, Odame I, et al. Chelation use and iron burden in North American and British thalassemia patients: a report from the Thalassemia Longitudinal Cohort. *Blood* 2012;**119**:2746-53.
43. *Girls UK growth chart 2-18 years*. Royal College of Paediatrics and Child Health; 2012. Available from: https://www.rcpch.ac.uk/sites/default/files/Girls_2-18_years_growth_chart.pdf [accessed 10th January 2019].
44. *Boys UK growth chart 2-18 years*. Royal College of Paediatrics and Child Health; 2012. Available from: https://www.rcpch.ac.uk/sites/default/files/Boys_2-18_years_growth_chart.pdf [accessed 10th January 2019].
45. United Kingdom Thalassaemia Society. *Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK, 3rd Edition*. London: United Kingdom Thalassaemia Society; 2016.
46. Javanbakht M, Keshtkaran A, Shabaninejad H, Karami H, Zakerinia M, Delavari S. Comparison of Blood Transfusion Plus Chelation Therapy and Bone Marrow Transplantation in Patients with β-Thalassemia: Application of SF-36, EQ-5D, and Visual Analogue Scale Measures. *Int J Health Policy Manag* 2015;**4**:733-40.
47. Seyedifar M, Dorkoosh FA, Hamidieh AA, Naderi M, Karami H, Karimi M, et al. Health-Related Quality of Life and Health Utility Values in Beta Thalassemia Major Patients Receiving Different Types of Iron Chelators in Iran. *Int J Hematol Oncol Stem Cell Res* 2016;**10**:224-31.
48. bluebird bio Inc. *Zynteglo TDT: UK Patient Preference report*. In; 2019.
49. National Institute for Health and Care Excellence (NICE). *Strimvelis for treating adenosine deaminase deficiency-severe combined immunodeficiency [HST7]*. NICE; 2018. Available from: https://www.nice.org.uk/guidance/hst7 [accessed 13th January 2020].
50. Inati A, Kahale M, Sbeiti N, Cappellini MD, Taher AT, Koussa S, et al. One-year results from a prospective randomized trial comparing phlebotomy with deferasirox for the treatment of iron overload in pediatric patients with thalassemia major following curative stem cell transplantation. *Pediatr Blood Cancer* 2017;**64**:188-96.
51. Angelucci E. Complication free survival long-term after hemopoietic cell transplantation in thalassemia. *Haematologica* 2018;**103**:1094-6.
52. Pepe A, Meloni A, Rossi G, Midiri M, Missere M, Valeri G, et al. Prediction of cardiac complications for thalassemia major in the widespread cardiac magnetic resonance era: a prospective multicentre study by a multi-parametric approach. *Eur Heart J Cardiovasc Imaging* 2018;**19**:299-309.
53. Angelucci E, Burrows N, Losi S, Bartiromo C, Hu XH. Beta-Thalassemia (BT) Prevalence and Treatment Patterns in Italy: A Survey of Treating Physicians. 2016;**128**:3533-.

54. Shenoy S, Angelucci E, Arnold SD, Baker KS, Bhatia M, Bresters D, et al. Current results and future research priorities in late effects after hematopoietic stem cell transplantation for children with sickle cell disease and thalassemia: a consensus statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on late effects after pediatric hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2017;**23**:552-61.
55. Rahal I, Galambrun C, Bertrand Y, Garnier N, Paillard C, Frange P, et al. Late effects after hematopoietic stem cell transplantation for beta-thalassemia major: the French national experience. *Haematologica* 2018;**103**:1143-9.
56. ONS. *National life tables, UK: 2015 to 2017*. 2018. Available from: https://www.ons.gov.uk/releases/nationallifetablesuk2015to2017 [accessed
57. Jobanputra M, Paramore C, Laird SG, McGahan M, Telfer P. Co-morbidities and mortality associated with Transfusion Dependent Beta-thalassaemia Patients in England: A 10-Year Retrospective Cohort Analysis - Draft manuscript. Draft manuscript.
58. *Summary of product characteristics for Zynteglo*: European Medicines Agency; 2019.
59. Matza LS, Paramore LC, Stewart KD, Karn H, Jobanputra M, Dietz AC. Health state utilities associated with treatment for transfusion-dependent beta-thalassemia. *Eur J Health Econ* 2019.
60. Busnelli A, Somigliana E, Benaglia L, Leonardi M, Ragni G, Fedele L. In vitro fertilization outcomes in treated hypothyroidism. *Thyroid* 2013;**23**:1319-25.
61. Scotland G, McLernon D, Kurinczuk J, McNamee P, Harrild K, Lyall H, et al. Minimising twins in *in vitro* fertilisation: a modelling study assessing the costs, consequences and cost–utility of elective single versus double embryo transfer over a 20-year time horizon. *Br J Obstet Gynaecol* 2011;**118**:1073-83.
62. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health* 2011;**14**:539-45.
63. Fryback DG, Dasbach EJ, Klein R, Klein BE, Dom N, Peterson K, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors *Med Decis Making* 1993;**13**:89-102.
64. Overview of analytic approach and results. In: Institute of Medicine, Stratton KR, Durch JS, Lawrence RS, editors. *Vaccines for the 21st century: a tool for decisionmaking*. Washington, DC: The National Academies Press; 2000. p. 53-92.
65. Appendix 17 Neisseria gonorrhea. In: Institute of Medicine, Stratton KR, Durch JS, Lawrence RS, editors. *Vaccines for the 21st century: a tool for decisionmaking*. Washington, D C: The National Academies Press; 2000. p. 257-66.
66. Jalkanen K, Aarnio E, Lavikainen P, Jauhonen H-M, Enlund H, Martikainen J. Impact of type 2 diabetes treated with non-insulin medication and number of diabetes-coexisting diseases on EQ-5D-5 L index scores in the Finnish population. *Health Qual Life Outcomes* 2019;**17**:117.
67. Solli O, Stavem K, Kristiansen IS. Health-related quality of life in diabetes: The associations of complications with EQ-5D scores. *Health Qual Life Outcomes* 2010;**8**:18.
68. NHS Improvement. *National schedule of reference costs*. Available from: https://improvement.nhs.uk/resources/reference-costs/#rc1718 [accessed 17th January 2020].
69. Joint Formulary Committee. *British National Formulary (online)* BMJ Group and Pharmaceutical Press; 2019. Available from: https://bnf.nice.org.uk/ [accessed 17th January 2020].
70. Curtis LA, Burns A. *Unit costs of health and social care 2018*. University of Kent; 2018. Available from: https://kar.kent.ac.uk/70995/ [accessed 17th January 2020].
71. Drezet A, Touzot F, Magalon J, Caccavelli L, Lezoray M, Taupin P, et al. *Budget impact analysis of gene therapy of hematopoietic stem cells for the management of beta-Thalassemia major*. In; 2019.
72. National Institute for Health and Care Excellence (NICE. *Costing statement: Blood transfusion. Implementing the NICE guideline on blood transfusion (NG24)*: NICE; 2015. Available from: https://www.nice.org.uk/guidance/ng24/resources/costing-statement-2177158141
73. Agrawal S, Davidson N, Walker M, Gibson S, Lim C, Morgan CL, et al. Assessing the total costs of blood delivery to hospital oncology and haematology patients. *Curr Med Res Opin* 2006;**22**:1903-9.

74. Bentley A, Gillard S, Spino M, Connelly J, Tricta F. Cost-utility analysis of deferiprone for the treatment of beta-thalassaemia patients with chronic iron overload: a UK perspective. *Pharmacoeconomics* 2013;**31**:807-22.
75. Karnon J, Tolley K, Oyee J, Jewitt K, Ossa D, Akehurst R. Cost-utility analysis of deferasirox compared to standard therapy with desferrioxamine for patients requiring iron chelation therapy in the United Kingdom. *Curr Med Res Opin* 2008;**24**:1609-21.
76. NHS England. *National Genomic Test Directory.Testing criteria for rare and inherited disease*: NHS England; 2019.
77. Department of Health and Social Care. *Drugs and pharmacuetical electronic market information (eMit)*. 2011. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit [accessed 10th December 2019].
78. Moller J, Davis S, Stevenson M, Caro JJ. Validation of a DICE simulation against a discrete event simulation implemented entirely in code. *Pharmacoeconomics* 2017;**35**:1103-9.
79. National Institute for Health and Care Excellence (NICE). *Cabozantinib for treating medullary thyroid cancer [TA516]*. NICE; 2018. Available from: https://www.nice.org.uk/guidance/ta516 [accessed 16th January 2019].
80. Davis S, Stevenson M, Tappenden P, Wailoo AJ. *NICE DSU Technical Support Document 15: Cost-effectiveness modelling using patient-level simulation* Sheffield: Decision Support Unit, School of Health and Related Research, University of Sheffield; 2014.

10 Appendices

10.1 Appendix 1: Drummond Checklist

Table 42 Quality assessment of included CEA study using Drummond et al. checklist completed by the ERG

	CEA quality assessment questions	Answer (Yes/No/Unclear)	Notes/Explanation for No or Unclear
1	Was the research question stated?	Yes	-
2	Was the economic importance of the research question stated?	Yes	-
3	Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	-
4	Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	-
5	Were the alternatives being compared clearly described?	Yes	-
6	Was the form of economic evaluation stated?	Yes	-
7	Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	-
8	Was/were the source(s) of effectiveness estimates used stated?	Yes	-
9	Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	-

10	Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	-
11	Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	-
12	Were the methods used to value health states and other benefits stated?	Yes	-
13	Were the details of the subjects from whom valuations were obtained given?	Yes	-
14	Were productivity changes (if included) reported separately?	Yes	-
15	Was the relevance of productivity changes to the study question discussed?	Yes	-
16	Were quantities of resources reported separately from their unit cost?	Yes	-
17	Were the methods for the estimation of quantities and unit costs described?	Yes	-
18	Were currency and price data recorded?	Yes	-
19	Were details of price adjustments for inflation or currency conversion given?	Yes	-

20	Were details of any model used given?	Yes	-
21	Was there a justification for the choice of model used and the key parameters on which it was based?	Partly	The company provided justification for using a discrete event simulation structure, however there was insufficient transparency in the original discretely integrated condition event simulation framework to allow validation.
22	Was the time horizon of cost and benefits stated?	Yes	-
23	Was the discount rate stated?	Yes	-
24	Was the choice of rate justified?	No	The company used a non-reference case discount rate.
25	Was an explanation given if cost or benefits were not discounted?	N/A	-
26	Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	-
27	Was the approach to sensitivity analysis described?	Yes	-
28	Was the choice of variables for sensitivity analysis justified?	Partly	Many variables were tested in sensitivity analyses, however some were implemented incorrectly (% transplant success) and some were not included despite being a driver of cost effectiveness (discount rate).
29	Were the ranges over which the parameters were varied stated?	Yes	-

30	Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	-
31	Was an incremental analysis reported?	Yes	-
32	Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	-
33	Was the answer to the study question given?	Yes	-
34	Did conclusions follow from the data reported?	Yes	-
35	Were conclusions accompanied by the appropriate caveats?	No	-
36	Were generalisability issues addressed?	No	There were many generalisability issues not addressed by the company.

10.2 Appendix 2: Critique of the company's search strategies for cost-effectiveness evidence

The company confirmed in their response to the points for clarification that the search strategies included in these two reports by Evidera were used to identify evidence for the SLRs included within the submission. The 2018 report by Evidera contained the description of the searches and full search strategies in Section 3.1.1, p. 14-15.[19] In the 2019 report by Evidera, the original searches were updated, with a description of the searches on p. 5 and the full search strategies included in Appendix D, p. 111-115.[17]

The following databases were searched on 19th May 2017: MEDLINE (via PubMed.com and Embase.com) and Embase (via Embase.com). Retrieval was limited to English language studies with an abstract, published from 2007 to 31st December 2017. The searches of MEDLINE and Embase were updated on 1st April 2019 along with searches of the following additional databases: EconLit

(via Ovid) and PsycINFO (via EbscoHost). All additional databases were searched from 2007 to 1st April 2019. Retrieval of records from MEDLINE, Embase and PsycINFO was limited to English language publications.

Specific conferences taking place from 2015 onwards were searched via Embase.com to identify relevant conference abstracts or posters: American Society of Hematology (ASH), European Hematology Association (EHA), British Blood Transfusion Society (BBTS), European Society for Blood and Marrow Transplantation (EBMT) and the International Society of Blood Transfusion. In addition, the following online conference websites were searched: ASH (2018), EHA (2018) and the International Society of Blood Transfusion (2018). Further unpublished studies or grey literature were identified through searches of the HTA database and the Cost Effectiveness Analysis (CEA) Registry.

The search strategies for all databases (MEDLINE, Embase, PsycINFO and EconLit) were structured appropriately using terms for thalassaemia combined with terms for either transfusion or iron chelation therapies. The term thalassemia major has been included within the intervention terms in most of the search strategies. This appears to be a mistake, however it would not have caused relevant studies to be missed. A lack of truncation was noted throughout all database strategies for some search terms – thalassemia, thalassaemia, anemia and anaemia. These terms could have been truncated as follows: thalassemi$, thalassaemi$, anemi$, anaemi$, to allow maximal retrieval of relevant records that use the same word stem but have different endings eg: thalassaemic, thalassaemias, anaemic, anaemias etc.

Subject headings for iron chelation therapies and blood transfusion were missing from the MEDLINE and Embase search strategies. It is usual practice for systematic review searches to include both textword searches of the title and abstract fields as well as relevant subject headings to ensure all relevant studies are retrieved.

The search strategies for EMBASE were limited by publication type to records that have been assigned as articles or articles in press eg: line #7, table 2, p. 14-15 in the 2019 report by Evidera. [17] This may have omitted erratums or corrections to published articles as well as other publication types such as book chapters, short surveys, reviews and conference papers.

Some minor reporting errors were found by the ERG relating to the searches. The PRISMA flow diagram (figure 1, p. 9, 2019 report by Evidera) had typing errors in the first box – the 2017 searches of PubMed retrieved 2398 results and the 2017 searches of Embase retrieved 2372 results.[17] In the company submission report, the PRISMA flow diagrams for the original review of economic evaluation and cost and resource use studies (Figure 1, Appendix G, p. 2) and the diagram for the

original review of HRQoL studies (Figure 1, Appendix H, p. 1) had typing errors in the first box – the 2017 searches of PubMed retrieved 2398 results and the 2017 searches of Embase retrieved 2372 results. In Appendix G of the company submission on p. 1, the year of initial search is reported incorrectly – this should be 19th May 2017.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on 29 January 2020** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Percentages for patient ethnicities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Percentages for patient ethnicities mentioned by the ERG are not correct according to our submission - Asian 52% instead of 60% [21/35], white 38% instead of 34% [12/35], other race 10% instead of 6% [2/35] **Pg. 13**	Replace: "Of the patients recruited, 52% were Asian, 38% were white and 10% were classed as 'other' race." With: Of the patients recruited, 60% were Asian, 34% were white and 6% were classed as 'other' race."	Factually inaccurate. Could lead to misinterpretation of CT data.	Correction made as proposed

Issue 2 Transfusion reduction data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
One of the transfusion-reduced patients is mentioned as having a reduction of [redacted]; this should be [redacted] **Pg. 36**	Replace: "[redacted] With: "[redacted]	Factually inaccurate. Could lead to misinterpretation of CT data	Not a factual inaccuracy – Table 29 of the CS and the accompanying text both state the reduction in the HGB-207 patient as being 54.2%. The text in question comes from a paragraph which discusses transfusion frequency. The 56.3% figure relates to change in volume.

Issue 3 Patient genotype classification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
There are differences regarding patients classified as IVS-I-5 or IVS-I-110 in the CSRs and our answers in clarification questions taken from the latest data-cut. The ERG considers the patients specified in the CSRs as IVS-I-5 or IVS-I-110 rather than those we specify in the clarification questions. While correct for Studies HGB-204 and HGB-205, this is not correct for Study HGB-207, where subject IDs listed in both the CSR column and PFC response column should be included. **Table 5 pg. 37**	Corresponding sentences below require amendments. For Row 'HGB-207,' change 'conclusion' box to say: Use both CSR and PFC Response data. For sentence below Table, change to 'Of the six patients identified in Table 5 as having severe non-β^0/ β^0 genotypes that were treated with Zynteglo, – [redacted]	Study HGB-207 excluded patients who had a β^0 mutation on both HBB alleles, but included patients that have either an IVS-I-5 or IVS-1-110 mutation on a single allele if the other allele was β^+ or β^e mutation. It is important to note that this is different from Study HGB-212, where patients were included only if they had a β^0/ β^0, β^0/IVS-I-110 or IVS-I-110/IVS-I-110 genotype.	Not a factual inaccuracy. The purpose of Table 5 was to "collate the outcomes on all patients with severe non-β^0/β^0 genotypes" using the various sources of data. Some patients with IVS-I-5 or IVS-1-110 mutations do not have severe non-β^0/β^0 genotypes. Study HGB-207 excluded patients who had an IVS-1-110 mutation together with a β^0 mutation. Patients who have either an IVS-I-5 or IVS-1-110 mutation on one allele and a β^+ or β^e mutation on the other allele are not considered as being severe non-β^0/ β^0 genotypes.

Issue 4 Clarification on patients included in the safety assessment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG mentions that patients aged under 12 years in HGB-207 (who were not	Delete the sentences: "However, patients aged under 12 years in HGB-207 (who were not part	While efficacy results from Study HGB-212 were not included in the CS as subjects falling within	After clarification provided in the follow-up to the FAC, the

part of the scope population) were included in the safety assessment (confirmed in the PFC response), despite the labels for Tables 37-41 and the corresponding text in the CS suggesting otherwise. **Pg. 40**	of the scope population) were included in the safety assessment (confirmed in the PFC response), despite the labels for Tables 37-41 and the corresponding text in the CS suggesting otherwise. No details have been provided about these patients in the company submission or the interim CSR for study HGB-207." Replace: "Adverse events (AE) were assessed in the intention-to-treat (ITT) population of 35 patients from studies HGB-204 (n=10), HGB-205 (n=4) and HGB-207 (n=[redacted])." With: Adverse events (AE) were assessed in the intention-to-treat (ITT) population of 35 patients aged =>12 years from studies HGB-204 (n=11), HGB-205 (n=4), HGB-207 (n=[redacted] and HGB-212 (n=[redacted]).	SmPC indication were not yet evaulabel for TI, safety results were included for these subjects.	changes proposed were made to the report. However, these changes caused inconsistencies in Section 4.2.3 of the ERG report and further changes needed to be made to the report to resolve these inconsistencies. The main changes were: 1. The final subsection, "Study HGB-212" was removed as it was no longer accurate 2. A new subsection was added to address the lack of clarity in how AEs had been reported

Issue 5 Incorrect description of vector copy number

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG describes vector copy number incorrectly **Pg. 13**	Replace: [redacted] With: [redacted]	Vector copy number refers to the average number of vector copies per cell, not the number of modified stem cells, which is provided by the percentage of cells transduced. Vector copy number and percentage of cells transduced are related, but distinct, measures of potential efficacy of Zynteglo. It is therefore important to utilise the correct definition when describing one or other term.	Correction made as proposed

Issue 6 Clarification on the effect of Zynteglo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The statement 'The ERG also highlight that there is insufficient evidence to support the assumption of permanent	The sentence should be removed.	Zynteglo works by adding functional copies of a beta-globin gene into CD34+ stem cells. Once a patient successfully	Not a factual inaccuracy. While there may be a clinical rationale for this assumption, as highlighted throughout the ERG

engraftment and an indefinite treatment effect in all patients.' is considered unfounded. **Pg .17**		engrafts and achieves transfusion independence, the benefits are expected to be lifelong, as noted in the Zynteglo SmPC. To date, all patients in our clinical programmes who have engrafted and achieved transfusion independence have continued to retain this status to last follow up.	report, more mature data and more patients' data would be required to support this assumption.

Issue 7 Clarification on the description of the complex PAS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The description that the ERG provides for the complex PAS in not accurate. **Pg. 70**	Replace: It is the ERG's understanding that [redacted]	The complex PAS timeframe is based on a number of factors and not intended to [redacted] from the clinical trials.	Not a factual inaccuracy – [redacted]. However, the ERG has clarified this statement.

	With: It is the ERG's understanding that the company have submitted a complex PAS to the Patient Access Scheme Liaison Unit (PASLU). The details of this PAS have not been finalised, however, the ERG understands the PAS consists of outcomes-based payments over a time period conditional on patients remaining transfusion-independent. The ERG has concerns over a PAS based on patient outcomes and length of time over which these outcomes will be judged. If payments are to be staggered over a time period, the ERG believes there will still be significant irrecoverable costs should patients become transfusion-dependent after the end of the payment period. In this case, the NHS will have paid the full acquisition cost and not received the lifetime benefits required to plausibly make Zynteglo a cost-effective treatment option. The timing and magnitude of the first payment must also be considered, when the complex PAS has been finalised.		

Issue 8 Inclusion of PSS perspective

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
As part of the validation checklist the ERG stated that only the NHS perspective had been accounted for, with the Personal Social Services (PSS) perspective being omitted. **Pg. 61 Table 6, and pg. 68**	Replace the row in Table 6 (p 61): With: Replace (pg. 68):	Factually inaccurate. PSS perspective has been included where appropriate e.g. the micro-costing for blood transfusion unit cost taken using the PSSRU.	Not a factual inaccuracy. The CS repeatedly stated how PSS costs were not accounted for (page 11, 158, 167, 208 of the CS), with the company stating how "it was not possible to quantify costs from the perspective of personal social services".

Perspective on costs	NHS and PSS	Partly	Only NHS costs have been considered

Perspective on costs	NHS and PSS	Yes	

	"The company's analysis adopted an NHS perspective only, and did not consider any costs incurred by Personal Social Services (PSS), which is not the perspective preferred in the NICE Methods guide" With: "The company's analysis adopted an NHS and Personal Social Services (PSS) perspective, in line with the NICE methods guide"		

Issue 9 Incorrect description of transfusion costs after Zynteglo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG describes the cost of transfusions after transplant with Zynteglo incorrectly **Pg. 58-59**	Delete the sentence: Additionally, the ERG noted that the model did not apply any cost of transfusions in the 90-day period after transplant, regardless of their subsequent transfusion status. It is unclear whether this is a modelling error or was intentional on the part of the company. The cost impact of excluding these transfusions is expected to be minimal in the present analysis; however, it could be problematic should an outcomes-based payment scheme for Zynteglo be introduced, when the timing of the assessment for the first outcome-based payment would be important.	Patients receive transfusion and chelation costs in the 90-day period post-transplant. At the 90-day point, if the patient achieves TI, they stop receiving transfusion costs but continue receiving chelation costs until the end of the iron normalisation period. This is outlined on Page 4 in the document *'Appendix A - EVA-20858-05_Zynteglo CEM_Technical Report_21Nov2019 [AIC]'*	Thank you for the additional clarification regarding this modelling point. We have removed mention of a modelling error in our report. However, the point still stands that patients are assumed to become TI in the model at an earlier time point than what was achieved in the trials, so the remaining text in the paragraph has been clarified and the paragraph header has been updated.

		provided with the ERG clarification responses. The wording states *"This is determined at 90 days post-transplant event (editable time). Until this determination, transfusions and chelation are continued (phlebotomy can be used) in all patients."*	

In addition to the above factual inaccuracies, to avoid confusion and/or misunderstanding, we would like to clarify the following issues:

Issue 10 Confusion related to the consequences of using a patient's own cells

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
The concern raised by the ERG 'However, there is concern around the consequences of returning the patient's original cells in the Zynteglo product back to the patient, and that it may lead to decreased haemoglobin production	Removal of sentence	It is unclear what the ERG are referring to as a basis for their concern. The Zynteglo drug product consists of the patient's own cells i.e. is an autologous cell population. Once the gene-corrected cells engraft, it is expected that they will begin to produce healthy beta-globin. We are confused as to why the use of the patient's own cells may lead to decreased haemoglobin	We understand that not all cells that are infused to patients will have been gene-corrected. For example, the median proportion of transduced cells in HGB-207 was reported in the CS as being [redacted] (pg 89 of CS). We have added this additional context for clarity.

and a return to a need for transfusions' **Pg. 73**		production and lead the patient to require transfusions.	

Issue 11 Text to mark confidential (AIC clinical data)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
• Patient ethnicity percentages • Age of oldest patient in Zynteglo trials • Patients with severe genotypes	Mark the following text in pg. 13: Of the patients recruited, [redacted] were Asian, [redacted] were white and [redacted] were classed as 'other' race. Mark the following text in pg. 33: The CS reported basic baseline data in terms of the race of patients included in the Zynteglo trials: [redacted] Asian, [redacted] white and [redacted] other (Table 18, p75 of CS). Mark the following text in pg. 23: Currently the oldest patients treated with Zynteglo were [redacted] Mark the following text in pg. 23: Of the [redacted] patients identified in Table 5 as having severe non-β^0/β^0 genotypes – i.e. homozygous for IVS-I-110 or IVS-I-5, or heterozygous for IVS-I-110 or IVS-I-5 together with a β^0 mutation – [redacted]. An initial reading of these data suggests	Data has not yet been released	Confidentiality markings made as appropriate

• Age of patient	that the likelihood of achieving TI in patients with severe non-β^0/β^0 genotypes [redacted] to that for patients with β^0/β^0 genotypes i.e. [redacted] For comparison, Study HGB-204 included 8 patients with β^0/β^0 genotypes (these patients are not included in the marketing authorisation). [redacted][5] Mark the following text in pg. 40: Of note, a [redacted], was assessed as Stage II/I pubic hair/genitalia at screening, then assessed as Stage I/I pubic hair/genitalia at Month 6 but had [redacted] to Stage III/III pubic hair/genitalia by Month 18		

Issue 12 Text to mark confidential (CIC commercial data)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
• Manufacturing process	Mark the following text in pg. 14: The Zynteglo manufacturing processes have evolved during the trial programme with the aim of [redacted]	Data is related to sensitive commercial information	Confidentiality markings made as appropriate

• Patient preference survey	[redacted] Mark the following text in pg. 39: These also [redacted] from the results of the UK patient (and caregivers) preference study the company undertook, which suggested that TDT patient uptake of Zynteglo treatment would be somewhat limited. The study was an online survey of [redacted] TDT patients and [redacted] caregivers (total n=[redacted]), [redacted]% of which had been living with beta-thalassaemia for [redacted] years or more. Of the [redacted] survey responders [redacted]% of patients agreed with the statement "Beta thalassaemia significantly impacts my quality of life" and [redacted]% indicated they would immediately accept a referral (to see a transplant specialist) and accept Zynteglo, were it offered.		

Issue 13 Text marked confidential that can be released

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
• TI response rate	Unmark the following text in **bold** in pg. 13: 'For the primary outcome – transfusion independence (TI) – a response rate of [redacted] **was seen in the 'transfusion evaluable' population.** [redacted]	Data was released in the ASH conference in December 2019	Although these are not factual inaccuracies the updated markings have been made as proposed.

• Number of patients in HGB-207 trial • Safety data	[redacted] Unmark the following text in **bold** in pg. 36: For the transplant population the rate of TI was [redacted]. Unmark the following text in **bold** in pg. 40: Adverse events (AE) were assessed in the intention-to-treat (ITT) population of 35 patients from studies HGB-204 (n=10), HGB-205 (n=4) and HGB-207 (**n=21**). Unmark the following text in **bold** in pg. 41: There were no safety issues related to the BB305 LVV in HGB-204, HGB-205 or HGB-207.[11, 12] There was [redacted], including [redacted] where the longest follow-up was 61.3 months after drug infusion. [redacted] who received Zynteglo experienced [redacted], but this was later confirmed to be [redacted] Unmark the following text in **bold** in pg. 42: The incidence of all SAEs in TDT patients was presented in Table 41 (pp 141-142) of the CS. The overall survival [redacted] **and** [redacted]		

• Chart Review	Unmark the following text in **bold** in pg. 49: The study included 165 patients, [redacted] of which were over 40 years old, whereas the oldest patient treated with Zynteglo in the trials was [redacted]. Patients had a mean of [redacted] transfusion episodes ([redacted] of patients had 16 or more transfusions per year) and a median of [redacted] units of blood transfused per year. It is noteworthy that although several patients were excluded from the Zynteglo trials for having comorbidities – advanced liver disease or cardiac disease – such patients were not excluded from this chart review study. This was reflected in the proportion of patients who had high liver iron concentrations ([redacted]). The prevalence of diabetes in the Chart Review was [redacted], hypogonadism prevalence was [redacted], and hypogonadotropic hypogonadism prevalence was [redacted]. These are much [redacted] prevalences than those reported in the study identified in the company's systematic review (see Section 4.3.4) which were used to derive risks of developing these conditions in the model.[redacted]		
• Complex PAS description	Unmark the following text in **bold** in pg. 70: It is the ERG's understanding that **the company have submitted a complex PAS to the Patient Access Scheme Liaison Unit (PASLU). The details of this PAS have not been finalised, however, the ERG understands the PAS consists of outcomes-based payments over time conditional on patients remaining transfusion-independent. The ERG has concerns over a PAS based on patient outcomes and length of time over which these outcomes will be judged. If**	Following the comment from the ERG regarding the markings for the proposed PAS are inconsistent, bluebird bio proposes the	

	payments are to be staggered over a time period matching the length of the follow up data, the ERG believes there will still be significant irrecoverable costs should patients become transfusion-dependent after the end of the payment period. In this case, the NHS will have paid the full acquisition cost and not received the lifetime benefits required to plausibly make Zynteglo a cost-effective treatment option. The timing and magnitude of the first payment must also be considered, when the complex PAS has been finalised.	release of this information on the description of the complex PAS.	

(please cut and paste further tables as necessary)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Zynteglo for treating transfusion-dependent beta-thalassaemia

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

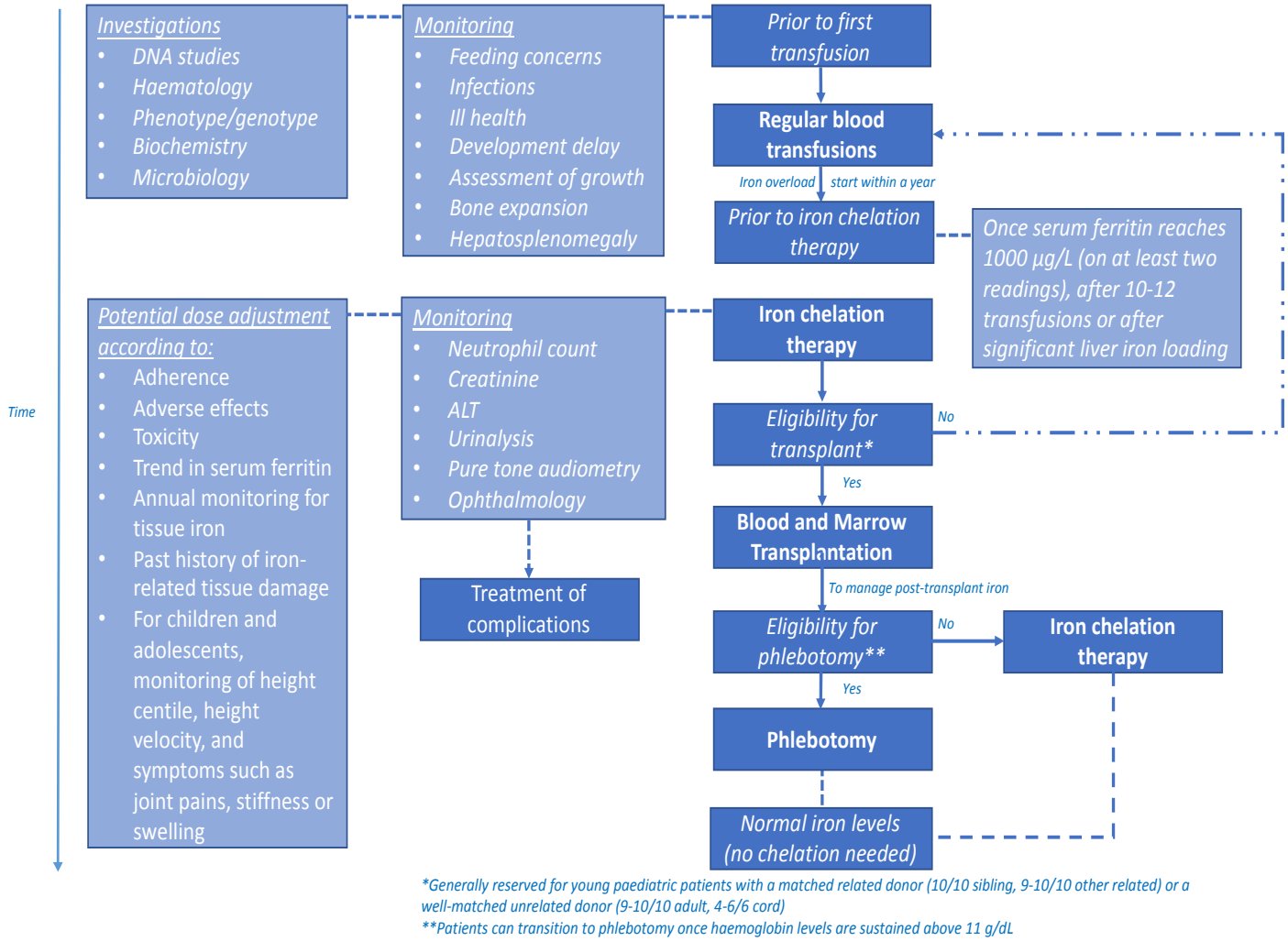
1. Topic background

1.1 Disease background

- Thalassaemia is a group of inherited blood disorders caused by a genetic mutation of the β-globin (HBB) gene that leads to reduced production of healthy red blood cells and haemoglobin in the body, which is used by red blood cells to carry oxygen.
- There are two basic groups of thalassaemia: alpha-thalassaemia and beta-thalassaemia. The most severe forms are known as transfusion-dependent thalassaemia (or thalassaemia major).
- Thalassaemia causes varying degrees of anaemia, leading to symptoms such as tiredness, weakness, shortness of breath and pale skin caused by the lack of haemoglobin. In transfusion-dependent beta-thalassaemia, haemoglobin production is so reduced that normal growth, development and quality of life can only be achieved by regular red cell transfusions from infancy, which leads to excess iron build up in the body. This build up is typically treated with ongoing iron chelation therapy. Excess iron build up, or 'iron overload', is associated with endocrine conditions (such as hypogonadism, growth delay and infertility), cardiac complications and liver disease.
- There are currently 1,033 people diagnosed with beta-thalassaemia major in the UK according to the National Haemoglobinopathy Registry.

1.2 Treatment pathway

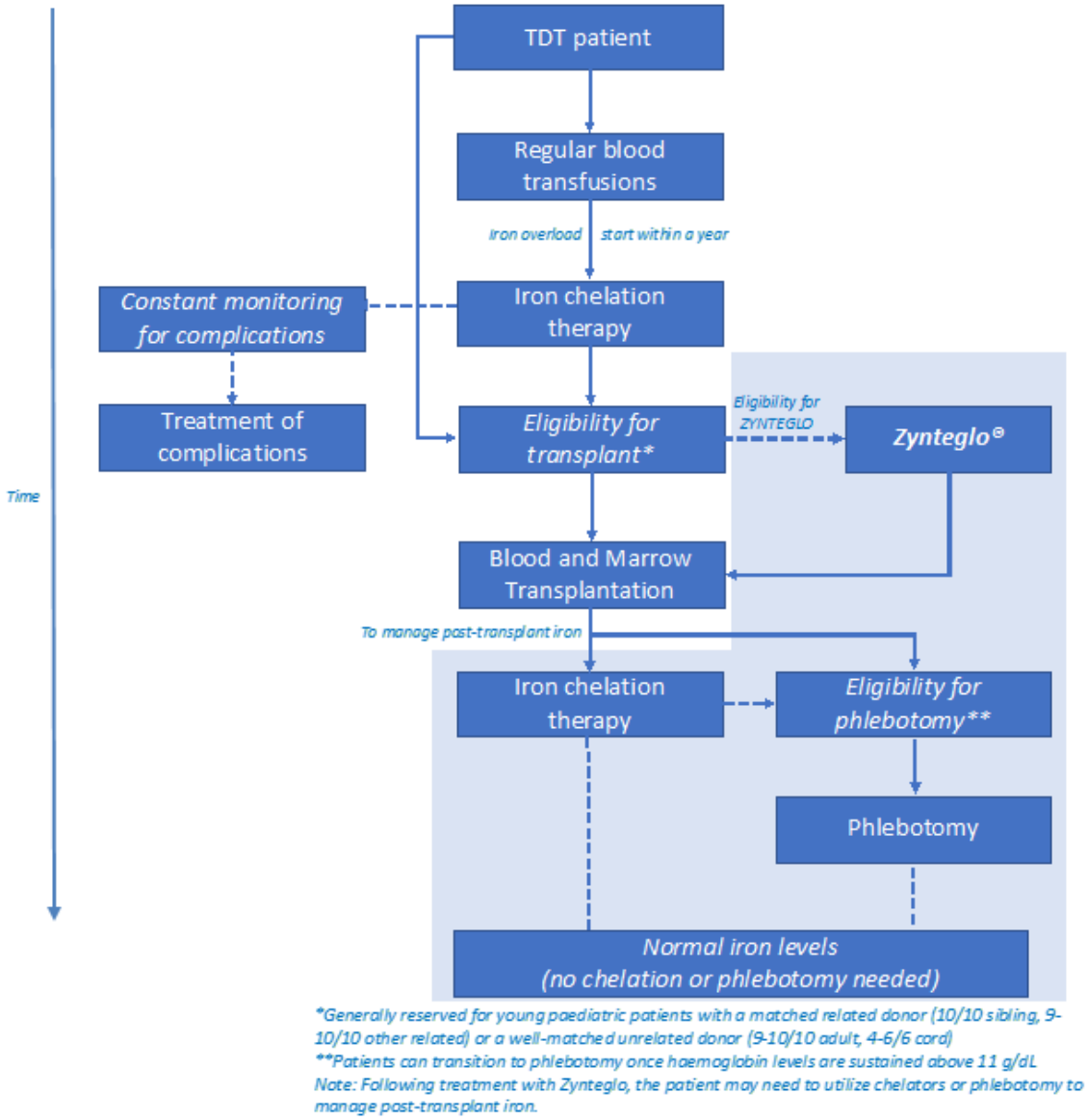
Current standard of care (adapted from UK Thalassaemia Society guidelines):



*Generally reserved for young paediatric patients with a matched related donor (10/10 sibling, 9-10/10 other related) or a well-matched unrelated donor (9-10/10 adult, 4-6/6 cord)

**Patients can transition to phlebotomy once haemoglobin levels are sustained above 11 g/dL

Proposed positioning of Zynteglo:



*Generally reserved for young paediatric patients with a matched related donor (10/10 sibling, 9-10/10 other related) or a well-matched unrelated donor (9-10/10 adult, 4-6/6 cord)
**Patients can transition to phlebotomy once haemoglobin levels are sustained above 11 g/dL
Note: Following treatment with Zynteglo, the patient may need to utilize chelators or phlebotomy to manage post-transplant iron.

1.3 Zynteglo

Conditional marketing authorisation (29 May 2019)	Zynteglo is indicated for the treatment of patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β^0/β^0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available. As part of the conditional authorisation, patients are expected to enrol in a registry in order to better understand the long-term safety and efficacy of Zynteglo.
Mechanism of action	Zynteglo is an autologous CD34+ cell enriched population that contains haematopoietic stem cells (HSCs) transduced with lentiviral vector (LVV) encoding the βA-T87Q-globin gene. The autologous CD34+ cells collected via mobilisation and apheresis are transduced with the BB305 LVV and are intended for infusion into the same patient following myeloablative conditioning. BB305 LVV is a replication-defective, self-inactivating LVV, that carries a modified functional copy of the β-globin (HBB) gene.
Administration	The minimum recommended dose of Zynteglo is 5.0 × 106 CD34+ cells/kg. Zynteglo is intended for autologous use and should only be administered once. Process: • Administration of mobilising agents, then apheresis to harvest patient's HSCs (one or more cycles, to obtain minimum target number of cells) • Pre-treatment myeloablative conditioning with chemotherapy (typically busulfan and cyclophosphamide) • Autologous haematopoietic stem cell transplant, modified stem cells given back to patient via intravenous infusion. The complete treatment process, from mobilisation to the end of inpatient stay, lasts 13-19 weeks.
Price	List price of Zynteglo 1.2-20x10^6 cells/mL dispersion for one-time infusion: £1,450,000 per patient excluding VAT. The company has a commercial arrangement (approved simple discount patient access scheme). This makes Zynteglo available to the NHS with a discount. The size of the discount is commercial in confidence. The company is in discussion with NHS England and NHS Improvement over another commercial arrangement ([redacted]).

1.4 Clinical evidence – HGB-204, HGB-205, HGB-207, LTF-303

- The company's evidence is from three single arm, single dose studies (HGB-204, HGB-205, HGB-207), with approximately 2 years of follow-up after drug infusion. HGB-204 and HGB-205 are completed phase 1/2 studies, while HGB-207 and HGB-212 are ongoing phase 3 studies. Evaluable data for patients with non-β^0/β^0 genotypes from HGB-212 is not currently available. There is also a multi-centre long-term safety and efficacy follow-up study (LTF-303) for an additional 13 years of follow-up for patients who completed the parent studies. The inclusion criteria for the clinical trials were limited to people aged under 50 years, therefore data regarding the effectiveness of Zynteglo is not available for individuals over the age of 50 years. However, the licensed indication includes people 12 years and over, with no cap on age.

- The key efficacy outcome in the parent studies is the proportion of subjects who meet the definition of 'transfusion independence' (TI), defined as a weighted average haemoglobin (Hb) ≥9 g/dL without any packed red blood cell (pRBC) transfusions for a continuous period of ≥12 months at any time during the study after Zynteglo infusion.

- So far, there are 24 TI evaluable patients overall in the three HGB parent studies. Being evaluable for TI is defined as patients that have completed their parent study, or achieved TI, or won't achieve TI in their parent study due to insufficient follow-up time remaining in parent study.

1.5 Key trial results

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

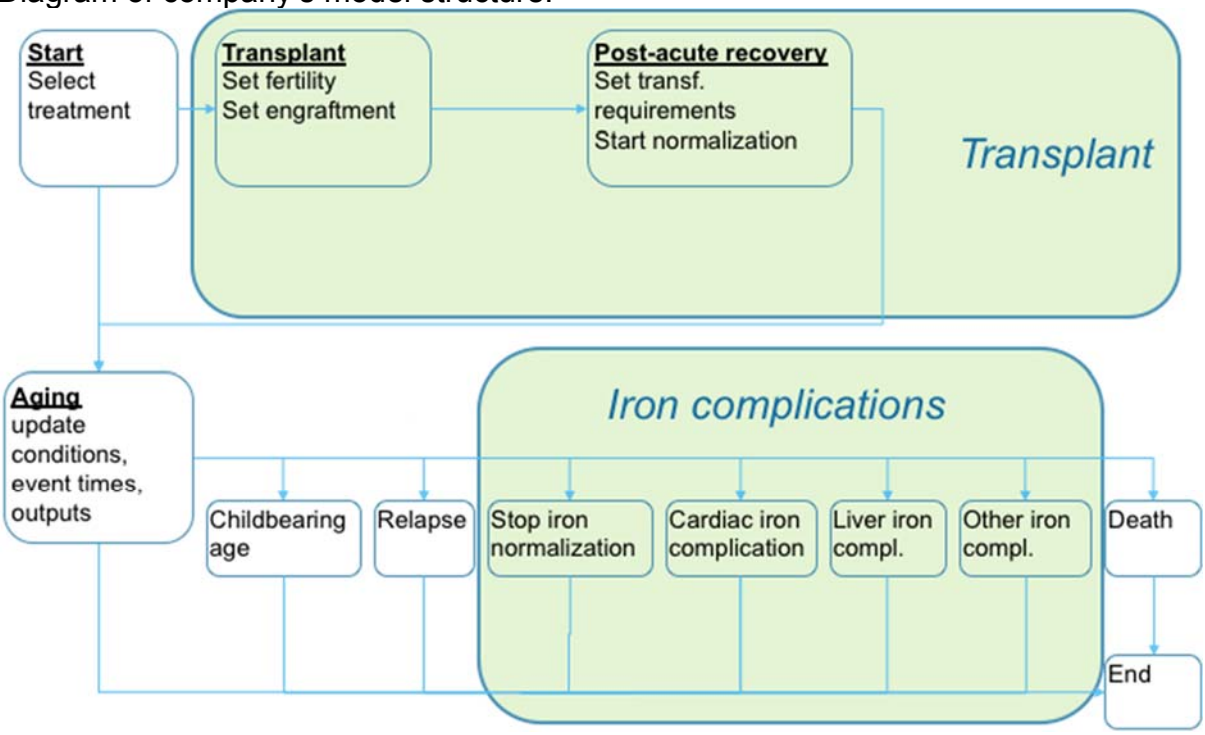
Parameter	Statistic	HGB-204	HGB-205	HGB-207	Overall
Number of TI-evaluable patients	n	10	4	10	24
TI at any time (Month 24 for HGB-204/205)	n (%) 2-sided 95% CI	8 (80.0) 44.4, 97.5	3 (75.0) 19.4, 99.4	9 (90.0) 55.5, 99.7	20 (83.3) 62.6, 95.3
Subjects with TI at Month 60	n (%) 2-sided 95% CI	1 (100.0) 2.5, 100.0	2 (100.0) 15.8, 100.0	0 -	3 (100.0) 29.2, 100.0

- For all non-β^0/β^0 subjects who achieved TI at any time (N=20), the median (min, max) duration of time from drug product infusion to last pRBC transfusion was [redacted]. Median (min, max) time to reach the definition of TI was 15.70 (14.9, 20.9) months.

1.6 Company's model structure, assumptions and inputs

- Discrete event simulation, specifically a discretely integrated condition event (DICE) simulation framework. Conceptualises the disease process and its management in terms of the 'conditions' and 'events' that patients can experience. Conditions are aspects of the model that persist over time, such as developing iron overload, while events are aspects that happen at a point in time, such as blood transfusion.

Diagram of company's model structure:



- Lifelong time horizon (capping maximum survival at age 100 years), company has used 1.5% discount rate for costs and quality-adjusted life years (QALYs).
- Comparator: pRBC transfusions and iron chelation therapy.
- Clinical effectiveness data from HGB-204, HGB-205 and HGB-207 trials.
- Model incorporates TI after transplant with Zynteglo, time to iron normalisation after transplant, assumed mortality impact of myeloablative conditioning and infertility disutility from myeloablative conditioning. Simulation of cardiac, liver and endocrine iron levels to predict development of complications from iron overload.
- Utilities derived from a vignette study conducted in UK general population sample, assumed quality of life impact of adverse events associated with Zynteglo would be reflected in utility decrement associated with transplantation.
- Company carried out a chart review of 165 adult and paediatric patients with TDT managed by NHS secondary care centres. This was a multi-centre, observational mixed-methodology study, involving a retrospective chart review and a prospective cross-sectional survey of patients with TDT, conducted in 9

centres in the UK. Used as data source for some of the model inputs such as average patient weight, comparator health-related quality of life (HRQoL) and resource use. The chart review did not exclude people with a β^0/β^0 genotype (proportion in chart review population unknown) or those with important comorbidities (such as advanced liver disease or cardiac disease), who would not have been eligible for Zynteglo. The age of people in the chart review did not match the Zynteglo trial population ([redacted] of chart review population were over the age of 30 [maximum age [redacted] years], whereas only 8.3% of the trial population were aged over 30 [all of whom were aged <35 years]).

2. Summary of the technical report

2.1 In summary, the technical team considered the following:

Issue 1 The reference case discount rate of 3.5% for discounting costs and QALYs should be used (see Issue 1 – Non-reference case discount rate).

Issue 2 The adjustment of utilities to reflect natural decline in HRQoL over time should be carried out using a whole-population dataset (not a subset made up only of those in perfect health), and as such, the ERG's preferred approach to disutility in the transfusion-dependent health state should be followed to avoid double counting, and better reflect the population seen in the clinical trials and the population who would likely receive Zynteglo in the NHS if it is approved. The analysis should also take into account the disutility associated with subcutaneous chelation during the iron normalisation period post-Zynteglo for transfusion-independent patients, not just the costs of this chelation (see Issue 2 – Utilities).

Issue 3 It is appropriate to incorporate endocrine abnormalities in the baseline population of the model, and use age category-specific patient weights. It is unclear if the efficacy evidence for Zynteglo

is generalisable to the potential UK patient population (see Issue 3 – Baseline characteristics of modelled population).

Issue 4 The base case population in the model should reflect the people in the NHS who may be eligible for Zynteglo, but it is uncertain what proportion of the population in the indication have a severe non-β^0/β^0 mutation (see Issue 4 – Underrepresentation of population with severe non-β0/β0 genotypes).

Issue 5 Chelation practices may have changed over time in NHS practice. A 4-year iron normalisation period is inappropriate, and a longer period is plausible. It is unknown whether patients who become transfusion-independent after Zynteglo will eventually have reduced cardiac iron levels which are considered safe (see Issue 5 – Iron overload treatment, iron normalisation and residual risk of developing iron-overload complications).

Issue 6 The mortality data used by the company for transfusion-dependent patients without cardiac complications is very outdated and is likely to be lower than modelled. The trial data for Zynteglo is too immature to know whether or not treatment effect is lifelong, or whether any patients relapse in terms of transfusion status or experience engraftment failure at any point after Zynteglo treatment. A non-zero engraftment failure rate has cost implications for the NHS (see Issue 6 – Unknown long-term outcomes – relapse (late graft failure), initial (primary) engraftment failure and mortality).

Issue 7 The pricing source for some of the therapies in the treatment pathway should be changed, to reflect discounts available to the NHS (see Issue 7 – Generic drug acquisition costs).

Issue 8 Evidence on the prices and impact of genotype testing and other testing the company will pay for is required (see Issue 8 – Genotyping, other testing the company will pay for, and impact on the NHS).

Issue 9 The costs of myeloablative conditioning should incorporate use of other drugs in conditioning regimens, not just busulfan. The mortality rate associated with myeloablative conditioning is unlikely to be 0%, and should be reflected in the Zynteglo arm of the model (see Issue 9 – Myeloablative conditioning).

Issue 10 It may be appropriate to simulate a higher number of hypothetical patients than is carried out in the company's base case model, in order to stabilise the ICER result (see Issue 10 – Number of patient profiles modelled).

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The clinical trial evidence is based on small numbers of patients who were classed as TI evaluable (n=24).
- Long-term maintenance of TI is unknown (longest follow-up to date is 61.3 months, in a small number of patients).
- Mortality in transfusion-dependent patients is unknown
- There is a lack of evidence in a key subgroup
- There is a lack of head-to-head evidence between Zynteglo and comparators, because the clinical trials were single-arm studies

2.3 The cost-effectiveness results include a commercial arrangement (simple discount patient access scheme) for Zynteglo.

2.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of over [redacted] per QALY gained (see Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate).

2.5 This intervention for this indication does not meet end-of-life criteria.

2.6 The technology is considered innovative – there are no other approved treatments addressing the underlying genetic cause of TDT.

2.7 The potential HRQoL impact on carers is unknown, both for current standard of care, and for the Zynteglo process. This impact is therefore not captured via QALYs in the modelling.

2.8 A potential equalities issue was raised (that in the UK, transfusion-dependent beta-thalassaemia is mostly seen in minority ethnic groups), but issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal.

3. Key issues for consideration

Issue 1 – Non-reference case discount rate

Questions for engagement	1. Is there any evidence on projected life expectancy for people with TDT treated optimally with current management strategies and therapies? 2. Should 3.5% or 1.5% be used as the discount rate for costs and QALYs in this appraisal?
Background/description of issue	The NICE guide to the methods of technology appraisal indicates that it is usually appropriate to discount costs and health effects at the same annual rate of 3.5%, and that sensitivity analyses using rates of 1.5% for both costs and health effects may be presented alongside the reference-case analysis (section 5.6). The criteria required are: • The treatment restores people who would otherwise die or have a very severely impaired life to full or near full health and • This is sustained over a very long period (normally at least 30 years) If these are met, then a discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. As well as this, the Appraisal Committee need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs (section 6.2.19 of methods guide). **The company** used a 1.5% discount rate for costs and benefits in its base case (see company submission [CS] B.3.2.4), and did not provide an analysis with the more commonly-used reference case discount rate of 3.5%, despite this being used in several other relevant cost-effectiveness studies in TDT it identified in the literature. The company claimed that Zynteglo restores people who would otherwise die or have a very severely impaired life to full or near full health, basing this on unpublished analysis of the Health Episode Statistics database and the company's UK chart review. These found that the median age at death for TDT patients in England was [redacted] years (over 2007-2016), with a mean utility of 0.69 for patients receiving blood transfusions and chelation. The company explained that, owing to Zynteglo being a gene therapy, there is rationale which provides confidence in its benefits being sustained over a long period, and that the growing evidence base shows it is

	highly likely the outcomes will be achieved. The company referenced the NICE highly specialised technologies appraisal of Strimvelis (a different gene therapy, used to treat a different condition), where the committee 'considered that it was likely that the alternative 1.5% discounting rate was intended to cover situations similar to this – that is, when costs are incurred up-front but benefits are accrued over a longer period'. The company also referenced the 2018 HM Treasury Green Book, that 'the recommended discount rate for risk to health and life values is 1.5%.' **The ERG** had a number of concerns relating to all aspects of the company's case for using the non-standard discount rate. Use of non-reference case discount rate leads to a substantial underestimate of the company's ICER. Considerable uncertainty remains regarding the company's justification for using this discount rate. • *Zynteglo restores people who would otherwise die or have a very severely impaired life to full or near full health:* ERG concerns - UK Thalassaemia Society (UKTS) state that 'the expectation is that well monitored and chelated patients will have a near normal life expectancy'; mortality figures given by the company are based on data that is up to 50 years old; lack of long term and generalisable survival data raises concerns regarding the statement that patients would 'otherwise die'; estimates of life expectancy must be based upon current clinical management, but evidence on projected life expectancy for patients treated optimally with current management strategies and therapies do not exist. Two studies in the literature derived utilities using EQ-5D and reported values of 0.86 and 0.87 for those with TDT on chelation therapy, which is supported by the analysis of 16 to 35 year olds with TDT in the company's chart review, whose HRQoL was reported as [redacted]. 61% of people with TDT disagreed that beta-thalassaemia significantly impacted upon their quality of life (from UK Patient Preference Report provided by company). Patients recruited to the Zynteglo trials also generally rated their HRQoL as similar to that of the general population prior to treatment. UKTS state that there are 'usually excellent outcomes for children and adults managed conventionally with transfusion and chelation, now that monitoring for iron overload is more accurate and chelation choices are wider.' • *Benefits are long term* ERG concerns - Durable clinical efficacy has been demonstrated to 61.3 months in a small number of patients, but lifelong benefits have not yet been shown. Two types of uncertainty here – applies to persistence of transduced cells, as well as ongoing haemoglobin production by the graft (patients remaining TI). ERG accept

	that results are promising but the evidence to suggest the life-long persistence of the graft in all patients is not yet available. • *Zynteglo will not commit the NHS to significant irrecoverable costs* ERG concerns - Potential cost to the NHS associated with anything but an indefinite treatment effect in all patients could be large. If any patients become transfusion-dependent at some point after Zynteglo, then not only would the full cost of Zynteglo have been incurred as well as any potential adverse events, such as infertility, leukaemia, and lymphoma, these costs would then be additional to the ongoing costs of transfusions and chelation. **The technical team** noted there were 13 years of overall survival data in the Strimvelis highly specialised technologies appraisal, and that the committee in that case decided to consider both discount rates in decision making, owing to uncertainty in whether long-term benefits of treatment would be achieved because of the limited evidence. The Zynteglo appraisal only has data for some patients for just over a third of the follow up time as the Strimvelis appraisal, and did not meet the criteria to be assessed as a highly specialised technology. The company has also assumed that there is no engraftment failure in its model (see Issue 6 – Unknown long-term outcomes – relapse (late graft failure), initial (primary) engraftment failure and mortality). The high acquisition cost could not be recovered by the NHS if the engraftment fails, with affected patients going back to transfusions and chelation.
Why this issue is important	The discount rate has a very large impact on the cost-effectiveness results. The ERG tested a scenario with a 3.5% discount rate, which increased the ICER from the corrected company base case of [redacted] to [redacted].
Technical team preliminary judgement and rationale	A 1.5% discount rate for costs and benefits is not appropriate for this appraisal, as the clinical criteria for consideration for this discount rate are not met, so the 3.5% discount rate for costs and QALYs should be used. Owing to the high cost of the technology and the immaturity of the evidence base, the introduction of the technology may well commit the NHS to significant irrecoverable costs.

Issue 2 – Utilities

<table>
<tr><td>Questions for engagement</td><td>3. Is the use of utility scores from vignette studies instead of HRQoL data from Zynteglo clinical trials appropriate for some of the utility inputs in the model? Is the HRQoL data from the clinical trials generalisable to that seen in NHS practice?
4. Have management of TDT and iron chelation practices drastically changed in terms of outcome and patient disutility over the last 35 years? Should the disutility for the transfusion-dependent state in the model be based on the mean utility of all patients ≥16 years in the chart review, or the re-analysis using only those patients in the chart review dataset aged 12 to 35 years without co-morbidities already being modelled?
5. What is the potential HRQoL impact of infertility after myeloablative conditioning? Should this be accounted for in the analysis, or removed due to lack of data specific to this clinical scenario?
6. Should the HRQoL impact from any subcutaneous chelation therapy during the iron normalisation period be taken into account for people who become transfusion-independent after receiving Zynteglo treatment?
7. Should the whole-population published dataset be used for the adjustment of utilities to take into account natural decline in HRQoL over time, or the subset excluding people who have existing/previous health problems?</td></tr>
<tr><td>Background/description of issue</td><td>HRQoL values were obtained in Zynteglo trials (HGB0205, 205 and 207), but several patients did not have baseline measurements, and the method for obtaining HRQoL scores from patients varied between and in trials (EQ-5D-3L, EQ-5D-Y, SF-36v2, PedsQL, and FACT-BMT). The utility data collected from these showed a trend of returning to baseline utility level after 12 months (see section B.2.6.5 of CS for detailed HRQoL data).
The methods guide indicates that adjustment of utilities may be needed (see section 5.3.7), to reflect the natural decline in HRQoL in the general population which occurs over time with age. A typical methodology used for this is described by Ara and Brazier (2011).
Table A: Company's base case utility decrements
<table>
<tr><th>Health state</th><th>Company base-case decrement</th><th>Source</th></tr>
<tr><td>Zynteglo treatment</td><td>0.31</td><td>Vignette study</td></tr>
<tr><td>Up to one-year post-Zynteglo</td><td>0.31</td><td>Vignette study</td></tr>
<tr><td>Transfusion-independent</td><td>0.02</td><td>Vignette study</td></tr>
</table>
</td></tr>
</table>

Transfusion-reduced	0.13	Assumption
Transfusion-dependent	0.27	Chart Review
Complication	**Company base-case decrement**	**Source**
Infertility	0.07	Busnelli et al., 2014; Scotland et al., 2011
Iron overload treatment for transfusion-independent patients during iron normalisation period	**Company base-case decrement**	**Source**
Subcutaneous chelation therapy	-	Not applied

a) Age-adjustment of utilities

The company used age-stratified EQ-5D utility scores for the general population based on the public in the UK with at least one health condition (from Ara and Brazier) to adjust for HRQoL changes over time. It applied utility decrements based on patients' transfusion status to these general population utilities, along with additional decrements for complications and infertility.

The ERG believed that the data subset chosen by the company from within the Ara and Brazier source was inappropriate, as it included only people in perfect health (with no previous health problems) in each age group. The ERG explained that, in effect, the company's base case then assumes people with beta-thalassaemia in the model would remain in perfect health for the rest of their life, and would never develop a condition beyond those directly related to beta-thalassaemia already included in the modelling. The ERG thought that the whole-population dataset (inclusive of all individuals regardless of their health) from the Ara and Brazier source should be used instead of the subset chosen by the company, explaining that it has been used extensively in cost-utility modelling in other NICE appraisals. If the company's preferred subset was used, this meant people with beta-thalassaemia in the model had utility scores higher than the general population of the same age (0.08, 0.11 and 0.19 higher than at age 40, age 60 and age 80 years respectively).

b) Source of utilities data and utility decrement for transfusion-dependent patients

The company decided not to use the utility values collected from the trials in its model. It considered those baseline values which had been collected to be 'artificially high', possibly due to an 'adjustment bias', so it would

	be hard to detect a utility benefit after treatment with Zynteglo (see section B.3.4 of CS). Instead, the company used the chart review and a vignette study to calculate the associated utility decrements (see **Error! Reference source not found.**), then applied these to general population utilities. For transfusion-dependent patients, patients undergoing Zynteglo treatment and up to one-year post-Zynteglo treatment in the model, the company derived the utility decrement for these states from a vignette study (time trade-off method used with 207 members of general public in England). The company applied a decrement to the utility score of patients in the model who were transfusion-dependent, based on data from company's chart review (medical records of 165 people with TDT in UK). Utility scores were generated using the EQ-5D-3L questionnaire scores for 94 patients ≥16 years, and the EQ-5D-Y for 20 patients aged 7 to 15 years. The company used the mean utility of all patients ≥16 years in the chart review to generate the utility decrement associated with being transfusion-dependent in the model (utility of 0.69, representing a decrement of 0.27). **The ERG** felt that the patient demographics in the chart review were very different from those in the Zynteglo trials, particularly the age distribution (see section 5.2.3 of ERG report), which means that the model may have double counted the effects of ageing (HRQoL data derived from an older population, while also adjusting utilities over time to account for ageing). As well as this, the ERG felt that using a mean utility score for transfusion-dependent patients based on an older population in the chart review might be inappropriate, as HRQoL may be lower than younger patients due to changing chelation practices and more optimal management in recent years. The ERG requested re-analysis of the chart review data, limiting to those aged 12 to 35 years and excluding those with existing co-morbidities that were already separately considered in the modelling (to avoid double counting those disutilities). The mean utility of this re-analysis population was [redacted]. The ERG preferred to use this utility for the transfusion-dependent state in the model, because it thought it was more comparable to the baseline value for patients included in the Zynteglo trials, and to the population who might be eligible for treatment in practice. The ERG explained that by removing older patients from the analysis, it avoids adjusting down an already age-adjusted utility value for age. This effectively 'double adjustment' resulted in an overly low utility for older patients in the company's base case. c) Disutility from infertility Myeloablative conditioning regimens given prior to Zynteglo may cause permanent sterility. As a result, modelled patients receiving Zynteglo are at risk of subfertility or infertility. **The company** used data on disutility from infertility from the literature.

	The ERG considered that the impact of infertility resulting from myeloablative conditioning ahead of Zynteglo treatment was not well understood and poorly captured with the EQ-5D tool, so the ERG believed it may not be appropriate to capture this particular impact in the appraisal. The ERG considered the source of the disutility value to not be generalisable to this clinical context, and that this particular infertility impact has only been used before when modelling for assisted reproduction technologies. A scenario with removal of this utility decrement increased the company's base case ICER by [redacted]. d) Disutility from iron chelation therapy treatment in period to iron normalisation for patients who have become transfusion-independent As discussed (see Issue 5 – Iron overload treatment, iron normalisation and residual risk of developing iron-overload complications), it may take some time for iron levels to normalise in people who become transfusion-independent after Zynteglo treatment. The Zynteglo trials showed that some people received iron chelation therapy after receiving Zynteglo. **The company** did not include a decrement in their modelling to capture the disutility from iron chelation therapy, experienced by those patients who have become transfusion-independent but whose iron levels have not yet normalised. **The technical team** noted that the CS mentioned disadvantages of subcutaneous chelators. **The ERG** wanted to add a utility decrement associated with iron chelation to the company's economic model for people who have become transfusion-independent but receive chelation therapy in the period to iron normalisation. The ERG's scenario including a utility decrement relative to the patient's baseline utility before Zynteglo treatment (equivalent to that captured in the company's vignette study), for patients who received subcutaneous iron chelators during the iron normalisation period post-Zynteglo, resulted in a small increase to the company's base case ICER ([redacted]).
Why this issue is important	Under or overestimating HRQoL will affect the ICER. Using the ERG's preferred adjusted chart review data for the utility decrement for the transfusion-dependent state increased the company's base case ICER by [redacted], and using the ERG's preferred whole-population dataset for age-related disutility increased the company's base case ICER by [redacted]. The cumulative impact of these changes increases the ICER by [redacted]. If the disutility associated with infertility from myeloablative conditioning is removed, this increases the company's base case ICER by [redacted], while including a utility decrement for transfusion-dependent patients still receiving subcutaneous chelation prior to iron normalisation increases the ICER by [redacted].

Technical team preliminary judgement and rationale	With the lifetime time horizon and resulting implausible utility values in the company's analysis compared to people of the same age in the general population without TDT, the whole-population dataset from Ara and Brazier should be used for age-adjusting utilities in the model, particularly as this approach has been used in other NICE appraisals. The technical team are then inclined to use the ERG's preferred approach for calculating the utility decrement for the transfusion-dependent state, to avoid double-counting the natural decline in HRQoL due to ageing along the model's time horizon. While the infertility impact incorporated by the company may not have been used outside of models for assisted reproductive technologies for people actively seeking fertility treatment, the committee may wish to consider this impact, as patients who receive myeloablative conditioning prior to Zynteglo when they are very young may face a disutility associated with any resulting infertility, and a patient may value this disutility differently over time. However, care may need to be taken to avoid double-counting if infertility HRQoL decrements are already taken into account elsewhere in the NHS (such as in cost-utility models for assisted reproduction). As the clinical trials for Zynteglo show that some patients who became transfusion-independent after Zynteglo treatment received subcutaneous chelation therapy during the iron normalisation period, the technical team believes that the HRQoL impact of this chelation therapy should be taken into account in the model, not just the cost of the chelation therapy.

Issue 3 – Baseline characteristics of modelled population

Questions for engagement	8. Is 20% a plausible proportion of people in the UK with TDT who have hypogonadism? Should hypogonadism be reflected in the baseline population entering the model? 9. Should the mean patient weight from the chart review be used in the model, or the ERG's age category-specific body weight approach instead? 10. Is it anticipated that any patients aged 35 years or over would be treated with Zynteglo in the NHS? Is the efficacy evidence for Zynteglo generalisable to the anticipated UK population? As the efficacy evidence from the Zynteglo trials is limited to a specific age range, should the evidence coming from the UK chart review also be limited to match this age range?
Background/description of issue	Endocrine abnormalities are considered the most common complications in people with TDT. After a certain concentration of iron accumulates in the pituitary, secretion of hormones is reduced. When severe enough, this

	causes a condition called hypogonadotropic hypogonadism – the most common endocrine problem in people with TDT, with a prevalence rate of over 50% in several large studies (see CS section B.1.3.2). Patient weight is used as an input in the model in order to calculate the costs of chelating agents which involve weight-based dosing. The marketing authorisation includes patients 12 years and older, but the company's UK chart review included patients younger than this, while the TI-evaluable population in the clinical studies only included patients aged ≥12 years and <35 years. **The company** clarified that people with TDT would still be eligible for Zynteglo if they have hypogonadotrophic hypogonadism or diabetes. The company used a mean patient weight of [redacted] in its model, based on the average weight of patients in the chart review. It explained that it used this source as it's also the source of data on resource use and the distribution of iron-loading for chelation agents. The company acknowledged that this is higher than the weight of patients in the clinical trials ([redacted]), which may be due to age and ethnicity differences. The company believe the mean weight in the chart review may be an underestimate, as missing data was mainly in adults. **The ERG** were concerned that the model did not account for the presence of endocrine disorders at baseline. As 20% of the chart review population had hypogonadism, the ERG applied this as a baseline value in the model as a scenario analysis. It also considered that the mean weight from the chart review is likely higher than in a lot of the eligible population at baseline, as many of them are less than 18 years old. At the clarification stage of the appraisal process, the company was asked to add functionality to the model to link patient weight to their age at baseline. Patients aged 12 to 17 years had a mean body weight of [redacted] in this scenario, while those aged 18 or over had a mean weight of [redacted]. When paediatric patients in the model reached 18 years old, their weight-based drug costs were then based on the mean adult patient weight going forward. **The company** stated that only patients up to the age of 34 are included in the efficacy population (patients evaluable for TI from clinical studies HGB-204, 205 and 207 [n=24]), and said that this population was chosen for the base case to reflect a cohort of patients wishing to receive a gene therapy. However, they did not provide clear justification to explain why people over this age would not want to receive a gene therapy. The marketing authorisation does not have an upper age limit for the patient population, while TI-evaluable participants in clinical trials for Zynteglo have an age range of ≥12 years and <35 years. **The ERG** noted several model inputs came from the company's UK chart review, which included patients aged up to [redacted], but the trial populations from which Zynteglo data were derived was limited to patients aged ≥12

<table>
<tr><td></td><td>years and <35 years. In the chart review, [redacted] of the population were over the age of 30 (max. age [redacted]), but only 8.3% of the trial population were aged over 30 (all of whom were aged <35).
Table B: Age distribution of patients in included trials versus chart review
<table><tr><th>Patient Age Distribution (Years)</th><th>Company base-case (clinical studies HGB-204, 205, 207) (n=[redacted])</th><th>Chart review population (n = 165)</th></tr><tr><td><12</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>12<18</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>18<30</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>30<40</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>40<50</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>50<60</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>≥60</td><td>[redacted]</td><td>[redacted]</td></tr></table></td></tr>
<tr><td>Why this issue is important</td><td>Having hypogonadism as a result of TDT has a HRQoL impact, and also leads to additional costs of treatment. The impact on the company's base case ICER is relatively small (+[redacted]), as the assumption applies to people on the transfusion and chelation therapy arm, as well as the Zynteglo arm.
Using different weights for paediatric and adult patients has a larger impact on the company's ICER (+[redacted]). This is important as patients aged 12 to 17 years represented [redacted] of the population in studies HGB-204, 205 and 207, and [redacted] of the population in NHS Hospital Episode Statistics (HES) data.</td></tr>
<tr><td>Technical team preliminary judgement and rationale</td><td>As hypgonadism is common in people with TDT, it is appropriate to reflect this in the baseline population entering the model, as iron build up and resulting complications may have occurred before Zynteglo could be given (minimum age for the indication in the marketing authorisation is 12 years).
Although there will be a sudden weight increase for people in the model when they reach 18 years old using the ERG's method, it is appropriate to apply age category-specific body weight instead of using the same weight for all patients. This is to better reflect the resource use in both arms of the model, particularly in light of the long time horizon, and that patients will usually spend the majority of their time in the model as an adult rather than paediatric patient.
It is unclear whether the clinical study data is generalisable to the potential UK population, and whether the data used from the UK chart review should be limited to match the age restrictions in the marketing authorisation.</td></tr>
</table>

	The committee may wish to consider whether the company's inclusion of an upper age of 34 years for Zynteglo treatment in their base case constitutes an equalities issue.

Issue 4 – Underrepresentation of population with severe non-β^0/β^0 genotypes

Questions for engagement	11. What proportion of the UK TDT population have a non-β^0/β^0 genotype? 12. What proportion of people with TDT who might be eligible for Zynteglo have a severe non-β^0/β^0 mutation? 13. Should the proportion of the modelled patient population with a severe non-β^0/β^0 mutation be increased from the company's base case value?
Background/description of issue	Severe non-β^0/β^0 mutations including IVS-I-5 and IVS-I-110 are included in the marketing authorisation for Zynteglo. These are associated with dramatically reduced β-globin production, behaving like a β^0 genotype despite being grouped with other non-β^0/β^0 genotypes. **The company** used data from its clinical trials for the proportion of patients with severe non-β^0/β^0 mutations in the baseline modelled population, [redacted] ([redacted]). **The ERG** were concerned that this value was too low. In beta-thalassemia carriers in the UK, IVS-I-5 and IVS-I-110 were the most common and fourth most common mutation, respectively (22.5% and 5.5% of carriers), and the ERG found evidence indicating that severe non-β^0/β^0 genotypes represent up to 28% of patients in the UK. Of the Zynteglo trial cohort 'transplant population', [redacted] ([redacted]) had severe non-β^0/β^0 genotypes. The ERG noted that the conditional licence requires the company to 'submit interim and final data from patients with a severe non-β^0/β^0 genotype such as IVS-I-110 included in Study HGB-212' but the company did not include this data in its submission, as it was thought to be too immature.
Why this issue is important	The ERG's exploratory analysis, where the proportion of the modelled population is increased to 28% instead of the company's [redacted], showed the resulting probability of transplant success decreased from 83.3% to [redacted], while the company's base case ICER increased by [redacted].
Technical team preliminary judgement and rationale	The base case population in the model should reflect the people in the NHS who may be eligible for Zynteglo, but it is uncertain what proportion of the population in the indication have a severe non-β^0/β^0 mutation such as IVS-I-5 and IVS-I-110.

Issue 5 – Iron overload treatment, iron normalisation and residual risk of developing iron-overload complications

Questions for engagement	14. Is combination chelation therapy used more in current clinical practice than previously? If so, will this trend continue? Should the analysis take this into account? What proportion of patients receive at least two oral chelation therapies in practice? 15. Is an iron normalisation period of 4, 5, 7 or 10 years plausible for patients who become transfusion-independent after Zynteglo treatment? Does this normalisation period apply to all patients who become transfusion-independent? 16. Are iron-overload complications still a risk after transfusion independence is reached, due to iron overload damage which occurred prior to Zynteglo treatment? 17. Will people who come off chelation therapy after transfusion independence or transfusion reduction is reached still have cardiac iron? How is this raised cardiac iron likely to impact their health over time?
Background/description of issue	Iron chelation therapy is required for a time in people who have received Zynteglo treatment for TDT, and become transfusion-independent/reduced. This is due to iron build-up in the body prior to Zynteglo, as well as from transfusions received after Zynteglo. a) Distribution of chelation types for iron overload treatment **The company** based the distribution of chelating therapies used in the model on the whole chart review population, where [redacted] of patients received a combination of oral and subcutaneous therapy. [redacted] of patients received two oral chelation therapies in combination. As the model only accounts for the cost of the higher cost therapy for patients on two oral chelation therapies, the company acknowledged that the model underestimates the cost of chelation. **The ERG** received advice from its clinical expert that chelation practices have changed over time, and that regimens used in patients treated currently may not match historic practices. As a result, the company were asked to provide the distribution of iron chelation agents in patients aged 12 to 35, to better reflect the current standard of care in people who would be eligible to receive Zynteglo. Re-analysis of the chart review data showed there was a greater proportion of patients in this age category who received combination therapy compared to the whole chart review population ([redacted] on an oral and subcutaneous combination, and [redacted] on a combination of two oral therapies, see Table 9 in ERG report). A scenario reflecting this had higher accrued cost of chelation treatments, leading to a reduction in the company's base case ICER of [redacted].

	b) Iron normalisation period **The company** assumed that iron levels were normalised after 4 years in all patients who became transfusion-independent, with reduced iron levels in transfusion-reduced patients assumed to be achieved in the model 1 year after Zynteglo treatment. Due to limited data availability, the assumption for transfusion-independent patients was based on published data from two sources on iron levels in patients that received allogeneic-HSCT. In particular, the company supported the 4-year normalisation assumption using a retrospective study which followed a small number of paediatric patients for 4 years, and found a 47% reduction in median ferritin levels after 4 years. **The ERG** considered that the 4-year time to normalisation assumption might be too optimistic, and that the studies the company found did not support this assumption of iron normalisation in all patients (neither source gave a timepoint by when all patients had normalised iron levels). The ERG explained that the data from the Zynteglo trials so far did not support the assumption, as the levels of some transfusion-independent patients were elevated even after 48 months of follow up, and many patients remained on iron removal treatments at the latest follow up. The ERG performed some exploratory scenarios to see what the effect would be if the iron normalisation period was 5, 7 or 10 years instead of 4 years. The ICER increases the longer the time to normalisation is, as patients incur additional chelation costs and are at higher risk of some complications associated with high iron levels. Iron normalisation periods of 5, 7 or 10 years result in an increase to the company's base case ICER of [redacted], [redacted], and [redacted], respectively. c) Complications due to iron overload in transfusion-independent patients **The company** assumed that patients who have normalised iron levels are no longer at risk of developing complications from iron overload. **The ERG**'s clinical adviser suggested that there may be some pre-existing irreversible damage caused by iron overload in many patients who would be eligible for Zynteglo treatment (not high enough to rule out treatment), so these patients could potentially develop complications from pre-existing iron overload damage in the long-term. The ERG explored the potential impact of this, by applying the rates of developing cardiac complications associated with low iron overload, to patients with normalised iron levels after Zynteglo. This was the most conservative scenario around this (complications in other organs not included, for example), but still lead to an ICER increase of [redacted]. d) Cardiac iron levels in the long term after Zynteglo treatment **The ERG** explained that cardiac iron overload is the major cause of death in beta-thalassaemia.

	A **clinical expert** involved in the appraisal confirmed that iron-related clinical complications are the major cause of reduced life expectancy in this group of patients and reduction to safe levels is extremely important. The expert highlighted that in the HGB-204 study there was a 56% reduction in liver iron from baseline to month 48, but that cardiac iron remained stable over this period, and patients were restarted on iron chelation to reduce iron levels. **The company** stated that from the latest long-term follow-up data, out of the 11 non-β0/β0 patients that have achieved TI from Studies HGB-204 and HGB-205, all continue to have normal cardiac T2* values through their last follow-up, with [redacted] patients demonstrating a cardiac T2* value at last follow-up that was [redacted] than their pre-treatment baseline. **The technical team** considered that is not clear whether patients who eventually stop all iron chelation therapy after Zynteglo will have cardiac iron levels that are considered safe, or what the impact of these raised cardiac iron levels will have on the patients and on the cost-effectiveness of Zynteglo.
Why this issue is important	While data is limited due to short follow-up in the trials so far, it is important that any assumptions made around chelation and iron normalisation in the model are informed by current clinical practice and experience, and the trial data that is available at the time of the appraisal. It is important to understand the potential impact of cardiac iron levels remaining raised after Zynteglo treatment, and whether (and at what time) patients reach a cardiac iron level that is considered safe.
Technical team preliminary judgement and rationale	The analysis should be adjusted to match the change in practice for chelation therapies over time, to better reflect the patient population who might be eligible for Zynteglo. The company's assumption of a 4-year normalisation period for all transfusion-independent patients is not appropriate. This is because [redacted] of the trial population had high iron levels at baseline, while at 48 months, [redacted] of transfusion-independent patients in the trial population still had a high iron level. 7 years seems a plausible iron normalisation period, as 5 years may not be a long enough period to achieve iron normalisation in all transfusion-independent patients based on the trial evidence so far. If it is possible for some patients who had some irreversible iron overload damage to receive Zynteglo, then the ERG's exploratory analysis is appropriate, particularly as it is conservative in its assumptions and the true ICER impact is likely even greater.

Issue 6 – Unknown long-term outcomes – relapse (late graft failure), initial (primary) engraftment failure and mortality

Questions for engagement	18. Is there any evidence to support the idea that the therapeutic effect of Zynteglo may not be lifelong? Should the analysis incorporate a percentage of patients relapsing after initially successful treatment with Zynteglo, and if so, is one of the ERG's scenarios appropriate? 19. Should primary engraftment failure be taken into account in the model? If so, what percentage of patients receiving Zynteglo but experiencing this engraftment failure would be plausible? What is a plausible mortality rate associated with this engraftment failure? 20. Is there any up to date data on the mortality of transfusion-dependent patients, particularly UK-specific? What is a plausible mortality rate for people in this health state?
Background/description of issue	Zynteglo is a gene therapy, and its method of action, inserting a functioning copy of a gene into the bone marrow, could theoretically lead to a lifelong effect if transfusion independence or transfusion reduction is reached. However, there is limited trial follow up in a small number of patients so far (24 TI evaluable patients, maximum follow up presented in the CS is 61.3 months), and the long-term follow up study is planned to give a total maximum follow up of 15 years. This will not represent lifetime follow up for the majority of patients, so the persistence of treatment effect (being transfusion-independent or needed fewer transfusions) over a patient's lifetime is unknown. Only a small number of people with TDT with a non-β^0/β^0 genotype have received Zynteglo so far, in non-UK centres, in clinical trials with inclusion/exclusion criteria that may differ from possible marketing authorisation conditions. Because of this, it is not known if a percentage of patients would experience engraftment failure (initial or late) in UK clinical practice. **The company** assumed that the engraftment procedure was successful in all patients in the model, because there were no engraftment failures in the Zynteglo trials. Its analysis also assumed there would be no graft loss leading to a return to transfusions for transfusion-independent patients, or an eventual increase in transfusions/return to TDT for transfusion-reduced patients after Zynteglo treatment. Due to lack of available data, the company applied standardised mortality ratios (SMRs) to transfusion-dependent patients in the model which were identified in the literature (one for those with cardiac complications and one for those without). For patients without cardiac complications, this SMR was 3.9, from a model of chelation agents in TDT, which used data from a US study following patients between 1965 and 1994. The SMR was then estimated from the mortality of these patients relative to 1998 general US mortality. As there was no SMR for those patients with reduced transfusions, the company assumed an SMR of 2.6 (midpoint between

	SMRs for transfusion-dependent and transfusion-independent using this source). The company modelled cardiac-related mortality separately, due to cardiac dysfunction being considered the most life-limiting complication in TDT. Regardless of transfusion status, all patients acquiring cardiac disease were modelled to have a 13% annual mortality rate (based on a rate applied in two cost-effectiveness models identified by the company). **The ERG** acknowledged that no events for loss of transfusion independence have been recorded so far, but there is currently insufficient trial follow-up and patient numbers to determine whether long-term permanent engraftment occurs in some patients. The ERG's clinical adviser indicated that the assumption of permanent engraftment for all patients treated with Zynteglo could be too optimistic. The ERG considered that the need to collect back-up cells for rescue treatment indicates that a risk of engraftment failure exists. Two exploratory scenarios of late graft failure were carried out by the ERG, to highlight the possible impact on cost-effectiveness if the company's assumption of no engraftment failure is not met. If every 10 years, 5% of transfusion-independent and transfusion-reduced patients 'relapse' and become dependent upon transfusions and iron chelation, the company's ICER for Zynteglo increases by [redacted] (or an increase of 26.9%). For the scenario where 10% of these patients relapse at 10 years instead, the company's base case ICER instead rises by [redacted] (62.1% increase). The ERG also carried out some exploratory analysis to find the effect of 1% and 5% of patients not having successful engraftment (so requiring rescue therapy, which the company assumed has a 54% mortality risk), which increased the ICER by [redacted] and [redacted] respectively. The ERG considered the source the company used for SMR rates for people who are transfusion-dependent without cardiac complications to be outdated, of limited generalisability (as it was based only on a sample of patients receiving subcutaneous chelation), and not relevant to current NHS practice due to improved iron chelation and patient monitoring (leading to more favourable mortality rates in people with TDT). The ERG used a lower SMR of 2.0 for transfusion-dependent patients in the model (mortality due to cardiac complications still separately accounted for, so this analysis is modelling survival of TDT patients who haven't developed cardiac problems). The resulting small decrease in the ICER comes from higher standard of care costs because more of these patients remain alive (outweighing increase in QALYs from mortality reduction).
Why this issue is important	The short duration of currently available follow up data, and small number of patients who have received Zynteglo in any of the trials, means the persistence of treatment effect (i.e. non-relapse) and the likelihood of engraftment failure in clinical practice is unknown. If any patients see an increase in transfusions needed after

	initial reductions following Zynteglo treatment, or any patients experience an engraftment failure, this could have a large impact on the ICER.
Technical team preliminary judgement and rationale	While the ERG's analyses of these scenarios are necessarily exploratory, it highlights the possible cost implications to the NHS if Zynteglo treatment does not have the same outcomes in practice as in the clinical trials. The analysis on relapse in particular shows a potentially large impact on the ICER if the number of Zynteglo-treated patients who experience a 'relapse' in terms of transfusions is non-zero, even if this occurs many years after they received the treatment. If relapse occurred at an earlier point in time than 10 years post-Zynteglo treatment, then the impact on the ICER would be greater, due to patients having to receive transfusions and chelation for a longer period of time. The data the company used to model mortality for transfusion-dependent patients who don't develop cardiac complications is more than 20 years old, so the SMR to be applied should be lower than the 3.9 in the company's base case.

Issue 7 – Generic drug acquisition costs

<table>
<tr><td>Questions for engagement</td><td>21. Should prices for 3 of the generic products in the treatment process (busulfan, ursodeoxycholic acid and desferrioxamine, see Table C) come from eMIT or BNF?</td></tr>
<tr><td>Background/description of issue</td><td>The company used drug acquisition costs from the British National Formulary (BNF) for therapies in the treatment process in its model.
The ERG thought prices from the drugs and pharmaceutical electronic market information tool (eMIT) were more representative of the prices the NHS actually pays for 3 of these therapies (see Table C), as they are generic products nationally available to the NHS at discounted prices.
Table C: Comparison of BNF and eMIT prices
<table>
<tr><td>Drug</td><td>Source in CS</td><td>BNF</td><td>eMIT</td></tr>
<tr><td>Busulfan</td><td>Assuming recommended daily dose 0.8mg/kg for 4 days (SmPC). Busulfan 60mg/10ml concentrate for solution for infusion vials (Accord Healthcare Ltd). Pack of 8 vials.</td><td>£1529.50</td><td>£386.14</td></tr>
<tr><td>Ursodeoxycholic acid</td><td>Assuming recommended dose of 10 mg/kg/day for 21 days (SmPC). Unit cost of Ursofalk (Dr. Falk Pharma UK Ltd) 150mg tablets (60 tablets per package)</td><td>£19.02</td><td>£8.46</td></tr>
<tr><td>Desferrioxamine</td><td>Assuming 6 times per week, dose 40 mg/kg. Cost per 500 mg vial.</td><td>£46.63</td><td>£34.06</td></tr>
</table>
The technical team noted that section 5.5.2 methods guide indicates that where there are nationally available price reductions, then the reduced price should be used in the analysis to best reflect the price relevant to the NHS.</td></tr>
<tr><td>Why this issue is important</td><td>This affects the modelling of drug acquisition costs for both arms in the model, such as for ongoing iron chelation therapy involving desferrioxamine, which may be needed for many years. The company reported that acquisition cost of chelation therapy was one of the parameters with the greatest impact on the ICER.
When eMIT prices are used for busulfan, ursodeoxycholic acid and desferrioxamine instead of BNF prices, the company’s base case ICER increases by [redacted]. When eMIT prices are used alongside a 3.5% discount rate for</td></tr>
</table>

	costs and benefits, the company's base case ICER increases to [redacted], which is [redacted] higher than if only the discount rate was changed.
Technical team preliminary judgement and rationale	The cost-effectiveness analysis should use prices that are as representative as possible to those the NHS actually pays, in line with the methods guide, so the eMIT prices should be used as model inputs for busulfan, ursodeoxycholic acid and desferrioxamine, instead of the BNF prices.

Issue 8 – Genotyping, other testing the company will pay for, and impact on the NHS

Questions for engagement	22. Where in the treatment pathway would current and future patients undergo genotype testing? How much does genotype testing for beta-thalassemia cost? What resources does this use (including staff time)? 23. What additional infrastructure and training requirements could be considered for this appraisal? 24. How much would the additional testing that the company has stated they will incur, cost, and how much NHS staff involvement would this require?
Background/description of issue	**The technical team** was aware that routine genotype testing has not been part of usual NHS practice in this area for all centres, and testing is needed to identify people with TDT who might be eligible for Zynteglo treatment. **The ERG** noted that the company stated that costs of genotype testing are incurred by the company. A **commissioning expert** in the area explained that 'the testing required to diagnose the specific genotype of a patient's thalassemia is part of the pathway of care for all patients, which is being reinforced through the designation of specialist centres following the national service review for haemoglobinopathy services. This is coming into place across the country and is already routinely undertaken as part of the initial diagnosis process in many specialist clinics, so there will not be additional genetic testing required for the incident population. However, there will be a requirement for genetic testing of the prevalent population who have not previously been tested to enable access to this technology.' The methods guide (section 5.9.1) states that 'the use of a technology may be conditional on the presence or absence of a particular biomarker (for example a gene or a protein). If a diagnostic test to establish the presence or absence of this biomarker is carried out solely to support the treatment decision for the specific technology, the associated costs of the diagnostic test should be incorporated into the assessments of clinical and cost effectiveness. A sensitivity analysis should be provided without the cost of the diagnostic test. When

	appropriate, the diagnostic accuracy of the test for the particular biomarker of treatment efficacy should be examined and, when appropriate, incorporated in the economic evaluation.' **The company**'s submission indicated that, along with thalassaemia genotyping, it will also incur the costs of the following: Tests pre-transplant: blood for replication competent lentivirus (RCL)11, vector copy number (VCN), globin high-performance liquid chromatography (HPLC), and globin in autologous cells. Post-transplant monitoring (collected at any time post-transplant if clinically indicated): blood for β-globin analysis including βA-T87Q-globin, blood for VCN, integration site analysis (ISA) and replication competent lentivirus (RCL) determination. However, the impact of this in terms of costs and staff resources was not modelled, and no information on prices or resource use for these was given in the CS.
Why this issue is important	It is important to capture the impact of using Zynteglo in clinical practice. Any likely constraints on the resources required to support the implementation of the appraised technology should be highlighted, and comment should be made on the impact this may have on the implementation timescale.
Technical team preliminary judgement and rationale	Genotyping and other tests the company has said they will incur should be fully costed. Scenarios should be run to show the effect on overall costs, incremental costs and the ICER of: • Genotyping costs being incurred by the NHS instead of the company (genotyping of all prevalent patients who are considered for Zynteglo treatment who have not already undergone genotype testing) • Other blood testing currently stated as being incurred by the company in the CS, being incurred by the NHS instead Any changes made should also be reflected in the budget impact submission.

Issue 9 – Myeloablative conditioning

Questions for engagement	25. What drugs do patients receive as part of myeloablative conditioning ahead of Zynteglo? Would a particular regimen be used in most centres in the UK? What constitutes current UK clinical practice in terms of drugs given for myeloablative conditioning ahead of allogeneic haematopoietic stem cell transplant?

	26. What is the impact on the cost-effectiveness results of taking into account other drugs given as part of a myeloablative conditioning regimen (not just busulfan)? 27. What is the mortality associated with myeloablative conditioning in the UK?
Background/description of issue	**The company** noted in its submission that transplant protocols and conditioning regimens vary among centres but involve conditioning, usually with a regimen based on busulfan and cyclophosphamide, with fludarabine being used increasingly in Europe. However, the company's submission has costed for myeloablative conditioning only using busulfan. The company state that the Zynteglo treatment process utilises 'a myeloablative conditioning approach commonly employed in clinical practice in the UK'. **The technical team** noted that the marketing authorisation for busulfan indicates that it is given as part of a combination, with cyclophosphamide, melphalan or fludarabine. The marketing authorisation for Zynteglo states that full myeloablative conditioning must be administered before infusion of Zynteglo.
Why this issue is important	It is important to have a clear understanding of the myeloablative conditioning regimen that would be used if Zynteglo was approved for use in the NHS. The current cost-effectiveness estimates may underestimate the true costs of myeloablative conditioning, thus impacting the ICER.
Technical team preliminary judgement and rationale	The cost of other drugs given alongside busulfan in line with its marketing authorisation should be incorporated in the cost-effectiveness model (taking into account drug acquisition cost, as well as any additional administration cost, cost of any additional visits if the drugs in the combination aren't given on the same schedule, as well as costs of any additional tests/monitoring required, and treatment of associated adverse events). Any changes made should also be reflected in the budget impact submission. The mortality rate associated with myeloablative conditioning is unlikely to be 0%, and should be reflected in the Zynteglo arm of the model.

Issue 10 – Number of patient profiles modelled

Questions for engagement	28. How many profiles should be simulated in the model, in order to reach a stable ICER and overcome random noise and first order uncertainty?
Background/description of issue	The economic model runs a number of 'profiles', which are hypothetical patients defined by age and gender, with each profile weighted to reflect the distribution of patients in the eligible treatment population. **The company's** model, a discrete event simulation, estimated results generated by 600 samples of profiles based on gender and 3 age bands (child, young adult, adult).

The ERG explained that stochastic models like discrete event simulation often need a large number of iterations in order to give stable results, as some variation will occur due to 'random noise' or first order uncertainty. To investigate this, the ERG re-ran the model with different numbers of profiles (100 to 50,000), and found that there was a lot of variation in the resulting ICER, especially when only a small number of patient profiles were generated, with the result seeming to stabilise when a larger number of profiles were generated.

The technical team observed that the ICER appeared to stabilise around 5,000 profiles (see Table D). The technical team also noted that the combination of using a larger number of profiles (5,000) as well as a SMR of 2.0 for transfusion-dependent patients increased the ERG's base case ICER by more than [redacted] (approximately a [redacted] increase).

Table D. Results of the company base case analysis based on different numbers of patient profiles

Number of profiles in the model	ICER	Difference from company model
100	[redacted]	[redacted]
500	[redacted]	[redacted]
600 (company base case)	[redacted]	-
1,000	[redacted]	[redacted]
5,000	[redacted]	[redacted]
10,000	[redacted]	[redacted]
20,000	[redacted]	[redacted]
50,000	[redacted]	[redacted]

To explore what drove the differences in the results, **the ERG** compared the outcomes of the company base case model (600 patient profiles) with the outcomes of the model with 5,000 profiles. When the number of profiles used in the model was increased to 5,000, the number of QALYs decreased in both arms. As well as this, the comparator arm costs decreased while the Zynteglo arm costs increased, with the cost difference mostly due to iron chelation (the life years difference was small, but may have contributed to the difference in chelation costs). The ERG remained unclear on why the model estimated a higher ICER with a greater number of profiles, and which was the most appropriate method to generate results.

Why this issue is important

Even though the potential UK patient population may be fairly small, it may be more appropriate to generate many more hypothetical patient profiles than this, in order to 'smooth out' variation in the ICER arising from random noise.

Technical team preliminary judgement and rationale	The committee may wish to consider scenarios with >600 simulated patients, as this could help stabilise the ICER, which may be important given the level of uncertainty for this topic.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	ICER	Change from base case
Updated company base case (company agreed to ERG's corrections of model errors)	–	[redacted]	–
1. 3.5% discount rate	Criteria for 1.5% discount rate not met, reference case rate used instead	[redacted]	+[redacted]
2. Whole-population set from Ara and Brazier for age-adjusting utilities	Avoid implicit assumption that all modelled patients with beta-thalassaemia will never develop any other unrelated health condition	[redacted]	+[redacted]
3. ERG's preferred approach for calculating the utility decrement for the transfusion-dependent state	Avoid double counting utility decrements due to natural HRQoL decreases across the lifetime time horizon	[redacted]	+[redacted]
4. HRQoL impact of subcutaneous chelation therapy for transfusion-independent patients in iron normalisation period should be taken into account in the model	HRQoL impact of required chelation treatment for this group of patients should be modelled, not just costs	[redacted]	+[redacted]
5. 20% hypogonadism in baseline population	Modelling should better reflect complications of TDT already present in patient population prior to Zynteglo therapy	[redacted]	+[redacted]
6. Age category-specific (paediatric and adult) mean weights used in model	People receiving Zynteglo will most likely spend most of their time in the model as adults, so it is appropriate to use	[redacted]	+[redacted]

	age category-specific weights for more accurate weight-based dosing in the model		
7. Chelation therapy distribution adjusted to match change in clinical practice	Combination therapies used more in people aged 12 to 35 years, and model doesn't have functionality to incorporate cost of two oral chelation therapies in combination.	[redacted]	-[redacted]
8. 7-year iron normalisation period for people who become transfusion-independent after Zynteglo	At baseline, [redacted] of the trial population had high iron levels, while at 48 months, [redacted] of transfusion-independent patients in the trial population still had a high iron level, so 5 years may not be a long enough period to achieve iron normalisation in all transfusion-independent patients.	[redacted]	+[redacted]
9. Cardiac complications from iron overload damage prior to Zynteglo modelled for people who become transfusion-independent	Some patients who may be eligible for Zynteglo would probably have a degree of irreversible iron overload damage which would not be undone with iron normalisation	[redacted]	+[redacted]
10. SMR of 2.0 applied for patients in the model who are transfusion-dependent and don't develop cardiac complications	Source in company's base case is outdated and iron chelation and patient monitoring have improved since then	[redacted]	-[redacted]
11. eMIT-sourced prices used for busulfan, ursodeoxycholic acid and desferrioxamine	Price inputs in the model should reflect those actually paid by the NHS	[redacted]	+[redacted]
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	[redacted]	+[redacted]

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Small patient numbers and immature evidence base	The trial results are still immature, and the number of patients treated is small, so uncertainty exists regarding the longevity of the Zynteglo	Cost-effectiveness estimates are likely to be optimistic.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	treatment effect, and the possibility of adverse events in the medium-to-long term.	
Immature evidence base in patients with more severe genotypes	The Zynteglo manufacturing processes have evolved during the trial programme with the aim of maximising transduction conditions to improve levels of vector copy number and subsequent HbAT87Q expression. It is possible that [redacted] may increase the probability of achieving TI in people with severe non-β^0/β^0 genotypes (compared to the previous processes used in the trial programme) but only results from the study HGB-212 and further data from HGB-207 can resolve this uncertainty. The primary outcome of HGB-212 is transfusion reduction (in HGB-207 it was transfusion independence) suggesting lower expectations of a TI response in people with more severe genotypes.	Cost-effectiveness estimates are likely to be optimistic.
Heterogeneity of effect	The level/extent of heterogeneity of effect (i.e. in achieving TI) remains an area of uncertainty. Heterogeneity based on genotype and the evolving manufacturing process is not addressed in the evidence.	Unknown.
Representativeness of the trial population, lack of evidence in key subgroup	The Zynteglo trial results have uncertain applicability to the population likely to receive Zynteglo in the NHS as the trial population might under-represent certain genotypes which are prevalent in the UK. Of patients recruited for HGB-204, HGB-205 and HGB-207, 60% were Asian, 34% were white and 6% were classed as 'other' race. The ethnicity distribution of the Zynteglo trial population does not appear to well represent the UK TDT population. In the UK, around 10-15% of people with thalassaemia are white, while 34% of the trial participants were white. This may mean that the proportion of the trial population with a severe non-β^0/β^0 IVS-I-5 genotype is not representative of the UK setting, since IVS-I-5 mutations are quite common in people of Indian or Pakistani descent who have thalassaemia.	ERG scenario analysis indicates that increasing the baseline proportion of the population with a severe non-β^0/β^0 mutation also increases the ICER and reduces the probability of transplant success. Cost-effectiveness estimates are likely to be optimistic.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Mortality rate for transfusion-dependent patients	The mortality rate for transfusion-dependent patients was an influential parameter in the analysis. The standardised mortality ratio (SMR) of 3.9 derived from the literature which the company applied to transfusion-dependent patients may not be appropriate. The source that it was derived from is likely to be obsolete in terms of its relevance to current NHS practice, due to improvements in iron chelation and patient monitoring which have led to more favourable mortality rates in TDT patients (the source used data over 20 years old). The most pessimistic estimate from the literature was chosen by the company.	The ERG tested the effect of using a lower SMR rate (2.0). This change in isolation lead to a small decrease in the ICER for Zynteglo, driven by the increased cost of standard of care (more of these patients remaining alive and requiring treatment), outweighing the increase in QALYs coming from the reduction in mortality. However, this lower SMR is an assumption due to lack of a contemporary data source, so the true SMR and impact on the ICER is unknown.
Data limitations for comparison to other therapies	As the Zynteglo trials were all single-arm studies, they did not compare to other therapies. Data on comparator therapies was identified by the company in the literature. The ERG considered the company's systematic reviews frequently limited in search dates, meaning studies weren't found. The company didn't report the details of its targeted reviews to fill in the data gaps. This means there may be uncertainty in the values used for clinical inputs for the comparator arm in the model.	Unknown.

Table 3: Other issues for information

Issue	Comments
Interpretation of the population	Both the NICE scope and the Zynteglo marketing authorisation refer to a ≥ 12 years β-thalassaemia population for which hematopoietic stem cell transplantation (HSCT) is appropriate, but a matched related donor is not available. The ERG considers that the reference to HSCT being 'appropriate' should primarily be interpreted as relating to fitness to receive conditioning chemotherapy prior to an autologous cell therapy (such as Zynteglo) – rather than allogeneic HSCT, because for the overwhelming majority of NHS patients ≥ 12 years allogeneic HSCT will not be considered appropriate. Allogeneic HSCT is not recommended for adults in the UK (and the company confirm this in its submission), and it is very rarely considered in patients aged ≥12 years, as the risks outweigh the benefits. In light of this, the ERG has some concerns about the interpretation of the restriction of "a matched related donor is not available" in the ≥12 years β-thalassaemia population, as it could leave some people without a viable transplant option if they are ≥12 years old but have a matched related donor.
Implementation of company model	Before the clarification stage of the appraisal process, the ERG found an error in the company's model (problem in the application of age-adjusted utilities - utilities of patients were not being updated beyond their baseline level), which the company corrected in an updated version of the model. Correction of these errors increased the ICER by [redacted]. The ERG then found further issues in the updated model (in the deterministic and probabilistic sensitivity analysis sections) and corrected these ahead of running additional analyses.
Innovation	The company considers the drug to be innovative. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	A potential equalities issue was raised at scoping and by a clinical expert during the appraisal. Thalassaemia is more prevalent in people of Mediterranean, Middle Eastern, South Asian and Southeast Asian descent. In the UK, transfusion-dependent beta-thalassaemia is mostly seen in ethnic minority populations, the largest groups being Pakistani, Indian and Bangladeshi. However, issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. The company did not identify any issues relating to equalities. The committee may wish to consider whether the company's inclusion of an upper age of 34 years for Zynteglo treatment in their base case constitutes an equalities issue.

Authors

Gary McVeigh

Appraisal committee chair

Amy Crossley

Technical lead

Caron Jones

Technical adviser

Linda Landells

Associate director

With input from the lead team:

Soo Fon Lim

Lead team member

Robert Hodgson

Lead team member

Malcolm Oswald

Lead team member

NICE National Institute for Health and Care Excellence

Technical engagement response form

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm** on **Thursday 26 March 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.

- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Ross Selby MRPharmS
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**bluebird bio UK**

Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Non-reference case discount rate

Is there any evidence on projected life expectancy for people with transfusion-dependent beta-thalassaemia (TDT) treated optimally with current management strategies and therapies?	In the context of the lack of contemporary published data describing outcomes in patients treated optimally with current approaches, bluebird bio conducted a study of the Hospital Episode Statistics (HES) database across the period 2007-2016. This demonstrated that despite advances in chelation treatment and iron monitoring, patients with TDT remain at increased risk of early death. The analysis found that over the ten-year period 2007–2016 in England, the in-hospital death rate in patients who had been diagnosed with TDT between April 2005 and March 2006 was [redacted]%, which was [redacted] than the [redacted] % of the age/sex-adjusted general population (figure below; [redacted]). Some patients with TDT may also have died outside the hospital setting which would not be reported in the HES database, so this could be an underestimate. Median age at death in TDT patients in this study was [redacted] years (Jobanputra et al. draft manuscript). We are aware of only two published studies, Modell et al (2008) and Weidlich et al (2016), that describe life expectancy in UK TDT patients: • Modell et al extrapolated life expectancy based on available UK Thalassaemia Register data up to 2003. The results indicated that since 2000 over 80% of TDT patients have a life expectancy of more than 40 years, but the authors noted that it was not possible to estimate beyond this point. • A 2016 paper by also examined life expectancy for TDT patients in the UK, based on the published literature and interviews with UK clinicians. The results indicated that the expected probability of survival at 50 years of age for a TDT patient treated with transfusions and chelation is 63%. Based on current ONS UK life tables, currently 96% of the general population is expected to live to age 50.

	Figure 1. Mortality data for β-thalassaemia patients in England and the general population of England and Wales  **The above evidence demonstrates that despite advances in chelation treatment and iron monitoring, patients with TDT remain at increased risk of early death compared to the general population. By correcting the underlying cause of the condition, Zynteglo restores people who would otherwise die or have a very severely impaired life to full or near full health.** ***References*** JOBANPUTRA, M., PARAMORE, C., LAIRD, S. G., MCGAHAN, M. & TELFER, P. Draft manuscript. Co-morbidities and mortality associated with Transfusion Dependent Beta-thalassaemia Patients in England: A 10-Year Retrospective Cohort Analysis - Draft manuscript. MODELL, B., KHAN, M., DARLISON, M., WESTWOOD, M. A., INGRAM, D. & PENNELL, D. J. 2008. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance, 10, 42-42. WEIDLICH, D., KEFALAS, P. & GUEST, J. F. 2016. Healthcare costs and outcomes of managing β-thalassemia major over 50 years in the United Kingdom. 56, 1038-1045.
Should 3.5% or 1.5% be used as the discount rate for costs and quality-adjusted life years (QALYs) in this appraisal?	TDT is a rare genetic condition that requires immediate treatment within the first few years of life (Cappellini et al., 2014), meaning that affected infants require transfusions from an early age in order to survive. As iron begins to build up in the body (despite the use of chelators), co-morbidities become evident from a young age. Zynteglo is a gene therapy that utilises an 'ex-vivo' approach by adding functional copies of the β-globin gene into the patient's own cells, thereby correcting the underlying cause of the condition. In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs (NICE, 2013).

	We are able to demonstrate that Zynteglo meets the criteria for non-reference case discounting, namely: • Zynteglo restores people who would otherwise die or have a very severely impaired life to full or near full health • By the nature of the gene therapy, there is scientific rationale that provides confidence in the benefits of Zynteglo being sustained over a very long period (see B.1.3.6.) ***Zynteglo restores people who would otherwise die or have a very severely impaired life to full or near full health*** The most severe forms of β-thalassaemia, such as transfusion-dependent thalassaemia (TDT), result in life-threatening anaemia with transfusion dependency and, as a consequence, a long-term risk of lethal iron overload introduced by the transfused blood (Cappellini et al., 2014, Olivieri, 1999). All patients with TDT face a lifelong regimen of frequent blood transfusions, coupled with chelation therapy and iron monitoring to manage the iron overload (Cappellini et al., 2014). Transfusions temporarily relieve symptoms of anaemia but do not address the underlying globin chain imbalance or restore normal erythropoiesis. Real world evidence indicates that TDT patients face clinically meaningful increases in levels of fatigue in the time period between their regular transfusions (ISPOR 2019, E-diary poster). Transfusions require significant investment of time, up to one full day for the transfusion process every 2 to 4 weeks (Cappellini et al., 2014, UKTS, 2016) (section B1.3.1. main submission). As part of the NICE Technical Engagement step for this appraisal, the United Kingdom Thalassaemia Society (UKTS) submitted a patient organisation statement in which they emphasised the impact of TDT on daily life. The UKTS submitted patients' views on the frequent drug transfusions, the possible multi-organ damage, and the life-threatening impact of severe complications such as heart and liver failure due to excess iron accumulation. Patients and carers commented on the "never ending" treatment, the difficulty of administering iron chelation and its significant side effects, and also on keeping up with the treatment plan. An important point also raised was the time patients and carers must take out of their family/educational/working life to manage their condition, while feeling a sense of guilt for taking time off to meet daily treatment demands. These would include time for cross matching, transfusions, diagnostic scans and consultations (National Institute for Health and Care Excellence, 2020b). UKTS also stated that, when considering current treatments, patients and their families want more to be done to improve their quality of life. Additionally, there is a high unmet need as there is no other ‘curative’ option for those patients unsuitable for a bone marrow transplant (primarily due to lack of matched related donor for adolescents and since allo-HSCT is not recommended for adults regardless of donor availability due to the risks outweighing potential therapeutic benefit.

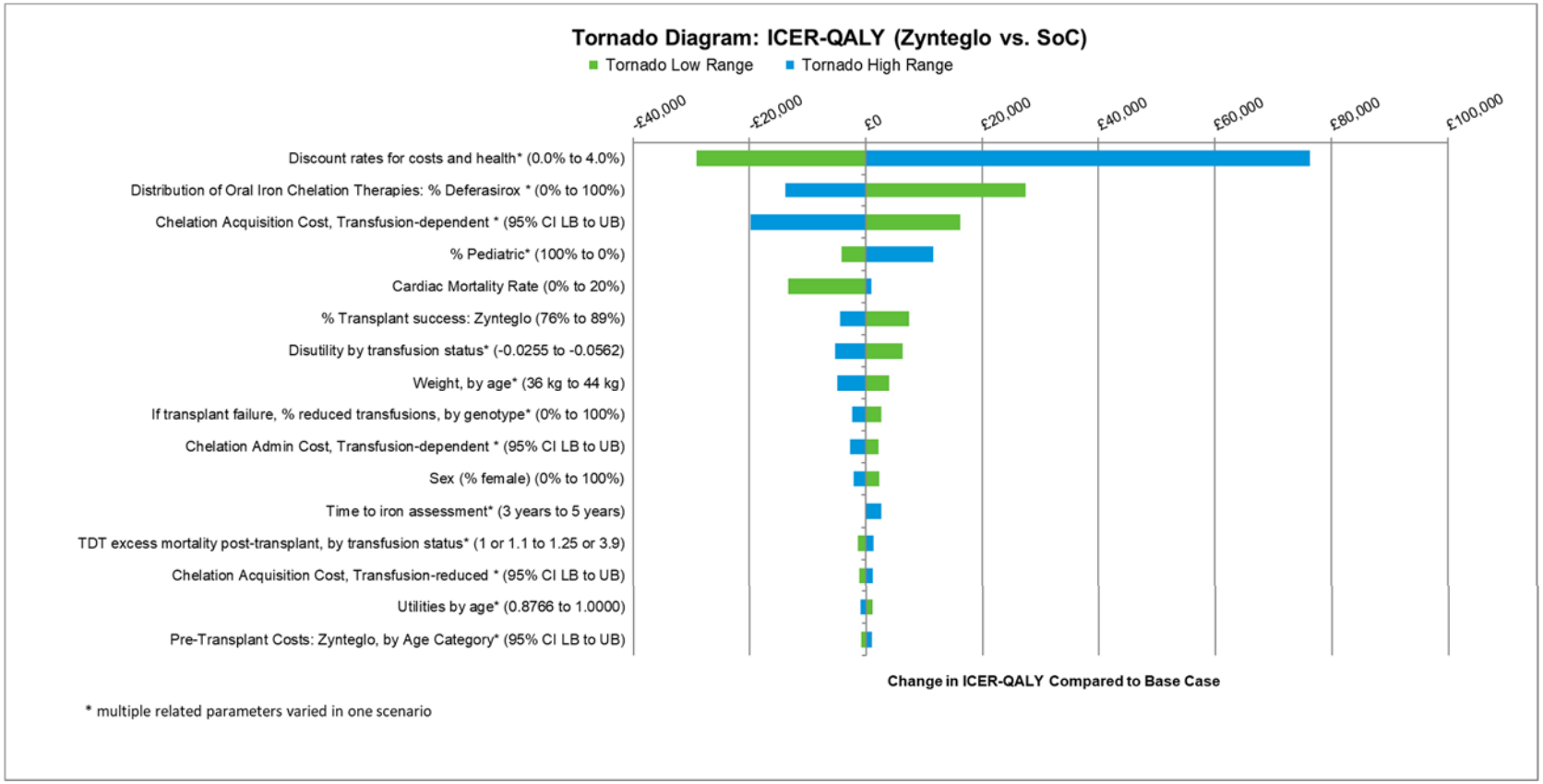
	A clinical expert statement was also submitted by Dr. Kate Ryan (Consultant Haematologist, Royal Manchester Infirmary Hospital), in which she mentions that thalassaemia and its treatment are associated with significant physical and psychological morbidity, resulting in reduced life expectancy, while Zynteglo leads to a reduction of morbidity and prolongs survival (National Institute for Health and Care Excellence, 2020b). In her statement, Dr. Ryan also highlights the unmet need for a treatment in patients >18 years in the UK and emphasises that, although allogeneic haematopoietic stem cell transplantation (HSCT) is a curative option for patients 12-18 years, it has significant risks of morbidity and mortality, and is limited by donor availability. Dr. Ryan states that Zynteglo will increase the length of life more than current care as there are still a significant proportion of patients that find it difficult to adhere to the current care lifetime requirement for iron chelation and multiple hospital visits. Furthermore, Dr. Ryan added that Zynteglo could improve quality of life for TDT patients over their whole lifetime (National Institute for Health and Care Excellence, 2020b). With TDT patients not receiving treatment that addresses the underlying genetic cause of the disease, mortality rates in the UK are [redacted] compared with the general population ([redacted] vs. [redacted] of the age/sex adjusted general population, [redacted]) with the median age of death being [redacted] years (historical UK cohort) (Jobanputra et al., Draft manuscript) (section B1.3.2. main submission). A recent 10-year retrospective cohort study identified comorbidity rates of [redacted]% among [redacted] TDT patients in England (Jobanputra et al., Draft manuscript), with those above 45 years old having rates of >50% for cardiac disease, osteoporosis, diabetes and endocrine disorders. These high rates of related co-morbidities show that, even with current treatment, patients have a severely impaired life as they have to manage underlying disorders coupled with a high mortality risk at the age of 45-50 years and beyond.Treatment with Zynteglo removes the burden of regular blood transfusions (transfusion independence [TI] in 83.3% of non-β^0/β^0 TDT patients from all studies [HGB-204, HGB-205, HGB-207, HGB-212]) (additional evidence submitted during technical engagement) and evidence from allo-HSCT suggests that patients achieving TI after treatment with Zynteglo can expect to lead as normal a life as possible, without daily interruption, allowing them to achieve their life aims (Caocci et al., 2016). (B1.3.7 main submission). Early results (up to Month 60) for the reduction in iron stores post-treatment (section B2.6.4. main submission) show that some of the non-β^0/β^0 patients who have completed their parent studies (those treated in Studies HGB-204 and HGB-205) and have achieved TI, have a decrease in burden according to liver iron content (LIC), cardiac T2* and serum ferritin. Patients become transfusion independent through treatment with Zynteglo and subsequently achieve normal iron levels will also no longer require chelation therapy reducing further the burden of current standard of care

	The Health-Related Quality of Life (HRQoL) results for TDT patients presented in the main submission (section B2.6.5.) should not be underestimated as the condition and current treatment have a significant impact. The WPAI results from the UK Chart Review suggest that activity impairment (50%) may be comparable to or higher than that reported in other chronic conditions, such as chronic obstructive pulmonary disease (13-65%) and rheumatoid arthritis (33%) (Miller et al., 2016). Due to the limitations in collecting Zynteglo HRQoL data from the clinical studies, a vignette study was also conducted in the UK general population to inform assumptions around the quality of life impact of TDT and Zynteglo. The vignette study indicated a utility of 0.93 for TI patients, 0.73 for patients receiving transfusions and oral chelation agents and 0.63 for patients receiving transfusion and subcutaneous chelation agents (B.3.4.5. main submission). bluebird bio would like to highlight the inconsistency between the Technology Appraisal team's view and that of the NICE Scientific Advice recently provided in the context of our registry study. The report included the following statement: [redacted] (National Institute for Health and Care Excellence, 2020a) **Benefits are sustained over a very long period (normally at least 30 years) and the long-term health benefits are likely to be achieved** Zynteglo has demonstrated durable clinical efficacy up to 61.3 months, with the ERG accepting that these are promising results, particularly as it relates to no significant changes observed in peripheral blood vector copy number (PB VCN) from Month 6 to last follow-up, which serves as a surrogate marker for persistence of transduced HSCs. However, the ERG also states that there is insufficient evidence to conclude with certainty that treatment will provide lifelong benefits. Given the nature of LVV-based gene therapies such as Zynteglo, the scientific plausibility supports lifelong treatment effects, and there is no evidence or scientific rationale that the effects diminish or reverse over time in patients that successfully engraft and achieve transfusion-independence. The EMA has recognised the expected life-long benefit of Zynteglo. In Section 5.1 of the SmPC it states: "Following successful engraftment and achievement of transfusion independence, the effects of the product are expected to be life-long." In the appraisal of voretigene neparvovec (HST11) clinical experts explained that a long-term treatment effect is biologically plausible, and that there is no biological reason for the expression of the RPE65 to stop after successful insertion. Whilst the committee was aware that there was substantial uncertainty about the long-term treatment effect, they concluded that there is a biological rationale for the treatment effect to be maintained.

	1.5% Discount Rate A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs. For adolescents and adults who are successfully treated with Zynteglo, the benefits would be expected to last over their lifetime, which would be expected to be over 30 years in the majority of cases. Over time, once the prevalent adult population, who currently have no curative treatment option, has been treated the eligible patient population will become teenagers and young adults, who will get the longest duration of benefit. It is noted that the age of the eligible population for Zynteglo is similar to the osteosarcoma population treated with mifamurtide (TA235) which was the first NICE appraisal where the committee accepted a 1.5% discount rate in the STA process to recognise the long term benefits of a potentially curative therapy. There are other examples of where the discount rate of 1.5% has been previously accepted in NICE appraisals with much shorter follow-up data than Zynteglo, which has 61.3 months follow up data, i.e.266 weeks). Treatment benefits have been accepted as lifelong in HST1 (eculizumab for treating atypical haemolytic uraemic syndrome) with long-term extension showing results to week 64 and HST2 (elosulfase alfa for treating mucopolysaccharidosis type IVa) with long-term extension data to week 120. The introduction of Zynteglo will not commit the NHS to significant irrecoverable costs. bluebird bio has proactively recognised a level of uncertainty and have proposed an outcomes-based scheme with NICE and NHSE that will ensure that the NHS will not be committed to significant irrecoverable costs. In addition, bluebird bio notes clear guidance from the UK Treasury Green Book (A2.54 p73): *"Discounting of resources relating to health and life issues is carried out using the appropriate standard discount rate of 3.5% declining after 30 years. The value of VPFs, SLYs and QALY effects should be discounted at the health rate of 1.5%, declining after 30 years."* Furthermore the Centre for Health Technology Evaluation, National Institute for Health and Care Excellence Report "Exploring the assessment and appraisal of regenerative medicines and cell therapy products" acknowledges *"the discounting rate applied to costs and benefits was found to have a very significant impact on analyses of these types of technologies."* It confirms further consideration should be made to the use of the 1.5% discount rates for such therapies.

	The Cell and Gene Therapy Catapult Centre of Excellence also supports the further consideration of the application of 1.5% discount rates for cell and gene therapies. The application of the 1.5% discount rate for health benefits for therapies with curative intent such as Zynteglo are a key area of consideration for the current NICE Methods Guide Review. **bluebird bio contends that the application of the 1.5% discount rate by NICE Appraisal Committees was implicitly introduced for new innovations such as gene therapies with the potential for lifelong benefits over 30 years and see no rationale for not following the current Methods Guide.** **In summary, by correcting the underlying cause of the condition, Zynteglo does meet the criteria for using the 1.5% discount rate.** **We have therefore retained the 1.5% discount rate in the updated basecase analyses and provided a sensitivity analysis with a 3.5% discount rate. NICE acknowledges that cost-effectiveness analyses are very sensitive to the discount rate used and this is confirmed in the updated deterministic sensitivity analyses (see Figure 2)**

Figure 2. Tornado diagram



References

CAOCCI, G., VACCA, A., PIRAS, E., SERRELI, V., DESSI, C., MARCIAS, M., RISSO, P. & LA NASA, G. 2016. Return to normal life after hematopoietic stem cell transplantation for thalassemia: a study of patients transplanted from matched sibling donors. *Bone Marrow Transplant,* 51**,** 1640-1641.

CAPPELLINI, M. D., COHEN, A., PORTER, J., TAHER, A. T. & VIPRAKASIT, V. 2014. Thalassemia International Federation: Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT), 3rd Edition.

JOBANPUTRA, M., PARAMORE, C., LAIRD, S. G., MCGAHAN, M. & TELFER, P. Draft manuscript. Co-morbidities and mortality associated with Transfusion Dependent Beta-thalassaemia Patients in England: A 10-Year Retrospective Cohort Analysis - Draft manuscript.

MILLER, P. S. J., HILL, H. & ANDERSSON, F. L. 2016. Nocturia Work Productivity and Activity Impairment Compared with Other Common Chronic Diseases. *PharmacoEconomics,* 34**,** 1277-1297.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE 2020a. NICE Scientific Advice: Report for Zynteglo (March 2020)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE 2020b. Technical Engagement Papers, Zyntelgo for treating transfusion-dependent beta-thalasaemia [ID968].

NICE. 2013. *NICE. Guide to the methods of technology appraisal 2013* [Online]. Available: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 [Accessed].

OLIVIERI, N. F. 1999. The beta-thalassemias. *N Engl J Med,* 341**,** 99-109.

RING, L., HÖFER, S., HEUSTON, F., HARRIS, D. & O'BOYLE, C. A. 2005. Response shift masks the treatment impact on patient reported outcomes (PROs): the example of individual quality of life in edentulous patients. *Health Qual Life Outcomes,* 3**,** 55.

UKTS 2016. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK, 3rd Edition.

Issue 2: Utilities	
Is the use of utility scores from vignette studies instead of health-related quality of life (HRQoL) data from Zynteglo clinical trials appropriate for some of the utility inputs in the model? Is the HRQoL data from the clinical trials generalisable to that seen in NHS practice?	The utility scores from the published UK vignette study are credibly estimated and can provide more reliable values (versus Zynteglo trial data) for the acute post-transplant period in the Zynteglo model. They provide comparable data to support the utility decrement for the overall TDT SoC population from the UK chart review. In addition, the baseline EQ-5D scores for patients in trial HGB-207 are more closely aligned to mean scores for younger patients from the UK chart review. However, in both situations the EQ-5D questions are not sensitive to the quality-of-life issues for TDT patients. This is evidenced by the following: 1) There have been no studies of utility decrement for the acute period of time following an 'autologous' myeloablative condition transplant for TDT patients. Thus, the vignette approach allowed for a detailed description of what a patient would face following an autologous transplant and this utility decrement has been used in the cost-effectiveness model. 2) As noted in the original submission for Zynteglo (page 180), EQ-5D data pre-transplantation with Zynteglo suggested utility values near to perfect health for many Zynteglo patients – the mean baseline score was 0.82 (median of 1). These scores are higher than those reported by TDT patients in the UK chart review (n= 94, mean score of 0.69 [SD 0.33]). For the subset of UK chart review patients of interest to the ERG (ages 12 to 35 and no comorbidities, n=34), the mean EQ-5D score was 0.86 (SD 0.23). It was noted previously that the trial EQ-5D baseline scores are not reflective of the quality of life impact of the condition. The fact that the patients elected to be enrolled in the Zynteglo studies, considering the myeloablative conditioning required, suggests that the patients have impaired quality of life, despite it not being reflected in the utility measure. This has been true for families deciding to have their children with TDT undergo allogeneic transplant which carries a non-zero acute mortality risk. The EQ-5D scores also may reflect that patients with TDT have adapted to life with a chronic condition and accordingly rate their quality of life higher with less regard to the impact of the disease and therefore not representative of the general public. This adaptation is common in serious chronic diseases, particularly those that are present from birth (Ring et al., 2005). An example of this would be the EQ-5D question on 'usual activities.' A TDT patient incorporates a full day every 2 to 5 weeks to receive a blood transfusion. That is, in essence, part of the usual activities that they consider normal in their life. An individual without TDT would consider having to start spending a day every 2 to 5 weeks for a blood transfusion a substantial impact on their usual activities (as indicated by the vignette study) but an individual with TDT could correctly answer that they have 'no problem' doing their usual activities.

	Furthermore, a treatment that would render the ongoing blood transfusions moot would not allow that TDT patient to have a higher score on that domain, as it is already at a level of 'no problems.' **In summary, the utility scores from the published UK vignette study are credibly estimated and can provide more reliable values (versus Zynteglo trial data) for the acute post-transplant period in the Zynteglo model. In addition, the baseline EQ-5D scores for patients in trial HGB-207 are more closely aligned to mean scores for younger patients from the UK chart review. However, in both situations the EQ-5D questions are not sensitive to the quality-of-life issues for TDT patients.** ***References*** RING, L., HÖFER, S., HEUSTON, F., HARRIS, D. & O'BOYLE, C. A. 2005. Response shift masks the treatment impact on patient reported outcomes (PROs): the example of individual quality of life in edentulous patients. Health Qual Life Outcomes, 3, 55.
Have management of TDT and iron chelation practices drastically changed in terms of outcome and patient disutility over the last 35 years? Should the disutility for the transfusion-dependent state in the model be based on the	We agree that management of individuals with TDT has improved over the past 35-year period, given more widespread use of iron monitoring practices (e.g. cardiac T2* MRI) and the advent of oral chelators. For the second part of the question, we believe that the utility data from the broader TDT population in the UK chart review should be considered. There are no published data that indicate the change in patient disutility over the past 35 years in the UK, to correspond with the clinical improvements noted above. Some studies have evaluated the specific utility impact of oral chelation versus subcutaneous chelation and one can infer that improvements due to oral chelation have improved the utility of living with TDT for some patients. However, those studies did not consider the broader patient impact of living with TDT. The primary objective of the chart review conducted by bluebird bio in the UK was to capture as representative and complete a picture as possible of the current management practices and outcomes for the general population of TDT patients in the UK. The protocol was driven by the views of 8 haematologists representing specialist centres across the UK that manage TDT patients. The chart review was not initiated to focus solely on the individuals with TDT who would be representative of Zynteglo trial patients, but rather the full scope of TDT patients in the UK. Both bluebird bio and the haematologists were satisfied that the study captured data on nearly 20% of all TDT patients in the UK so could be considered representative of contemporary clinical practice in the UK.

mean utility of all patients ≥16 years in the chart review, or the re-analysis using only those patients in the chart review dataset aged 12 to 35 years without co-morbidities already being modelled?	The chart review data therefore reflect current real world practice in the UK, and we believe it is important to consider the sample as widely as possible in order to capture the noticeable variation in EQ-5D scores in the population, which may stem from multiple factors besides just age and lack of specific comorbidities (variables of interest mentioned by the ERG). As shown in the table below, even when restricting the chart review sample by excluding patients with the comorbidities mentioned by ERG, there remains a wide range in EQ-5D scores in most age bands. **Table 1. EQ-5D results** [redacted] It is also important to note that the current economic model only uses a single input value for the utility decrement due to TDT SoC. The model does not allow for this value to change as the patient ages in the model. The only value that changes is the population-level, age-specific general utility decrement based on the UK population. **Thus the ERG's use of 'baseline' EQ-5D (the [redacted] value) does not change over time, which greatly underestimates the reduction in quality of life for TDT patients as they age per chart above and the same holds when looking at the full TDT population from the chart review.**

	References BLUEBIRD BIO INC 2019. An observational study to evaluate the routine management, healthcare resource use and outcomes for patients with transfusion-dependent β-thalassaemia treated in the United Kingdom (TDT Chart Review).
What is the potential HRQoL impact of infertility after myeloablative conditioning? Should this be accounted for in the analysis, or removed due to lack of data specific to this clinical scenario?	**We agree with NICE and the ERG that there are limited data to support the modelled infertility decrement and support the removal of this decrement in the model analyses.**
Should the HRQoL impact from any subcutaneous chelation therapy during the iron normalisation period be taken into account for people who become	**We accept that the HRQoL impact (utility decrement) for subcutaneous chelation therapy during the iron normalisation period should be taken into account and have incorporated this revision in our analyses.**

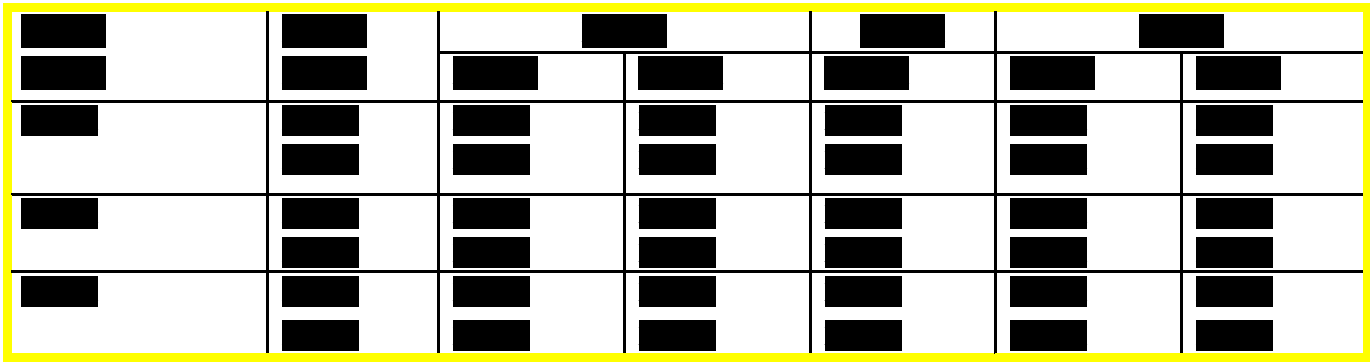
transfusion-independent after receiving Zynteglo treatment?	
Should the whole-population published dataset be used for the adjustment of utilities to take into account natural decline in HRQoL over time, or the subset excluding people who have existing/previous health problems?	**We have implemented the whole population utility dataset in the revised basecase analysis.**
Issue 3: Baseline characteristics of modelled population	
Is 20% a plausible proportion of people in the UK with TDT who have hypogonadism? Should hypogonadism be	**Based on data from the UK TDT chart review, we agree with the 20% figure as plausible for the proportion of individuals in the UK with TDT who have hypogonadism and have incorporated this baseline population value in the updated model analyses.**

reflected in the baseline population entering the model?	
Should the mean patient weight from the chart review be used in the model, or the ERG's age category-specific body weight approach instead?	**We agree that the model should better reflect the variation in body weight by age for individuals with TDT in the UK, based on chart review data, and have implemented the category-specific body weight approach in our model analyses.**
Is it anticipated that any patients aged 35 years or over would be treated with Zynteglo in the NHS? Is the efficacy evidence for Zynteglo generalisable to the anticipated UK population? As the efficacy evidence	Age is not a variable that determines a patient's eligibility for treatment. Considering that the Zynteglo indication does not stipulate an upper age limit for treatment, eligibility should instead be determined based on the individual patient's fitness to safely undergo autologous-HSCT using myeloablative conditioning, provided other criteria for treatment such as transfusion-dependence and genotype are met. To date, results in the oldest treated subjects have been positive and are no different than results in younger patients. Furthermore, bluebird bio have analysed correlations between age and HbA^{T87Q} expression at month 6, which is a strong predictor of achieving transfusion independence, for the non-β^0/β^0 cohort across TDT studies and no relationship based on the correlation co-efficient [redacted] and R^2 ([redacted]) [redacted]. Therefore, based on the available data, extrapolation of results to patients older than the subjects treated to date is plausible. **Therefore, we believe that the evidence from full UK chart review should be used in the model, rather than being limited to match the age range treated to date within clinical trials.**

from the Zynteglo trials is limited to a specific age range, should the evidence coming from the UK chart review also be limited to match this age range?	
Issue 4: Underrepresentation of population with severe non-β^0/β^0 genotypes	
What proportion of the UK TDT population have a non-β^0/β^0 genotype?	bluebird bio commissioned genotyping studies at the Oxford Reference Laboratory, Manchester Molecular Haematology Service and sourced data from Dr Paul Telfer at the Royal London Hospital to inform the approximate genotype breakdown in England. **Taken together, these data suggest approximately [redacted] % of UK patients have a non-β0/β0 genotype based on [redacted] non-β0/β0 genotype patients out of a total of [redacted] .** Source Document 1: Oxford National reference laboratory for haemoglobinopathies, Excel Spreadsheet of last 5-year anonymised data • Total patients = [redacted] • Non β^0/β^0 patients = [redacted] • β^0/β^0 patients = [redacted] Source Document 2: Barts Health NHS Trust, Haematology, Email from Dr Paul Telfer, Aug 2017 • Total patients = [redacted] • Non β^0/β^0 patients = [redacted] • β^0/β^0 patients = [redacted]

	Source Document 3: Molecular Haematology Service, Central Manchester Haematology Service, Email from Dr Steve Keeney, Feb 2019 • Total patients = [redacted] • Non β^0/β^0 patients = [redacted] • β^0/β^0 patients = [redacted]
What proportion of people with TDT who might be eligible for Zynteglo have a severe non-β^0/β^0 mutation?	The 2019 Manchester Molecular Haematology Service genotype data (n=[redacted]) represent the only data bluebird is able to utilise to inform the response to this question since it is the only study that provides specific genotypes for TDT patients, managed in a representative centre in England. From this study of adult TDT patients, [redacted] patients with non-β^0/β^0 mutations were considered to have a severe non-β^0/β^0 mutation, noted in **bold** and <u>underlined</u> text in Table 3 (see separate document, Appendix 3)
Should the proportion of the modelled patient population with a severe non-β^0/β^0 mutation be increased from the company's base case value?	The proportion of the modelled patient population with a severe non-β^0/β^0 mutation should not be adjusted because TI effects are assumed to be the same across non-severe and severe subjects. Further analyses of clinical trial data demonstrate there are no apparent differences in TI characteristics between subjects with severe non-β0/β0 genotypes versus non-severe non-β0/β0 genotypes and ranges were [redacted] between these groups (see Table 7 below and Appendix: Additional Evidence)

Table 7. PB VCN, HbA^{T87Q}, and Unsupported Total Haemoglobin Values at [redacted] for Non-β^0/β^0 Subjects ≥12 Years of Age Treated in Phase 3 Studies by Genotype Severity (Subjects who Completed the Month 6 Visit)



Data as of 02 December 2019 (bluebird bio inc, 2019a)
Abbrev.: Hb, haemoglobin; HbA^{T87Q}, haemoglobin containing $\beta^{A\text{-}T87Q}$-globin; PB VCN, peripheral blood vector copy number
[redacted] [c]Unsupported total Hb level is defined as the total Hb measurement level without any acute or chronic pRBC transfusions within 60 days prior to the measurement date.

Issue 5: Iron overload treatment, iron normalisation and residual risk of developing iron-overload complications

Is combination chelation therapy used more in current clinical practice than previously? If so, will this trend continue? Should the analysis take this into account? What proportion of patients receive at least two oral	bluebird bio consulted with two thalassaemia experts from London to inform our response to this question, Dr Paul Telfer (Royal London Hospital) and Dr Farrukh Shah (Whittington Hospital). Their responses indicate that combination therapy is increasing and that this trend is likely to continue: Dr Telfer responded with '*I suspect that a greater proportion of patients are being treated with combined chelation therapy over the past 2-3 years, and despite relatively little published evidence and some ambiguity in national guidelines, some of the specialists (ourselves included) are becoming freer with use of dual combinations to tailor to individual patient requirements. So there is more use of DFX plus DFO and DFX plus DFP. The doses may not be maximal of the individual chelators, and we are generally choosing dosing regimens which are below maximal recommended dose of individual drug. I think the proportions shown in the chart review would be as accurate as we can get at present. I suspect there will be a slight increase in usage as clinicians become more familiar with the different combinations.'* Dr Shah's response was as follows *'The simple answer is yes, the two oral drugs are used more and more in combination, on a rough guess I would say around [redacted] % are now taking the 2 oral drugs in combination. Combination therapy using standard regime of*

chelation therapies in practice?	*desferal and deferiprone have been used for many years and is part of standard of care for severe iron overload especially those with myocardial iron overload (around 18% of our population was on this at the last audit).* *I am now putting patients on oral combination (especially those who were doing subcutaneous DFO and DFP) to primarily relieve them of the need of doing subcutaneous DFO on 2 or 3 days a week when Deferasirox will do the same job. It is also being used in those patients on Deferasirox where there is cardiac iron and we want the iron to shift out of the heart and the patient refuses to use desferral.* *From a trend perspective I expect it to continue in the long term.'* The model has now been updated to accurately reflect iron chelation clinical practice in the UK as above where a proportion of patients are modelled to receive two oral agents as well as combination of oral and parenteral therapy.
Is an iron normalisation period of 4, 5, 7 or 10 years plausible for patients who become transfusion-independent after Zynteglo treatment? Does this normalisation period apply to all patients who become transfusion-independent?	In order to address the time period of 'plausible' iron normalisation, we evaluated the latest data cut (June 12 2019) of subjects meeting the Zynteglo indication and transfusion-independence status across clinical studies as described in Table 1 below. Of the [redacted] subjects at baseline, data are available for [redacted] subjects at 12 months for cardiac t2*. [redacted] had normal values, i.e. T2* > 20 ms, which was maintained out to month 60 where data are available. Thus, bluebird bio have adopted a one-year time point for cardiac iron normalisation post-Zynteglo. In terms of liver iron content the data indicate that at month 12, [redacted] of subjects had reached a liver iron level < 7 mg/g and [redacted] of subjects had attained this level at month 60. A threshold of <7mg/g liver iron content was selected based on the the UKTS 2016 standards which state that clinical observations in genetic haemochromatosis suggest that levels between 3-7 mg/g dw - the range seen in heterozygotes - should not result in hepatic or endocrine toxicity (UKTS Standards 2016). Based on these data, bluebird bio agrees with the ERG scenario of 5-year time period to achieve normal liver iron levels. Serum ferritin has limited utility in determining tissue specific iron levels and downstream risk of organ toxicity. A recent publication (Taher 2017) describes this issue as 'serum ferritin is an acute phase reactant that fluctuates with inflammatory, infectious, and other stress states. Therefore, its reliability for the assessment of iron overload remains limited. Clinicians must use well-informed medical judgment before using serum ferritin as the sole tool to assess iron overload.' In the UK, where MRI imaging is widely available for assessment of liver and cardiac iron loading, imaging remains the preferred method for iron quantitation (Dr Kate Ryan, personal communication).

	Notwithstanding these considerations, [redacted] subjects had achieved a ferritin level of <1000ng/ml at month 60 (specifically [redacted] ng/ml), which which were the [redacted] that reached normal cardiac and liver iron levels at this timepoint. We have reflected the one year and five year iron data in the model (see Table 2), and adjusted SF and LIC in year 1, by proportionately reducing the percentage of patients in each iron category equally to match baseline levels. **Table 2. Efficacy and Morlality inputs sheet of Zynteglo cost-effectiveness model** [redacted]

	Table 3. Summary of Iron Parameters over time [redacted] ***References*** UKTS 2016. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK, 3rd Edition. TAHER, A. T. & SALIBA, A. N. 2017. Iron overload in thalassemia: different organs at different rates. Hematology Am Soc Hematol Educ Program, 2017, 265-271.
Are iron-overload complications still a risk after transfusion independence is reached, due to iron overload damage which occurred prior to Zynteglo treatment?	bluebird bio are of the view that significant cardiac iron loading resulting in myocardial damage may lead to a persistent risk of arrhythmia despite correction of cardiac siderosis, which may arise in the case of atrial fibrillation from mechanisms apparently unrelated to iron overload (Capellini, 2014). However, for other tissues such as the liver, no carryover risk of prior iron overload in that tissue is expected post-Zynteglo and following iron normalisation. As discussed on the Technical Engagement teleconference, the proposed approach to uniformly apply the annual cardiac complication rate [redacted] for TDT individuals with 'low' cardiac iron to all transfusion-independent patients who have had their iron normalised is felt to markedly overstate the risk associated with the 'potential irreversible cardiac iron damage' scenario described by NICE/ERG. The model as it currently stands does not allow assignment of the percentage of TI individuals who would be deemed to have irreversible cardiac damage. Thus, the current inputs in the model are needed to 'approximate' this scenario. This can be accomplished pragmatically by lowering the annual cardiac complication rate applied to the 'normalized iron' TI patients. bluebird has evaluated the available evidence to estimate how much the annual cardiac complication rate should be lowered for iron-normalized TI patients: • Levels of cardiac iron according to T2* in current UK TDT patients o Based on the bluebird bio TDT chart review, [redacted] of individuals aged 12 to 35, and without comorbidities that would preclude treatment with Zynteglo, had a T2* value > 10 ms so would be eligible for treatment based on these parameters • For Zynteglo-treated individuals in the model relevant to the NICE scenario for irreversible cardiac damage the rate of cardiac complications is informed by

	o bluebird bio's analysis of HES data for TDT patients, the 10-year rate of cardiac disease was as follows: ▪ For those aged 10 to 34 [HES analysis did not allow for break out for ages 12-35]: • [redacted] had 'any' cardiac disease: [redacted] • [redacted] had arrhythmias (considered irreversible risk): [redacted] • Thus, the data indicate a substantial majority of patients who would be treated with Zynteglo, at the point in time of receipt of the therapy, likely have acceptable cardiac T2* levels; and the HES data indicate that irreversible damage is minimal in this population Thus given the model is applying the cardiac risk on an annual basis to all patients who achieve TI status, we propose to lower the annual cardiac complication rate for 'normalised iron' TI patients by a factor of [redacted] (using the complication rate for low cardiac iron), or [redacted] ***References*** *CAPPELLINI, M. D., COHEN, A., PORTER, J., TAHER, A. T. & VIPRAKASIT, V. 2014. Thalassemia International Federation: Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT), 3rd Edition.*
Will people who come off chelation therapy after transfusion independence or transfusion reduction is reached still have cardiac iron? How is this raised cardiac iron likely	As noted above, of the [redacted] patients achieving transfusion independence (TI) status and reaching 12 months of follow-up, [redacted] had normal cardiac T2* levels (i.e. > 20 ms) and this has been maintained for individuals reaching additional time points. Thus, cardiac iron levels are considered normalised.

to impact their health over time?	
Issue 6: Unknown long-term outcomes – relapse (late graft failure), initial (primary) engraftment failure and mortality	
Is there any evidence to support the idea that the therapeutic effect of Zynteglo may not be lifelong? Should the analysis incorporate a percentage of patients relapsing after initially successful treatment with Zynteglo, and if so, is one of the ERG's scenarios appropriate?	In clinical trials to date, all patients that successfully engrafted and achieved transfusion-independence have maintained this status out to longest follow-up. As described in section B.1.3.6. Gene therapy for the treatment of TDT of the company submission, Zynteglo utilises an 'ex-vivo' approach by adding functional copies of the β-globin gene into the patient's own cells, which corrects the underlying cause of the condition. As the cells used are the patient's own i.e. autologous, this approach eliminates major problems such as finding a suitable donor, graft rejection or GvHD (UKTS, 2018). To achieve persistent durability of efficacy in the case of ex vivo, LVV-based gene therapies such as Zynteglo, treatment must result in the establishment of a population of undifferentiated, long-term HSCs in the bone marrow which carry the gene of interest, integrated into their genome. Based on the mechanism of action of Zynteglo, which involves the insertion of functional copies of β-At87q into long-term repopulating HSCs, durable clinical efficacy has been demonstrated out to [redacted] months, underscoring stable integration of the vector in the HSCs, and consequently, stable expression of the transgene in erythroid cells. Therefore, it is expected that the effects of the treatment will be life-long, and clinical data for patients that have successfully engrafted and achieved transfusion-independence across clinical studies support this view. The EMA has recognised the expected life-long benefit of Zynteglo. In Section 5.1 of the SmPC it states: "Following successful engraftment and achievement of transfusion independence, the effects of the product are expected to be life-long." **In summary, there is no evidence to support the idea that the therapeutic effect of Zynteglo may not be lifelong. We therefore, do not accept the ERG's exploratory scenario that incorporated a percentage of patients relapsing after initially successful treatment with Zynteglo.**

	References *UKTS. 2018. Gene Therapy [Online]. Available: https://www.ukts.org/livingwith/treatment/gene-therapy/ [Accessed August 2019].* *ZYNTEGLO SMPC 2019. EMA SmPC Zynteglo.*
Should primary engraftment failure be taken into account in the model? If so, what percentage of patients receiving Zynteglo but experiencing this engraftment failure would be plausible? What is a plausible mortality rate associated with this engraftment failure?	Across LentiGlobin clinical trials in TDT and sickle cell disease (SCD) (n= [redacted] ; [redacted] TDT subjects, [redacted] SCD subjects), no patients have experienced primary engraftment failure. Owing to the autologous nature of the cells used, the need for myeloablative conditioning and the threshold minimum dose of Zynteglo, this is not expected to occur as the treatment enters commercial use. Engraftment failure was discussed in the Technical Engagement teleconference. The available data suggest that [redacted] of stem-cell engraftment is representative of clinical practice and the Zynteglo trials. Given the autologous nature of Zynteglo which mitigates allogeneic complications such as failed engraftment or graft failure, and in the absence of evidence of engraftment failure observed across trials, this should not be included in the economic model. The ERG also recognises that to assume that patients will become transfusion-dependent at some point after Zynteglo and incur costs for potential adverse events may be unreasonably pessimistic. **On this basis primary engraftment failure should not be implemented in the model.**
Is there any up to date data on the mortality of transfusion-dependent	There is a distinct lack of recent publications describing mortality rates in transfusion-dependent patients in the UK, which was the principal reason underpinning bluebird bio's commissioning of the Hospital Episode Statistics database analysis. This study demonstrated that of the [redacted] TDT patients included, [redacted] were known to be alive in 2018, [redacted] were lost to follow-up, and [redacted] had died. The crude 10-year mortality rate of [redacted] % ([redacted]), was more than [redacted] greater than the age/sex adjusted mortality rate of the general

patients, particularly UK-specific? What is a plausible mortality rate for people in this health state?	population (95%CI: [redacted]). Median age of death was [redacted] years (IQR 29-52), with a mean age of [redacted] years (Jobanputra et al, manuscript in development). Please also refer to Figure 1 above which demonstrates the increased mortality for patients with TDT seen in the in-patient setting. **We have implemented the ERG's preferred SMR value in our updated basecase analyses.** ***References*** JOBANPUTRA, M., PARAMORE, C., LAIRD, S. G., MCGAHAN, M. & TELFER, P. Draft manuscript. Co-morbidities and mortality associated with Transfusion Dependent Beta-thalassaemia Patients in England: A 10-Year Retrospective Cohort Analysis - Draft manuscript.
Issue 7: Generic drug acquisition costs	
Should prices for 3 of the generic products in the treatment process (busulfan, ursodeoxycholic acid and desferrioxamine) come from eMIT or BNF?	**We agree that the prices for generic products are more appropriately based on eMIT prices rather than BNF list prices. We note that the eMIT database was last updated 4 March 2020 and have therefore implemented the following eMIT prices in our updated analyses**: *Name & Pack Size* — *Weighted Average Price* Busulfan 60mg/10ml solution for infusion / Packsize 8 — £367.81 Desferrioxamine 500mg powder for solution for injection vials / Packsize 10 — £47.81 Ursodeoxycholic acid 150mg tablets / Packsize 60 — £8.09 https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit Last updated 4 March 2020, Accessed 8 March 2020.
Issue 8: Genotyping, other testing the company will pay for, and impact on the NHS	
Where in the treatment pathway would current and future patients	Table 58 (page 190) in the original company submission included genotype testing costs being incurred by bluebird bio. This was an error in the listing in the table and had not been carried forward in the model. We understand that genotyping for patients with TDT is routinely available and funded by the NHS, and that incident patients are tested in routine clinical practice in the NHS.

undergo genotype testing? How much does genotype testing for beta-thalassemia cost? What resources does this use (including staff time)?	It is our understanding that with evolving practice, clinicians can request genotype testing for prevalent patients being managed in specialist units. **Therefore, genotype testing is not an additional cost relating to the introduction of Zynteglo in the NHS.**
What additional infrastructure and training requirements could be considered for this appraisal?	The infrastructure and expertise to treat these patients in the main part already exist in the NHS apheresis service and transplant centres, especially where they have experience of transplanting haemoglobinopathy patients. **bluebird bio has been working proactively with NHSE's Commissioning Team to share information to enable the service to be commissioned in an appropriate number of service providers and has committed to investing time and resources to support and upskill the relevant cross-functional teams within the treatment centres.**
How much would the additional testing that the company has stated they will incur, cost, and how much NHS staff involvement would this require?	Additional blood tests specific to Zynteglo, such as PB VCN and HbAT87Q are conducted in bluebird bio laboratories; no charge is made to the NHS for these tests. For the UK patients who consent to be included in the registry (the objective being to enrol approximately [redacted] patients across Europe), one additional blood draw would be required per year as part of the 15-year follow up EMA post-marketing commitment. This additional blood draw is likely to be taken during routine follow up appointments. To this end, we have included one follow-up consultant-led appointment for every patient each year for 15 years within the in model, potentially over estimating the follow up costs for patients receiving Zynteglo. Other routine tests would be conducted annually for all patients with TDT irrespective of whether they have received Zynteglo or they remain on standard of care transfusions and chelation therapy.

	These routine tests are not additional requirements post Zynteglo, and therefore have not been included in the model since they apply to all patients equally and would therefore cancel each other out across the Zynteglo and standard of care cohorts.
Issue 9: Myeloablative conditioning	
What drugs do patients receive as part of myeloablative conditioning ahead of Zynteglo? Would a particular regimen be used in most centres in the UK? What constitutes current UK clinical practice in terms of drugs given for myeloablative conditioning ahead of allogeneic haematopoietic stem cell transplant?	Clinical studies of Zynteglo only utilised single-agent busulfan for myeloablative conditioning. It is expected, based on the study designs and data generated thereof, that single-agent busulfan will also be used for conditioning in UK clinical practice. **bluebird bio has consulted with transplant physicians in the UK who concur with this view as there is no evidence to support use of an alternative conditioning regimen. This was clarified and aligned upon during the Technical Engagement teleconference.**
What is the impact on the cost-effectiveness	**N/A based upon our response above.**

results of taking into account other drugs given as part of a myeloablative conditioning regimen (not just busulfan)?	
What is the mortality associated with myeloablative conditioning in the UK?	**No treatment-related mortality has been observed in the Zynteglo clinical studies to date.** The safety profile of intravenous busulfan is well established, and pharmacokinetic drug monitoring is required to ensure patients are not under or over-exposed to this agent, therefore the mortality risk associated with busulfan conditioning at the dose ranges described in the SmPC is expected to be negligible.
Issue 10: Number of patient profiles modelled	
How many profiles should be simulated in the model, in order to reach a stable ICER and overcome random noise and first order uncertainty?	bluebird bio acknowledges that the ERG considered the model to be more stable with a higher number of profiles. When conducting stability tests, we defined stability in terms of the purpose of the analyses, that is, reaching a binary decision based on where the ICER lies relative to NICE thresholds. We considered the model to be stable at 600 profiles. Increasing the number of profiles to 10,000 increases stability as defined by the ERG, but it also increases the model runtime by an order of magnitude without providing significant additional information regarding cost-effectiveness. “Stability” should not be defined in terms of a small change in the ICER but in terms of the decision relevant range. To put it in terms of “first-order uncertainty” the stochastic uncertainty is sufficiently minimised with 600 profiles.

Appendices

Technical Engagement Response

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

July 2020

Appendix 1. Updated base case analyses

In response to the NICE Technical Report and following the technical engagement teleconference we have updated our basecase cost-effectiveness analyses. We have taken on board the feedback from both the ERG and NICE and have fully implemented the following ERG and/or NICE preferred assumptions within the revised model:

- Whole population set from Ara and Brazier for age-adjusting utilities
- HRQoL impact of subcutaneous chelation therapy for transfusion-independent patients in iron normalization period
- 20% hypogonadism in baseline population
- Age category-specific (paediatric and adult) mean weights used in model
- Chelation therapy distribution adjusted to match change in clinical practice including proportion of patients being treated with two oral chelation agents (i.e. both deferasirox and deferiprone)
- SMR of 2.0 applied for patients in the model who are transfusion-dependent and don't develop cardiac complications
- eMIT-sourced prices used for bulsulfan, ursodeoxycholic acid and desferrioxamine (updated to March 2020 eMIT prices)
- Removal of the disutility for infertility

In addition, the following assumptions have been altered in the revised model based upon discussion during the technical engagement teleconference and subsequent additional clarification provided in the Technical Response form:

- Iron normalisation period for people who become transfusion independent after Zynteglo
- Cardiac complications from iron overload damage prior to Zynteglo modelled for people who become transfusion-independent

We have provided additional clarification and justification in the Technical Response form for the remaining model inputs where we feel strongly that this needs further committee discussion:

- 1.5% discount rate in our base case analyses; 3.5% discount rate has been included as sensitivity analysis
- ERG's preferred approach for calculating the utility decrement for the transfusion-dependent state

The updated base case results for Zynteglo versus transfusions and iron chelation therapy are shown in Table 1, which includes the simple discount patient access scheme. Zynteglo is associated with 12.59 years increased incremental survival, 11.16 discounted incremental QALYs. Zynteglo is associated with incremental costs of [redacted] per patient compared to chronic transfusions and iron chelation and the ICER is [redacted] per additional QALY gained.

Table 1. Base case results using simple PAS

Technologies	Total costs (discounted, £)	Total LYG (undiscounted)	Total QALYs (discounted)	Incremental costs (£)	Incremental LYG (undiscounted)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	42.41	17.40				
Zynteglo	[redacted]	55.00	28.56	[redacted]	12.59	11.16	[redacted]
Abbreviations: BSC, Best Standard of Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Deterministic (DSA) and probabilistic sensitivity analyses (PSA) were conducted for the base case.

PSA was conducted using 300 patient profiles and 1,000 iterations. The results of the PSA are presented in Table 2, Figure 1 and Figure 2. The results are consistent with the deterministic base case, with QALY results remaining stable and cost results showing variation for both Zynteglo and the comparator. This can be seen when looking at the spread of the individual iterations, with all paired comparisons showing large QALY gains and large variability in incremental cost.

Table 2. Probabilistic sensitivity analysis results (300 patient profiles and 1,000 iterations) using simple PAS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Transfusions and iron chelation therapy	[redacted]	17.60			
Zynteglo	[redacted]	28.27	[redacted]	10.56	[redacted]

Figure 1. Cost-effectiveness plane: updated model

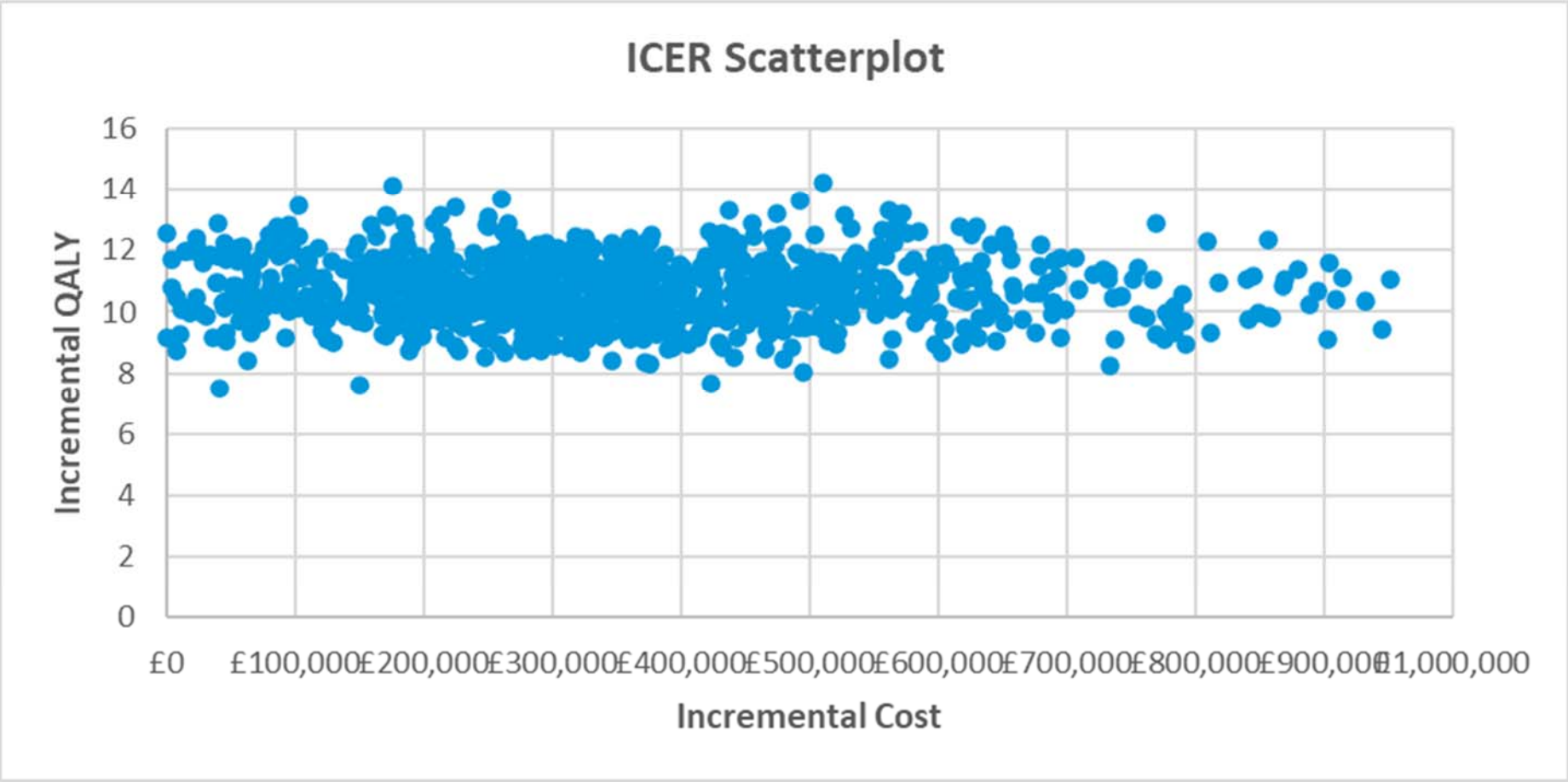
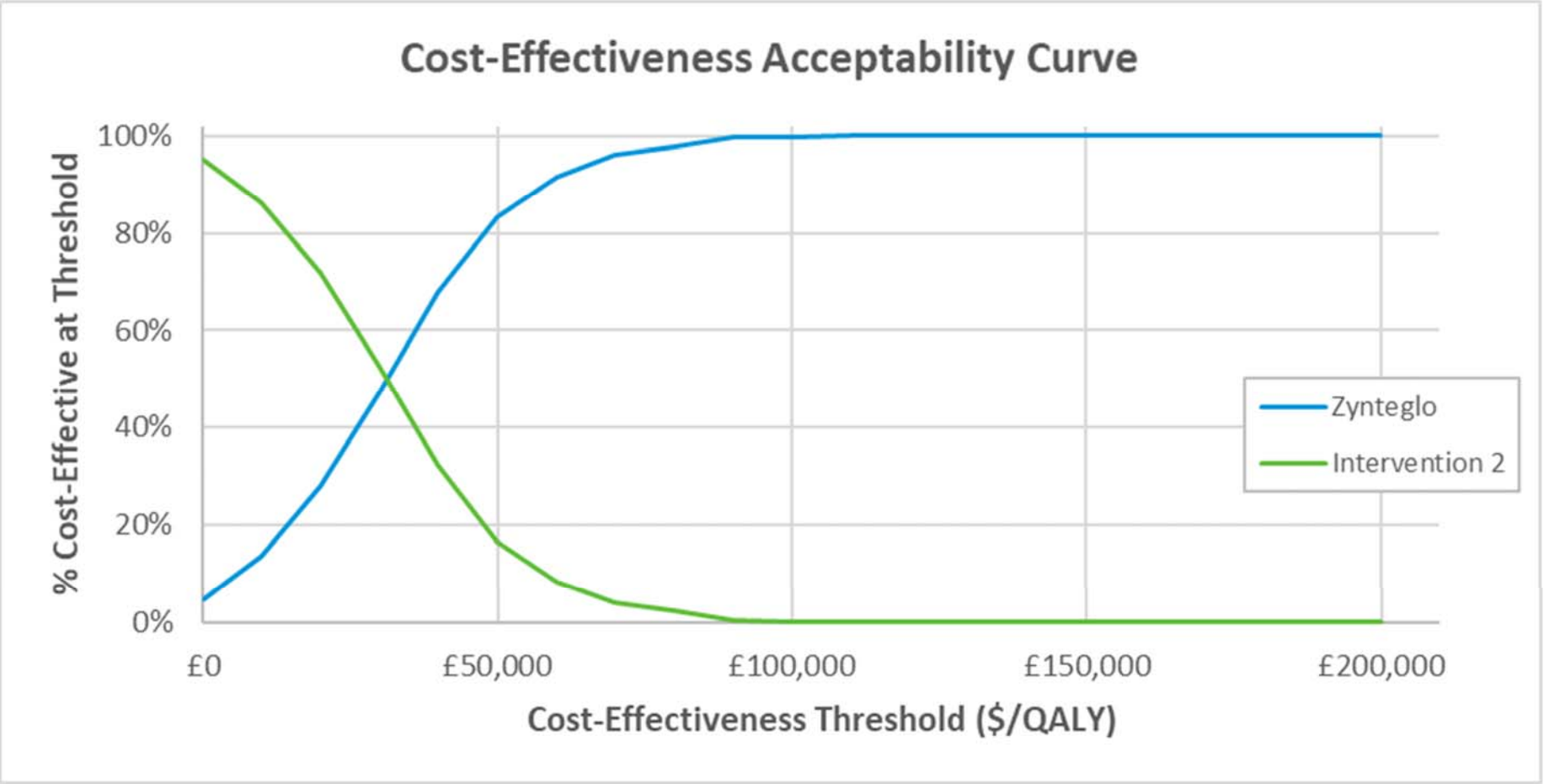
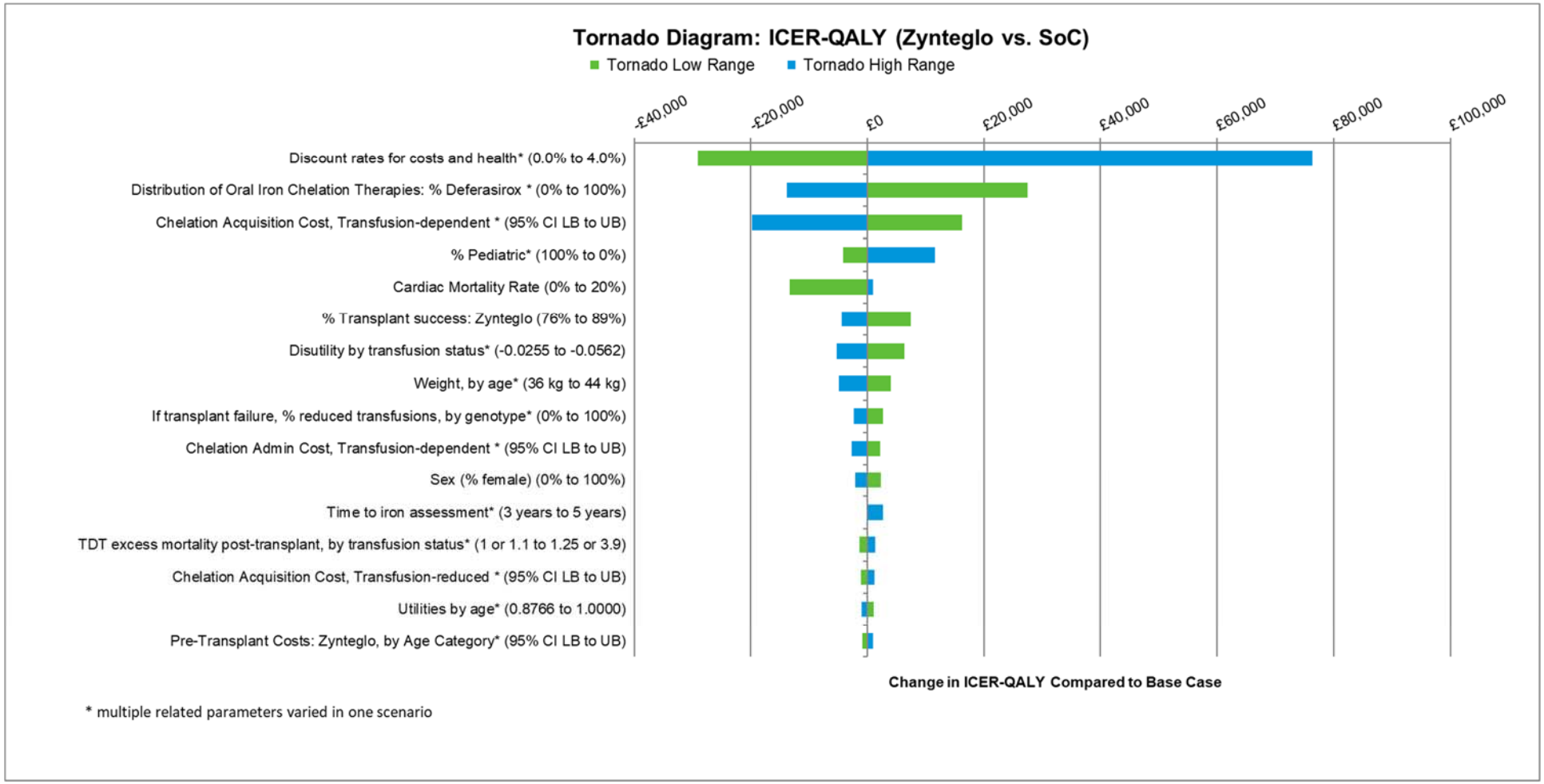


Figure 2. Cost-effectiveness acceptability curve: updated model



The 3.5% discount rate has been incorporated into the DSA. The results of the updated DSA can be seen in Figure 3, the results are consistent with the original company submission DSA and demonstrate how the cost-effectiveness results are extremely sensitive to the discount rate used.

Figure 3. Tornado diagram illustrating deterministic sensitivity results



Appendix 2. Study Disposition Figures

Updated study disposition figures for HGB-207 and HGB-212 are presented below:

Figure 4. Study disposition figure for HGB-207 (TDT non-β^0/β^0, all ages)

Reference: (bluebird bio inc, 2019)

Figure 5. Study disposition figure for HGB-212 (TDT non-β^0/β^0, ≥12 years)

Reference: (bluebird bio inc, 2019)

Appendix 3. Manchester Molecular Haematology Service Genotype Data

Table 3. Manchester Molecular Haematology Service data with TDT patient genotypes managed in a representative centre in England

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Note: Adult TDT patients, with a severe non-β^0/β^0 mutation, have been noted in **bold** and <u>underlined</u> text

References

BLUEBIRD BIO INC 2019. 2nd December 2019 TLFs for HGB-207, HGB-212 and LTF-303.

Appendix – Clinical data to support the NICE Single Technology appraisal for Zynteglo [ID968]

Contents

Tables

Figures

Abbreviations

Abbreviation	Definition
Hb	Haemoglobin
HbA	haemoglobin A (i.e., adult haemoglobin)
HbA^{T87Q}	haemoglobin containing $\beta^{A\text{-}T87Q}$-globin
HBB	β-globin gene
KOL	key opinion leader
PB	peripheral blood
pRBC	packed red blood cell
SmPC	summary of product characteristics
TDT	transfusion-dependent β-thalassemia
TI	transfusion independence
VCN	vector copy number

1. Introduction to Recent Efficacy and Safety Data for Zynteglo

The most recent data cut for efficacy analyses was performed on 02 December 2019 for subjects treated with Zynteglo in ongoing Phase 3 Studies HGB-207 and HGB-212, including follow-up data for any of these subjects enrolled in long-term follow-up Study LTF-303. Efficacy data for subjects with non-β^0/β^0 genotypes ≥12 years of age treated in Phase 3 studies are presented in Section 2, with additional analyses provided for subjects with a severe non-β^0/β^0 genotype in Section 3. A summary of key efficacy data for subjects treated in Phase 1/2 Studies HGB-204 and HGB-205 per the updated Summary of Product Characteristics (SmPC) published as of 14 November 2019 is provided in Section 4. An overall summary of transfusion independence across all studies is provided in Section 5. The most recent data cuts for safety analyses were performed on 26 August 2019 and 29 November 2019, and a summary of safety data is provided in Section 6. Due to the nature of these data cuts, the summary will not be as comprehensive as that provided from the June 2019 data cut in the original company submission.

2. Summary of Efficacy data for Non-β^0/β^0 subjects ≥12 years of age treated in Phase 3 Studies

As of 02 December 2019, [redacted] subjects with a non-β^0/β^0 genotype ≥12 years of age have been treated in Phase 3 Studies HGB-207 (N=[redacted]) and HGB-212 (N=[redacted]). Duration of follow-up for these [redacted] treated subjects ranged from [redacted] months post-drug product infusion. For these [redacted] subjects, ages ranged from [redacted] years at the time of consent/assent; [redacted] were male and [redacted] were female; [redacted] identified as White and [redacted] identified as Asian (bluebird bio inc, 2019a).

2.1. Peripheral Blood Vector Copy Number and HbA^{T87Q}

[redacted] treated subjects with a non-β^0/β^0 genotype ≥12 years of age had [redacted] which [redacted] through last follow-up. The kinetics of peripheral blood vector copy number (PB VCN) were [redacted] with previous data, with PB VCN levels [redacted] after drug product administration before [redacted] by approximately [redacted] and [redacted] through last follow-up. PB VCN at [redacted] ranged from [redacted] c/dg (N=[redacted]) and at [redacted] ranged from [redacted] c/dg (N=[redacted]). The [redacted] subjects with the longest follow-up had [redacted] PB VCN values out through [redacted], with median (min, max) PB VCN at [redacted] of [redacted] c/dg (bluebird bio inc, 2019a).

Figure 1. Peripheral Blood VCN Over Time Among Non-β^0/β^0 Subjects ≥ 12 Years of Age (Studies HGB-207 and HGB-212)

[redacted]

Data as of 02 December 2019 (bluebird bio inc, 2019a)
The circle markers represent the medians.

[redacted] subjects who received Zynteglo [redacted] expression of $\beta^{A\text{-}T87Q}$-globin. The kinetics of HbA^{T87Q} were also [redacted] with previous data cuts, with HbA^{T87Q} levels [redacted] after drug product infusion before [redacted] by approximately [redacted] and [redacted] through last follow-up. For treated subjects with a non-β^0/β^0 genotype ≥12 years of age, HbA^{T87Q} at [redacted] ranged from [redacted] g/dL (N=[redacted]) and at [redacted] ranged from [redacted] g/dL (N=[redacted]). The [redacted] subjects with the longest follow-up had [redacted] HbA^{T87Q} levels out through [redacted] with median (min, max) HbA^{T87Q} at [redacted] of [redacted] g/dL. The low minimum HbA^{T87Q} at Month 30 is due to a subject who did not achieve TI and who restarted regular pRBC transfusions, which thereby suppressed their HbA^{T87Q} production (bluebird bio inc, 2019a).

Figure 2. Median HbA^{T87Q} Over Time Among Non-β^0/β^0 Subjects ≥ 12 Years of Age (Studies HGB-207 and HGB-212)

[redacted]

Data as of 02 December 2019 (bluebird bio inc, 2019a)
The circle markers represent the medians.

Results presented in this section are [redacted] with the conclusions previously presented and [redacted] that there is [redacted] of the $\beta^{A\text{-}T87Q}$-globin gene into long-term haematopoietic stem cells (HSCs), and [redacted] of the $\beta^{A\text{-}T87Q}$-globin gene in cells of the erythroid lineage derived from transduced long-term progenitor HSCs, supporting the potential for life-long, [redacted] of $\beta^{A\text{-}T87Q}$-globin in patients treated with Zynteglo (bluebird bio inc, 2019a).

2.2. Transfusion Independence

2.2.1. Proportion of Subjects to Achieve Transfusion Independence

Transfusion independence (TI) is defined as maintaining a weighted average Hb ≥9.0 g/dL without any pRBC transfusions for a continuous period of ≥12 months after drug product infusion, starting at least 60 days after last pRBC transfusion. Subjects are considered evaluable for TI if they have achieved TI, will not achieve TI in their parent study, or completed their parent study. As of 02 December 2019, [redacted] subjects with a non-β^0/β^0 genotype ≥12 years of age in Phase 3 studies were evaluable for TI, and [redacted] of these [redacted] subjects ([redacted] 95% confidence interval of [redacted]) have achieved TI (bluebird bio inc, 2019a).

Table 1. Transfusion Independence for Non-β^0/β^0 Subjects ≥ 12 Years of Age Treated in Phase 3 Studies (TP)

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data as of 02 December 2019 (bluebird bio inc, 2019a)
Abbrev.: CI, confidence interval; TI, transfusion independence
Error! Reference source not found. Subjects evaluable for TI are defined as subjects who have achieved TI, will not achieve TI in their parent study, or completed their parent study.
Error! Reference source not found. Denominator based on the number of subjects evaluable for TI.
Error! Reference source not found. The Clopper-Pearson Exact method is used to calculate the 2-sided 95% CI for the proportion of subjects meeting this criterion.

[redacted] subjects who have achieved TI [redacted] TI through last follow-up, including any long-term follow-up in LTF-303 as applicable, demonstrating [redacted]. Median (min, max) time from drug product infusion to last pRBC transfusion prior to TI was [redacted] months post-drug product infusion, with [redacted] subjects who have achieved TI receiving their last pRBC transfusion within [redacted] post-drug product infusion. Median (min, max) time from drug product infusion to reach TI was [redacted] months. As of 02 December 2019, the median (min, max) observed duration of TI was [redacted] months. The median (min, max) weighted average Hb during TI for these subjects was [redacted] g/dL, with [redacted] maintaining a weighted average Hb during TI [redacted] g/dL (bluebird bio inc, 2019a).

Table 2. Characterisation of Transfusion Independence for Non-β^0/β^0 Subjects ≥ 12 Years of Age Treated in Phase 3 Studies (TI Subjects Only)

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data as of 02 December 2019 (bluebird bio inc, 2019a)
Abbrev.: DPI, drug product infusion; Hb, haemoglobin; pRBC, packed red blood cell; TI, transfusion independence

The [redacted] TI-evaluable subjects who have not achieved TI as of 02 December 2019 and will not achieve TI in the parent study have [redacted] and the [redacted] amongst[redacted] non-β^0/β^0

subjects ≥12 years of age treated in a Phase 3 study with available clinical data (bluebird bio inc, 2019a).

Figure 3. Duration of transfusion and transfusion-free periods in non-β^0/β^0 Subjects ≥ 12 Years of Age Evaluable for Transfusion Independence (Studies HGB-207 and HGB-212)

[redacted]

Data as of 02 December 2019 (bluebird bio inc, 2019a)
Includes data through last available visit (including visits in Study LTF-303 as applicable)

2.2.2. Prediction of Transfusion Independence

Predictions of TI using [redacted] HbA^{T87Q} or unsupported total Hb were made for [redacted] of the [redacted] non-β^0/β^0 subjects ≥12 years of age who were not yet TI-evaluable due to limited follow-up time (Table 3; the [redacted] had [redacted] of follow-up as of 02 December 2019). A logistic regression model demonstrated a [redacted] between [redacted] and the probability of achieving TI. In addition, [redacted] at [redacted] is a good predictor for TI as among the [redacted] TI-evaluable non-β^0/β^0 subjects across all studies in the Zynteglo clinical development program (including subjects from Studies HGB-204, HGB-205, HGB-207, and HGB-212), regardless of age, [redacted] subjects who had unsupported total Hb ≥9 g/dL at [redacted] achieved TI. [redacted] subjects who did not have unsupported total Hb ≥9 g/dL at [redacted] also achieved TI; therefore, [redacted] is also a conservative predictor for TI. In summary, predictive modeling based on either[redacted] is a robust method for predicting efficacy outcomes, showing [redacted] subjects who completed the [redacted] Visit but were not yet TI-evaluable are likely to achieve TI with high probability (bluebird bio inc, 2019a).

Table 3. Prediction of Achieving TI Based on HbA^{T87Q} and Unsupported Total Hb Levels for Non-β^0/β^0 Subjects ≥ 12 Years of Age Who Completed the [redacted] Visit (Phase 3 Studies HGB-207 and HGB-212)

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data as of 02 December 2019 (bluebird bio inc, 2019a)
Error! Reference source not found. Age at informed consent/assent
Abbrev.: Hb, haemoglobin; M, Month; TI, transfusion independence

Based on these predictions, [redacted] of these non-β^0/β^0 subjects ≥12 years of age who completed the [redacted] Visit but were not yet TI-evaluable will likely achieve TI with a [redacted] probability of achieving TI based on their [redacted]. The probability of achieving TI could not be predicted for the remaining [redacted] who had [redacted] of follow-up post drug product infusion; note that [redacted] had unsupported total Hb of [redacted] at the [redacted] Visit ([redacted]) and therefore is [redacted] if these Hb levels are [redacted] (bluebird bio inc, 2019a).

Thus, overall: in Phase 3 Study HGB-207 [redacted] ([redacted]) of non-β^0/β^0 subjects ≥12 years of age who have completed at least their [redacted] Visit have either achieved TI ([redacted]) or are predicted to achieve TI ([redacted]); in Phase 3 Study HGB-212, [redacted] ([redacted] of non-β^0/β^0 subjects ≥12 years of age who have completed at least their [redacted] Visit have either achieved TI ([redacted]) or are predicted to achieve TI ([redacted]); and across both Phase 3 Studies HGB-207 and HGB-212, [redacted] ([redacted]) of non-β^0/β^0 subjects ≥12 years of age who have completed at

least their [redacted] Visit have either achieved TI ([redacted]) or are predicted to achieve TI ([redacted]) (bluebird bio inc, 2019a).

Figure 4. Duration of transfusion and transfusion-free periods in non-β^0/β^0 Subjects ≥ 12 Years of Age Who are Predicted to Achieve Transfusion Independence (Studies HGB-207 and HGB-212)

Data as of 02 December 2019 (bluebird bio inc, 2019a)

2.3. Total Haemoglobin Over Time

Total Hb values in the absence of pRBC transfusions for at least the [redacted] (i.e., unsupported total Hb) were assessed over time. Non-β^0/β^0 subjects ≥12 years of age who have achieved TI [redacted] of total Hb in the absence of transfusions, with total Hb ranging from [redacted] g/dL at [redacted] and [redacted] g/dL at last follow-up (N=[redacted]). Overall, these results continue to support that subjects who have achieved TI in Phase 3 studies have achieved [redacted] total Hb levels in the absence of transfusions, with median total Hb that is markedly above the 9 g/dL threshold required for TI and is [redacted] through last follow-up (bluebird bio inc, 2019a).

Figure 5. Median Unsupported Total Hb Over Time Among Non-β^0/β^0 Subjects ≥ 12 Years of Age Who Achieved Transfusion Independence (Studies HGB-207 and HGB-212)

Data as of 02 December 2019 (bluebird bio inc, 2019a)
The circle markers represent the medians.
Unsupported total Hb level is defined as the total Hb measurement level without any acute or chronic pRBC transfusions within 60 days prior to the measurement date.

3. Summary of Efficacy Data for Non-β^0/β^0 subjects ≥12 years of age Treated in Phase 3 Studies, By Genotype Severity

3.1. Background on β-globin gene (HBB) Genotypes

The production of β-globin is required to produce haemoglobin A (HbA), a heterotetramer comprised of 2 α-globin and 2 β-globin chains ($\alpha_2\beta_2$) that accounts for >95% of the haemoglobin (Hb) in the blood of adults. β-thalassemia is a rare hereditary blood disorder caused by the absence or reduced production of β-globin, resulting in an excess of uncomplexed α-globin which precipitates and leads to premature death of erythroblasts and ineffective erythropoiesis, causing the anemia characteristic of patients with β-thalassemia (Galanello and Origa, 2010).

Human β-globin is encoded by the *HBB* gene, located on chromosome 11, and in humans, there are 2 copies of the *HBB* gene. Mutations lead to different variants of the *HBB* gene and each variant is known as an allele. The combination of alleles carried by an individual is that individual's genotype.

Hundreds of mutations in the *HBB* gene that are associated with the phenotype of β-thalassemia have been identified. Mutations that result in no production of β-globin protein are collectively referred to as β^0 mutations (Cao and Galanello, 2010) Mutations that result in reduction, but not complete absence, of production of β-globin protein are collectively referred to as β^+, or non-β^0, mutations. Comprehensive descriptions of different *HBB* mutations, as well as qualitative and general predictions of the clinical impact of given mutations on β-globin expression (i.e., β^0 versus non-β^0) are summarised in the standard online reference

(http://globin.cse.psu.edu/). Patients with β-thalassemia who have β^0 mutations in both *HBB* alleles are described as having a β^0/β^0 genotype, and all other *HBB* genotypes are described as non-β^0/β^0 genotypes.

The global expanse of the Zynteglo clinical development program resulted in the treatment of subjects with transfusion-dependent β-thalassemia (TDT) with different *HBB* mutations that encode a wide range of endogenous β-globin expression. Although subjects with a non-β^0/β^0 genotype by definition all produce some endogenous β-globin, different *HBB* mutations result in different amounts of β-globin production, and different combinations of *HBB* mutations result in a wide range of total endogenous β-globin production among individuals with a non-β^0/β^0 genotype. For example, some non-β^0 mutations lead to very minimal production of functional β-globin and are considered severe, including the IVS-I-110 G→A mutation (HGVS nomenclature: *HBB*:c.93-21G>A), the IVS-I-5 G→C mutation (HGVS nomenclature: *HBB*:c.92+5G>C), the IVS-II-654 C→T mutation (HGVS nomenclature: *HBB*:c.316-197C>T), and the IVS-II-5 G→C mutation (HGVS nomenclature: *HBB*.c.315+5G>C) [(Borgna-Pignatti and Galanello, 2009) and globin gene server http://globin.bx.psu.edu/]. Individuals with severe non-β^0 mutations in both *HBB* alleles, or a severe non-β^0 mutation on one allele paired with a β^0 mutation in the other allele, are considered to have a severe non-β^0/β^0 genotype due to their markedly low levels of endogenous β-globin production; thus in the spectrum of disease severity, subjects with a severe non-β^0/β^0 genotype are generally phenotypically closer to subjects with a β^0/β^0 genotype. Individuals with a severe non-β^0 mutation in one allele paired with a non-severe non-β^0 mutation in the other allele are not considered to have a severe non-β^0/β^0 genotype. Note that β-globin production across genotypes is a continuum, and there is not a distinct boundary between “severe” and “non-severe” non-β^0/β^0 genotypes. All non-β^0/β^0 genotypes, regardless of severity or β-globin mutation, are included within the indication for Zynteglo as per the SmPC.

The Phase 3 Studies HGB-207 and HGB-212 were originally designed based on results from Phase 1/2 studies suggesting that *HBB* genotype would have a substantial impact on the ability of subjects to achieve TI due to differences in endogenous β-globin production. Guided by the clinical results from our Phase 1/2 studies and feedback from key opinion leaders (KOLs), the Phase 3 Studies HGB-207 and HGB-212 were divided into non-β^0/β^0 and β^0/β^0 genotypes to allow the studies to have endpoints of TI and transfusion reduction, respectively, which best reflected the Phase 1/2 clinical experience. KOLs also noted that the severe non-β^0 mutation IVS-I-110 was of particular relevance because of its relative prevalence in Italy and Greece where bluebird bio had Phase 3 clinical study sites. Based on this, the IVS-I-110 mutation was excluded from Study HGB-207 (when either homozygous or compound heterozygous with a β^0 mutation) and included in Study HGB-212 along with subjects with a β^0/β^0 genotype. (Subjects with an IVS-I-110 mutation paired with a non-severe non-β^0 mutation in the other allele are included in Study HGB-207, as these subjects are not considered to have a severe non-β^0/β^0 genotype). While there are other non-β^0 mutations that are considered severe as described above, because of the geographic scope of our clinical studies, these other severe non-β^0 mutations were not individually called out in Zynteglo’s Phase 3 studies. Potentially because of migration patterns, [redacted] with the severe non-β^0 mutation IVS-I-5 were treated in Study HGB-207, but this was not anticipated at the time of

protocol design. Nevertheless, optimisation of the drug product manufacturing process appears to have made [redacted] The [redacted] achieved in Phase 3 studies, which by themselves appear to be [redacted] to bring most subjects to TI, have resulted in the observation that [redacted]

Zynteglo is indicated for the treatment of patients 12 years and older with TDT who do not have a β^0/β^0 genotype (Zynteglo SmPC, 2019). This indication population includes all non-β^0/β^0 genotypes, including all non-β^0/β^0 genotypes with the non-β^0 IVS-I-110 mutation or the non-β^0 IVS-I-5 mutation regardless of homozygosity or heterozygosity. Patients with a β^0/β^0 genotype, who make no endogenous β-globin, are currently not included in the Zynteglo indication; however, Studies HGB-204 and HGB-212 have included some subjects with a β^0/β^0 genotype and emerging data for these subjects from Phase 3 Study HGB-212 have been promising.

3.2. Clinical Data

As of 02 December 2019, [redacted] subjects with a severe non-β^0/β^0 genotype ≥12 years of age have undergone mobilisation in Phase 3 studies ([redacted] in Study HGB-207 with the IVS-I-5 mutation and [redacted] in Study HGB-212 with the IVS-I-110 mutation), of whom all have been treated with Zynteglo. There are [redacted] subjects ≥12 years of age who have a severe non-β^0 mutation but are not considered to have a severe non-β^0/β^0 genotype because the severe non-β^0 mutation is paired with a non-severe non-β^0 mutation in the other allele. Non-β^0/β^0 subjects ≥12 years of age in Phase 3 studies with a severe non-β^0 mutation are listed in Table 4 and the subjects with a severe non-β^0/β^0 genotype are indicated (bluebird bio inc, 2019a).

Table 4. Non-β^0/β^0 Subjects ≥12 Years of Age in Phase 3 Studies with a Severe Non-β^0 Mutation

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Data as of 02 December 2019 (bluebird bio inc, 2019a)

Table 5. Transfusion Independence for Non-β^0/β^0 Subjects ≥12 Years of Age Treated in Phase 3 Studies by Genotype Severity (TP)

[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data as of 02 December 2019 (bluebird bio inc, 2019a)
Abbrev.: TI, transfusion independence
Error! Reference source not found. Subjects evaluable for TI are defined as subjects who have achieved TI, will not achieve TI in their parent study, or completed their parent study.
Error! Reference source not found. Denominator based on the number of subjects evaluable for TI.

Numbers are [redacted] for subjects ≥12 years of age with a severe non-β^0/β^0 genotype but no meaningful effect of genotype was observed. The severity of non-β^0/β^0 genotype [redacted] on achieving TI in Phase 3 studies: [redacted] TI-evaluable subjects with a non-severe non-β^0/β^0 genotype achieved TI and [redacted] TI-evaluable subjects with a severe non-β^0/β^0 genotype achieved TI. Table 6 presents the characterisation of TI for subjects ≥12 years of age with a non-β^0/β^0 genotype, separated by genotype severity. There are [redacted] in TI characteristics between subjects with severe versus non-severe non-β^0/β^0 genotypes and ranges were [redacted] between these groups (bluebird bio inc, 2019a).

Table 6. Characterisation of Transfusion Independence for Non-β^0/β^0 Subjects ≥12 Years of Age Treated in Phase 3 Studies by Genotype Severity (TI Subjects Only)

[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data as of 02 December 2019 (bluebird bio inc, 2019a)
Abbrev.: DPI, drug product infusion; Hb, haemoglobin; pRBC, packed red blood cell; TI, transfusion independence

In addition, [redacted] subject ≥12 years of age with a severe non-β^0/β^0 genotype who completed the [redacted] Visit but was not yet TI-evaluable ([redacted]) was predicted to achieve TI (see Section 2.2.2). Thus, overall, for subjects with a severe non-β^0/β^0 genotype treated in Phase 3 studies, [redacted] ([redacted]) of non-β^0/β^0 subjects ≥12 years of age who have completed at least their [redacted] Visit have either achieved TI ([redacted]) or are predicted to achieve TI ([redacted]) (bluebird bio inc, 2019a).

Table 7 presents pharmacodynamic parameters for treated subjects ≥12 years of age with a non-β^0/β^0 genotype at [redacted], separated by genotype severity (bluebird bio inc, 2019a).

Table 7. PB VCN, HbA^{T87Q}, and Unsupported Total Haemoglobin Values at [redacted] for Non-β^0/β^0 Subjects ≥12 Years of Age Treated in Phase 3 Studies by Genotype Severity (Subjects who Completed the Month 6 Visit)

[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data as of 02 December 2019 (bluebird bio inc, 2019a)
Abbrev.: Hb, haemoglobin; HbA^{T87Q}, haemoglobin containing $\beta^{A\text{-}T87Q}$-globin; PB VCN, peripheral blood vector copy number
[redacted] **Error! Reference source not found.**Unsupported total Hb level is defined as the total Hb measurement level without any acute or chronic pRBC transfusions within 60 days prior to the measurement date.

As for TI achievement and characteristics, subject numbers are [redacted] of genotype was observed in this analysis of pharmacodynamic parameters and ranges were [redacted] between groups.

4. Summary of Efficacy Data for Non-β^0/β^0 Subjects ≥12 Years of age Treated in Phase 1/2 Studies HGB-204 and HGB-205

Clinical data for subjects treated in Phase 1/2 Studies HGB-204 and HGB-205 are available in the SmPC (Zynteglo SmPC, 2019) and efficacy data for transfusion independence, transfusion reduction, and total Hb are presented below.

Twenty-two subjects with TDT ≥12 years of age have been treated with Zynteglo in Phase 1/2 Studies HGB-204 (N=18) and HGB-205 (N=4), of whom 14 had a non-β^0/β^0 genotype (N=10, HGB-204; N=4, HGB-205). All subjects completed HGB-204 and HGB-205 and enrolled for long-term follow-up in Study LTF-303. The median (min, max) duration of follow-up was 40.48 (29.3, 58.6) months. All subjects remain alive at last follow-up.

Of the 14 non-β^0/β^0 subjects ≥12 years of age treated in Phase 1/2 studies, 11/14 (78.6%, 95% CI 49.2%-95.3%) achieved TI by Month 24. Among these 11 subjects who have achieved TI, the median (min, max) weighted average Hb during TI was 10.51 (9.3, 13.2) g/dL. All subjects who have achieved TI at any time have maintained TI at Month 30 with a min, max duration of TI of 21.2+, 56.3+ months (N=11). The median (min, max) time to last pRBC transfusion was 0.46 (0.2, 5.8) months following Zynteglo infusion.

Figure 6. Duration of transfusion and transfusion-free periods in non-β^0/β^0 Subjects ≥ 12 Years of Age (Studies HGB-204 and HGB-205)

[redacted]

Data as of 12 June 2019 (bluebird bio Inc, 2019b)
Includes data through last available visit (including visits in Study LTF-303 as applicable)

In the three subjects who did not achieve TI, reductions of 100%, 86.9% and 26.8% in transfusion volume requirements and of 100%, 85.3% and 20.7% in transfusion frequency were observed between Month 6 through Month 24 visit when compared to their pre-study levels of pRBC transfusions. These [redacted] subjects who did not achieve TI included the [redacted] subjects with a severe non-β^0/β^0 genotype who were treated in the Phase 1/2 studies ([redacted] with an IVS-I-110/IVS-I-110 genotype in Study HGB-205 and [redacted] with an IVS-I-5/IVS-I-5 genotype in Study HGB-204, who [redacted]). This observation is related to the fact that the [redacted] in Phase 3, the [redacted] of HbA^{T87Q} achieved resulted in the observation that [redacted] attained in subjects and the subjects' ability to achieve TI as discussed in Section 3.

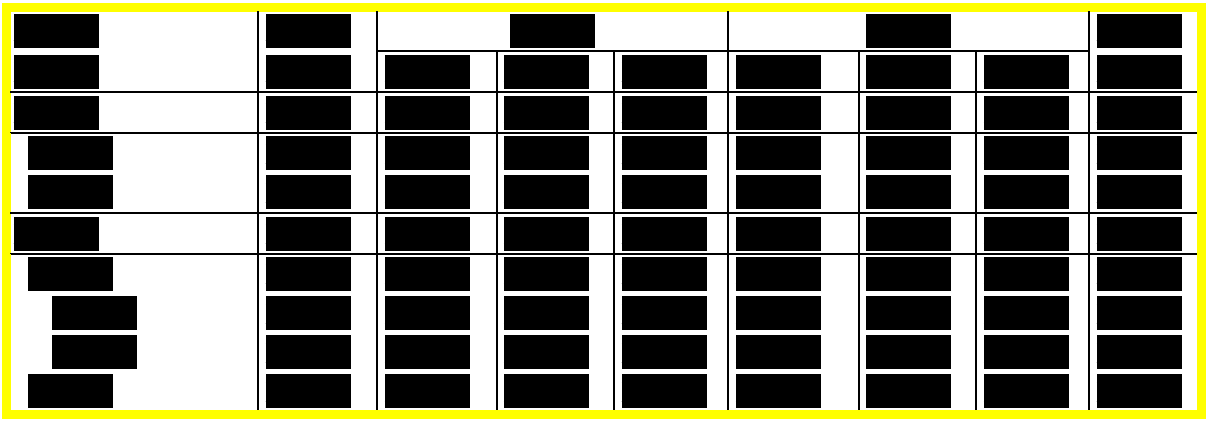
In Phase 1/2 studies, the median (min, max) total Hb at Month 6 for subjects who had not received a transfusion for the prior 60 days was 10.60 (7.6, 13.4) g/dL (N=11). Unsupported total Hb remained stable at Month 24 with a median (min, max) of 10.60 (8.8, 13.7) g/dL (N=12) and at Month 36 with a median (min, max) of 11.30 (7.8, 13.5) g/dL (N=11).

These results demonstrate the durability of response out through Month 60 post drug product infusion (longest follow-up for subjects treated in a Phase 1/2 study) and continue to support the therapeutic concept that a one-time infusion with Zynteglo can result in lifelong, potentially curative, benefit for patients with TDT.

5. Overall Summary of Transfusion Independence

Zynteglo has demonstrated clear and clinically meaningful benefit in subjects with TDT, with the great majority of subjects achieving or predicted to achieve TI, across all phases of clinical studies.

Table 8. Evaluation of Transfusion Independence for Non-β^0/β^0 Subjects ≥12 Years of Age (TP)

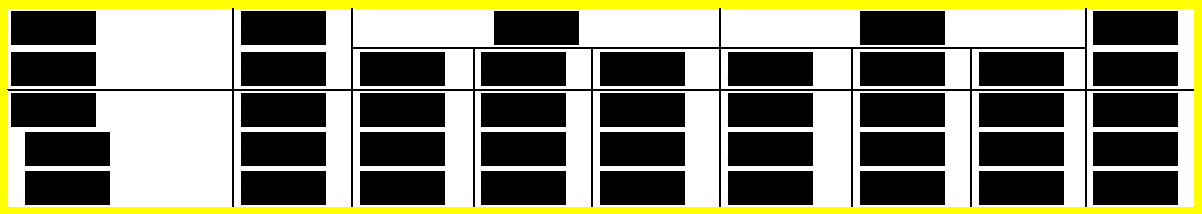


Error! Reference source not found.Subjects evaluable for TI are defined as subjects who have achieved TI, will not achieve TI in their parent study, or completed their parent study.

Error! Reference source not found.Denominator based on the number of subjects evaluable for TI.

Error! Reference source not found.Denominator based on number of subjects who are evaluable for TI prediction.

Table 9. Overall Proportion of Non-β^0/β^0 Subjects ≥12 Years of Age Who Have Achieved TI or Are Predicted to Achieve TI (TP)



Error! Reference source not found. Subjects evaluable for TI are defined as subjects who have achieved TI, will not achieve TI in their parent study, or completed their parent study.
Error! Reference source not found. Subjects evaluable for TI prediction if they are not yet evaluable for TI but have available Month 6 HbAT87Q or total Hb data.
Error! Reference source not found. Denominator based on the number of subjects evaluable for TI or evaluable for TI prediction.

6. Summary of Safety

A summary of safety data is provided below for all subjects of all ages with TDT treated with Zynteglo across all studies in the Zynteglo clinical development program, including Phase 1/2 Studies HGB-204 and HGB-205, Phase 3 Studies HGB-207 and HGB-212, and long-term follow-up Study LTF-303. As of 26 August 2019, subjects with TDT have been treated with Zynteglo, aged years (non-β^0/β^0 and β^0/β^0).

All treated subjects had successful neutrophil engraftment, with median (min, max) day of neutrophil engraftment on (N=). of these subjects also achieved platelet engraftment, with median (min, max) day of platelet engraftment calculated to be Day . treated subject who had not yet achieved platelet engraftment as of 26 August 2019 achieved platelet engraftment on based on information in the safety database as of 29 November 2019.

Results of integration site analyses (ISA) , and there was derived from BB305 lentiviral vector.

There have been to the safety profile of Zynteglo for the overall population of subjects with TDT or for non-β^0/β^0 subjects ≥12 years of age. As of 29 November 2019, SAEs with underlying TDT or the known side effects of the procedures and pharmacotherapy that are entailed in the mobilisation, apheresis, and conditioning pretreatment. The benefit-risk profile for the Zynteglo treatment regimen

7. References

BLUEBIRD BIO INC 2019a. 2nd December 2019 TLFs for HGB-207, HGB-212 and LTF-303.

BLUEBIRD BIO INC 2019b. June 2019 integrated TLFs for HGB-204, HGB-205, HGB-207 and LTF-303.

BORGNA-PIGNATTI, C. & GALANELLO, R. 2009. The thalassemias and related disorders: quantitative disorders of haemoglobin synthesis. *In:* GREER, J. P. (ed.) *Wintrobe's Clinical Hematology, Edition 12.*

CAO, A. & GALANELLO, R. 2010. Beta-thalassemia. *Genet Med,* 12**,** 61-76.

GALANELLO, R. & ORIGA, R. 2010. Beta-thalassemia. *Orphanet Journal of Rare Diseases,* 5**,** 11-11.

ZYNTEGLO SMPC 2019. EMA SmPC Zynteglo.

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

Clarification question: patient numbers

September 2020

1. Please provide the following with references/source details/assumptions made wherever possible (in a short standalone Word document, with confidentiality marking as appropriate):

Expected number of patients:

- who would be tested each year
- the subsequent number of those tested who were found to be eligible for Zynteglo treatment
- If these numbers aren't available, then
    - the expected incident number of patients each year
    - the current prevalent patients

Response:

Expected number of patients who would be tested/year and the subsequent number of those tested who were found to be eligible for Zynteglo treatment (i.e. non-β0):

To be eligible for treatment with Zynteglo, patients with TDT need to be 12 years or older, not have access to a matched related donor and not have a β0/ β0 genotype. In addition, patients must be fit to undergo the treatment.

Issue 8 in the NICE Technical Report states: “A commissioning expert in the area explained that ‘the testing required to diagnose the specific genotype of a patient’s thalassemia is part of the pathway of care for all patients, which is being reinforced through the designation of specialist centres following the national service review for haemoglobinopathy services. This is coming into place across the country and is already routinely undertaken as part of the initial diagnosis process in many specialist clinics, so there will not be additional genetic testing required for the incident population. However, there will be a requirement for genetic testing of the prevalent population who have not previously been tested to enable access to this technology.’”

We therefore understand that with evolving NHS clinical practice, genotype testing is carried out routinely for incident patients and clinicians can request genotype testing for prevalent patients being managed in specialist units. Therefore, we expect any prevalent patient being considered for treatment with Zynteglo to be tested as part of routine care and eligible patient numbers are best estimated from prevalent and incident patient calculations. We provided full details of our estimates for prevalent and incident patients in our response to clarification question A20 (November 2019).

NICE National Institute for Health and Care Excellence

Technical engagement response form

Zynteglo for treating transfusion-dependent beta-thalassaemia [ID968]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm** on **Thursday 26 March 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Cell and Gene Therapy Catapult**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Non-reference case discount rate	
Is there any evidence on projected life expectancy for people with transfusion-dependent beta-thalassaemia (TDT) treated optimally with current management strategies and therapies?	
Should 3.5% or 1.5% be used as the discount rate for costs and quality-adjusted life years (QALYs) in this appraisal?	In two recent publications first by Sculpher and Palmer* (The Centre for Health Economics at University of York) and subsequently by Boyson and Watson** (Centre for Health Technology Evaluation at NICE) the difference between NICE's methods and those proposed in the Treasury's Green Book relating to discounting in economic appraisal is acknowledged; and in the latter it is reported that the topic will receive considerable attention in the upcoming NICE methods review. NICE generally requires a 3.5% annual discount rate on costs and health outcomes. However, the Green Book recommends a discount rate of 1.5% per annum on health outcomes. Discounting disproportionately impacts the benefits of therapies with high upfront costs but longer-term benefits (such as ATMPs which is why the NICE Regenerative Medicine Study in 2016 highlighted the need for further consideration on reducing the discount rate to 1.5%). Given that long-term evidence on sustainability of effect is very difficult to generate in time for launch (without delaying patient access significantly), traditional assessment frameworks could penalise ATMP companies for the lack of such evidence at the time of HTA. Where the uncertainty over value claims is considered significant, performance-based managed entry arrangements could be leveraged; this is particularly important for ATMPs where manufacturing costs are considerably greater than traditional medicines, therefore their commercial viability is at substantial risk when simple discount patient access schemes together with the 3.5% discount rate on long term health outcomes (in economic appraisals) are used as means to deal with uncertainty. *Sculpher, M., Palmer, S. After 20 Years of Using Economic Evaluation, Should NICE be Considered a Methods Innovator?. *PharmacoEconomics* **38,** 247–257 (2020)

	Boyson, M., Watson, I. Reflections on NICE's Uptake of New Methods: Past, Present, and the 2020 Review. PharmacoEconomics **38, 243–245 (2020)
Issue 2: Utilities	
Is the use of utility scores from vignette studies instead of health-related quality of life (HRQoL) data from Zynteglo clinical trials appropriate for some of the utility inputs in the model? Is the HRQoL data from the clinical trials generalisable to that seen in NHS practice?	
Have management of TDT and iron chelation practices drastically changed in terms of outcome and patient disutility over the last 35 years? Should the disutility for the transfusion-dependent state in the model be based on the mean utility of all patients ≥16 years in the chart review, or the re-analysis using only those patients in the chart review dataset aged 12 to 35 years without co-morbidities already being modelled?	
What is the potential HRQoL impact of infertility after myeloablative conditioning? Should this be accounted for in the analysis, or removed due to lack of data specific to this clinical scenario?	
Should the HRQoL impact from any subcutaneous chelation therapy during the iron normalisation period be taken into account for people who become transfusion-independent after receiving Zynteglo treatment?	

Should the whole-population published dataset be used for the adjustment of utilities to take into account natural decline in HRQoL over time, or the subset excluding people who have existing/previous health problems?	
Issue 3: Baseline characteristics of modelled population	
Is 20% a plausible proportion of people in the UK with TDT who have hypogonadism? Should hypogonadism be reflected in the baseline population entering the model?	
Should the mean patient weight from the chart review be used in the model, or the ERG's age category-specific body weight approach instead?	
Is it anticipated that any patients aged 35 years or over would be treated with Zynteglo in the NHS? Is the efficacy evidence for Zynteglo generalisable to the anticipated UK population? As the efficacy evidence from the Zynteglo trials is limited to a specific age range, should the evidence coming from the UK chart review also be limited to match this age range?	
Issue 4: Underrepresentation of population with severe non-β^0/β^0 genotypes	
What proportion of the UK TDT population have a non-β^0/β^0 genotype?	
What proportion of people with TDT who might be eligible for Zynteglo have a severe non-β^0/β^0 mutation?	

Should the proportion of the modelled patient population with a severe non-β^0/β^0 mutation be increased from the company's base case value?	
Issue 5: Iron overload treatment, iron normalisation and residual risk of developing iron-overload complications	
Is combination chelation therapy used more in current clinical practice than previously? If so, will this trend continue? Should the analysis take this into account? What proportion of patients receive at least two oral chelation therapies in practice?	
Is an iron normalisation period of 4, 5, 7 or 10 years plausible for patients who become transfusion-independent after Zynteglo treatment? Does this normalisation period apply to all patients who become transfusion-independent?	
Are iron-overload complications still a risk after transfusion independence is reached, due to iron overload damage which occurred prior to Zynteglo treatment?	
Will people who come off chelation therapy after transfusion independence or transfusion reduction is reached still have cardiac iron? How is this raised cardiac iron likely to impact their health over time?	
Issue 6: Unknown long-term outcomes – relapse (late graft failure), initial (primary) engraftment failure and mortality	
Is there any evidence to support the idea that the therapeutic effect of Zynteglo may not be lifelong? Should the analysis incorporate a percentage of patients relapsing after initially successful treatment	

with Zynteglo, and if so, is one of the ERG's scenarios appropriate?	
Should primary engraftment failure be taken into account in the model? If so, what percentage of patients receiving Zynteglo but experiencing this engraftment failure would be plausible? What is a plausible mortality rate associated with this engraftment failure?	
Is there any up to date data on the mortality of transfusion-dependent patients, particularly UK-specific? What is a plausible mortality rate for people in this health state?	
Issue 7: Generic drug acquisition costs	
Should prices for 3 of the generic products in the treatment process (busulfan, ursodeoxycholic acid and desferrioxamine) come from eMIT or BNF?	
Issue 8: Genotyping, other testing the company will pay for, and impact on the NHS	
Where in the treatment pathway would current and future patients undergo genotype testing? How much does genotype testing for beta-thalassemia cost? What resources does this use (including staff time)?	
What additional infrastructure and training requirements could be considered for this appraisal?	
How much would the additional testing that the company has stated they will incur, cost, and how much NHS staff involvement would this require?	

Issue 9: Myeloablative conditioning	
What drugs do patients receive as part of myeloablative conditioning ahead of Zynteglo? Would a particular regimen be used in most centres in the UK? What constitutes current UK clinical practice in terms of drugs given for myeloablative conditioning ahead of allogeneic haematopoietic stem cell transplant?	
What is the impact on the cost-effectiveness results of taking into account other drugs given as part of a myeloablative conditioning regimen (not just busulfan)?	
What is the mortality associated with myeloablative conditioning in the UK?	
Issue 10: Number of patient profiles modelled	
How many profiles should be simulated in the model, in order to reach a stable ICER and overcome random noise and first order uncertainty?	

Single Technology Appraisal (STA)

Betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia

ERG addendum: review of company's response to technical engagement

Produced by CRD Technology Assessment Group, University of York, Heslington, York YO10 5DD

Date 18th September 2020

Source of funding

This report was commissioned by the NIHR HTA Programme as project number 18/54/11

Declared competing interests of the authors

None

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted], all depersonalised data (DPD) are [redacted].

Table of Contents

Table of Tables

Table of Figures

1 Overview

This addendum to the Evidence Review Group (ERG) report presents the ERG's critique of the additional evidence provided by bluebird bio in their responses to the technical engagement questions which emerged from the NICE technical report.

The NICE technical engagement questions covered 10 key issues for consideration. The technical report provided the technical team's preliminary scientific judgement on each issue. The company's responses to the technical engagement questions indicated that they accepted the technical team's preliminary judgement on Issue 7, along with some aspects of Issue 2 and 3. The company's responses to all the other issues are discussed in Section 2.

Issue	Resolved?
Issue 1: Non-reference case discount rate	
1. Is there any evidence on projected life expectancy for people with TDT treated optimally with current management strategies and therapies?	Unresolved
2. Should 3.5% or 1.5% be used as the discount rate for costs and QALYs in this appraisal?	Unresolved
Issue 2: Utilities	
3. Is the use of utility scores from vignette studies instead of HRQoL data from betibeglogene autotemcel clinical trials appropriate for some of the utility inputs in the model? Is the HRQoL data from the clinical trials generalisable to that seen in NHS practice?	Unresolved
4. Have management of TDT and iron chelation practices drastically changed in terms of outcome and patient disutility over the last 35 years? Should the disutility for the transfusion-dependent state in the model be based on the mean utility of all patients ≥16 years in the chart review, or the re-analysis using only those patients in the chart review dataset aged 12 to 35 years without co-morbidities already being modelled?	Unresolved
5. What is the potential HRQoL impact of infertility after myeloablative conditioning? Should this be accounted for in the analysis, or removed due to lack of data specific to this clinical scenario?	Unresolved
6. Should the HRQoL impact from any subcutaneous chelation therapy during the iron normalisation period be taken into account for people who become transfusion-independent after receiving betibeglogene autotemcel treatment?	Resolved
7. Should the whole-population published dataset be used for the adjustment of utilities to take into account natural decline in HRQoL over time, or the subset excluding people who have existing/previous health problems?	Unresolved
Issue 3: Baseline characteristics of modelled population	
8. Is 20% a plausible proportion of people in the UK with TDT who have hypogonadism? Should hypogonadism be reflected in the baseline population entering the model?	Resolved
9. Should the mean patient weight from the chart review be used in the model, or the ERG's age category-specific body weight approach instead?	Resolved
10. Is it anticipated that any patients aged 35 years or over would be treated with betibeglogene autotemcel in the NHS? Is the efficacy evidence for betibeglogene autotemcel generalisable to the anticipated UK population? As the efficacy evidence from the betibeglogene autotemcel trials is limited to a specific age range, should the evidence coming from the UK chart review also be limited to match this age range?	Unresolved

Issue 4: Underrepresentation of population with severe non-β^0/β^0 genotypes	
11. What proportion of the UK TDT population have a non-β^0/β^0 genotype?	Unresolved
12. What proportion of people with TDT who might be eligible for betibeglogene autotemcel have a severe non-β^0/β^0 mutation?	Unresolved
13. Should the proportion of the modelled patient population with a severe non-β^0/β^0 mutation be increased from the company's base case value?	Unresolved
Issue 5: Iron overload treatment, iron normalisation and residual risk of developing iron-overload complications	
14. Is combination chelation therapy used more in current clinical practice than previously? If so, will this trend continue? Should the analysis take this into account? What proportion of patients receive at least two oral chelation therapies in practice?	Resolved
15. Is an iron normalisation period of 4, 5, 7 or 10 years plausible for patients who become transfusion-independent after betibeglogene autotemcel treatment? Does this normalisation period apply to all patients who become transfusion-independent?	Unresolved
16. Are iron-overload complications still a risk after transfusion independence is reached, due to iron overload damage which occurred prior to betibeglogene autotemcel treatment?	Unresolved
17. Will people who come off chelation therapy after transfusion independence or transfusion reduction is reached still have cardiac iron? How is this raised cardiac iron likely to impact their health over time?	Unresolved
Issue 6: Unknown long-term outcomes – relapse (late graft failure), initial (primary) engraftment failure and mortality	
18. Is there any evidence to support the idea that the therapeutic effect of betibeglogene autotemcel may not be lifelong? Should the analysis incorporate a percentage of patients relapsing after initially successful treatment with betibeglogene autotemcel, and if so, is one of the ERG's scenarios appropriate?	Unresolved
19. Should primary engraftment failure be taken into account in the model? If so, what percentage of patients receiving betibeglogene autotemcel but experiencing this engraftment failure would be plausible? What is a plausible mortality rate associated with this engraftment failure?	Unresolved
20. Is there any up to date data on the mortality of transfusion-dependent patients, particularly UK-specific? What is a plausible mortality rate for people in this health state?	Unresolved
Issue 7: Generic drug acquisition costs	
21. Should prices for 3 of the generic products in the treatment process (busulfan, ursodeoxycholic acid and desferrioxamine) come from eMIT or BNF?	Resolved
Issue 8: Genotyping, other testing the company will pay for, and impact on the NHS	
22. Where in the treatment pathway would current and future patients undergo genotype testing? How much does genotype testing for beta-thalassemia cost? What resources does this use (including staff time)?	Resolved
23. What additional infrastructure and training requirements could be considered for this appraisal?	Resolved
24. How much would the additional testing that the company has stated they will incur, cost, and how much NHS staff involvement would this require?	Unresolved
Issue 9: Myeloablative conditioning	
25. What drugs do patients receive as part of myeloablative conditioning ahead of betibeglogene autotemcel? Would a particular regimen be used in most centres in the UK? What constitutes current UK clinical practice in terms of drugs given for myeloablative conditioning ahead of allogeneic haematopoietic stem cell transplant?	Resolved
26. What is the impact on the cost-effectiveness results of taking into account other drugs given as part of a myeloablative conditioning regimen (not just busulfan)?	Resolved

27. What is the mortality associated with myeloablative conditioning in the UK?	Resolved
Issue 10: Number of patient profiles modelled	
28. How many profiles should be simulated in the model, in order to reach a stable ICER and overcome random noise and first order uncertainty?	Unresolved

2 Description and critique of additional evidence

2.1 Issue 1: Non-reference case discount rate

Life expectancy for people with TDT

The ERG report detailed the lack of relevant evidence on the current life expectancy of patients with TDT identified in the company's systematic literature review (ERG Report, Section 4.3.4 and 5.2.6.5). In response to the Technical Report, the company presented results of an analysis of hospital episodes statistics (HES) data which demonstrated that between 2007 and 2016, the in-hospital death rate in patients diagnosed with TDT between April 2005 and March 2006 was [redacted]%, higher than the age/sex-adjusted general population rate of [redacted]%.

The ERG does not consider the comparison of in-hospital death rates with general population death rates (i.e. not in hospital) to be meaningful as patients in hospital are more likely to die by definition, whether or not they have TDT. The meaningful comparison would be the mortality rates of TDT patients eligible for betibeglogene autotemcel (i.e. over 12 years old and fit enough to receive treatment) compared to the mortality rate in similar individuals in the general population.

The company also state that the median age at death in TDT patients in this study was 45 years.[1] It is not immediately clear how this was estimated, but the study also found that of the 612 TDT patients in the cohort, 557 were known to be alive in 2018, and 38 had died. This suggests that the median age of death was estimated from those who already died, which tautologically implies that the median age of death in those who die earlier in the follow up period is low.

Additional studies highlighted by the company in response to the Technical Report,[2, 3] present limited follow-up data and enrol patients managed with different techniques and chelators, increasing the uncertainty in the relevance of these studies to the current decision problem.

The ERG considers that there may be a reduction in life expectancy of TDT patients treated optimally with current management strategies and therapies, but evidence presented is not convincing and it is impossible to quantify the amount of reduction in life expectancy.

The most appropriate discount rate

Regarding whether a 3.5% or 1.5% discount rate should be used, the company's response to the Technical Report maintains that a 1.5% rate for costs and QALYs is appropriate. The ERG does welcome the company's inclusion of a 3.5% discount rate in the sensitivity analyses of the economic model provided in their response to the Technical Report, albeit 3.5% is not included in the company's base case. The NICE methods guide[4] states that in the case of non-reference discounting, *"sensitivity analyses using rates of 1.5% for both costs and health effects may be presented alongside the reference-case analysis"*. Therefore, the ERG presents the probabilistic results of the company's base case ICER using a 3.5% discount rate (see Section 3.1).

The company asserts that the criteria for non-reference case discounting are met. The criteria, as outlined in the NICE methods guide[4] are:

> *In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs.*

The assertion that TDT patients would otherwise die without betibeglogene autotemcel is not based on appropriate evidence. The limited and outdated evidence available in fact lends weight to the argument that patients do not "otherwise die" without betibeglogene autotemcel as high proportions of patients survived beyond 40 years[2] and 50 years.[3] However, as described above, this evidence should not be used for decision making.

The Royal College of Pathologists and British Society for Haematology stated in their response to the Technical Report that they expect betibeglogene autotemcel will have no impact on length of life compared to current care. Furthermore, in the most recent edition of Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK,[5] it is stated that *"the expectation is that well monitored and chelated patients will have a near normal life expectancy"* (as described in ERG Report, Section 5.2.5.1).

The issue of whether TDT individuals will have a severely impaired quality of life (QoL) is a further area of concerns for the ERG. The ERG does agree with the company that the burden of TDT both in

terms of the potential symptoms of anaemia, TDT complications and the impact of treatment on daily life may impact on QoL. However, as detailed in the ERG report, two studies in the literature derived utilities using EQ-5D and reported values of 0.86[6] and 0.87[7] for those with TDT on chelation therapy. These values suggest that TDT is associated with only a modest reduction in quality of life, and are supported by the analysis of 16-35 year olds with TDT in the Chart Review, whose HRQoL was reported as [redacted] (see ERG Report, Section 5.2.7). The ERG considers that with modern chelation practices and standards of monitoring which minimise adverse events, patients can lead fulfilling lives.

Additional consideration should be given to the QoL of those eligible for betibeglogene autotemcel. Eligible patients will need to be in good enough health to withstand conditioning; betibeglogene autotemcel trials excluded patients with cardiac T2* < 10 msec by MRI and patients with evidence of liver disease. Therefore, treated patients are likely to be suffering less from TDT complications than the general TDT patient population.

Although the ERG recognises that there is some impact of TDT on patients' lives, evidence that their lives are "severely impaired" has not been presented.

The company's assertion that benefits are sustained over a very long period (normally at least 30 years) is a further area of concerns for the ERG. There remains a lack of long-term data to support the assumption that transfusion independence (TI) benefits are life-long, as this depends on *"successful engraftment and achievement of TI"* (as noted by the EMA)[8] for which data on only a limited number of patients are available (see ERG Report, Section 4.2.2.1).

Finally, the company's response to the Technical Report details the company's justification that betibeglogene autotemcel will not commit the NHS to significant irrecoverable costs. The company's response describes the proposed outcomes-based scheme with NICE and NHSE. It is the ERG's understanding that there is no outcomes-based scheme and that the drug acquisition cost (£[redacted]) will be paid at the initiation of treatment. Significant irrecoverable costs could therefore be endured by the NHS should patients fail to achieve and maintain TI.

Given the considerable uncertainty around whether betibeglogene autotemcel meets the criteria for using non-reference case discounting and the potential for committing the NHS to potentially significant irrecoverable costs, the ERG retains the 3.5% discount rate for costs and QALYs in the base case.

2.2 Issue 2: Utilities

2.2.1 Issue 2a: Source of utility values

As data were not reliably collected during the acute period following myeloablative therapy and betibeglogene autotemcel infusion, the utilities from the vignette study may be informative for the purpose of estimating the magnitude of the utility decrement incurred by patients during the acute post-transplant period. Validation against utility studies of other patient groups receiving autologous stem cell transplant would have been useful.

The ERG does not consider the utilities from the vignette study the most appropriate representation of HRQoL associated with TDT at baseline, given the two sources of EQ-5D data available which are taken directly from TDT patients. The NICE methods guide emphasises that HRQoL should be reported directly by patients. In cases where directly collected EQ-5D data are inappropriate for modelling purposes, this must be demonstrated using sufficiently convincing evidence. Quality of life is not objective, and an unaffected member of the general public cannot understand how an individual with a chronic condition values their own QoL in response to changes in disease activity and treatment, based only upon vignettes. Adapting to life with a chronic condition is a feature common to many chronic diseases assessed by NICE, and is explicitly captured in how EQ-5D is valued.

Given the similarity of the HRQoL of the trial population at baseline ([redacted]) with the equivalent population in the Chart Review ([redacted]), it does not appear reasonable for the company to dismiss both these patient-derived values as unrealistic. In their response, the company describes the difficulties of living with TDT and how patients sought alternative treatment in betibeglogene autotemcel to support the inclusion of an additional HRQoL decrement in the model. However, the ERG highlights that the trial and Chart Review values already represent a utility decrement of ~ 0.1 compared to the general population values for this age group. This is not an insubstantial utility decrement, and thus may already encompass the reduced baseline HRQoL compared to the general population as described by the company. As patients and their families will be fully aware of the natural history and the potential impact on their future quality of life, this is likely to be a motivating factor for seeking gene therapy, rather than being indicative of the current burden of the disease on their health.

2.2.2 Issue 2b: Utilities across different age groups

The ERG does not agree that the full chart review population utility data should be considered in the manner suggested by the company. It is inappropriate to include the HRQoL of patients aged 35 to > 50 to estimate the utility of those aged < 35 at baseline. It is also inappropriate to reduce the utility of younger patients at baseline to reflect increased disease burden in later life. If the company believes utilities should be lower in older patients to reflect a purported rapid decline in HRQoL, then the economic model should be adapted to include such a decline.

The structure of the company's model allows patients to incur utility decrements as and when they suffer from events and complications related to their TDT. If the company believes these are not sufficiently representative of the reductions in QoL patients might suffer due to the onset of other complications, then these additional reductions should be included in the model.

Secondly, the lower QoL observed in older patients is not necessarily suggestive of the sudden severe decrease in quality of life suggested by the company. Given the new treatments developed in the last 10-15 years and improvements in blood product screening, the ERG would not expect patients initiating treatment today to have a utility of 0.33 by the age of 50 because of the progress made in disease management.

The company updated their base-case analysis in recognition of the following points made in the ERG report concerning utilities:

- The company agree with NICE and the ERG that there are limited data to support the modelled infertility decrement and support the removal of this decrement in the model analyses. This has been removed from the company's base-case.
- The company accept that the HRQoL impact (utility decrement) for subcutaneous chelation therapy during the iron normalisation period should be taken into account and have incorporated this revision in their base-case.
- The company have implemented the whole population utility dataset in the revised base case analysis (i.e. not using the dataset for those in perfect health)

2.3 Issue 3: Baseline characteristics of modelled population

Hypogonadism

The company agree with the 20% figure as plausible for the proportion of individuals in the UK with TDT who have hypogonadism and incorporated this into their base-case.

Patient weight

The company agreed that the model should better reflect the variation in body weight by age for individuals with TDT in the UK, and incorporated this into their base case analysis. Patient weight is used as an input in the model in order to calculate the costs of chelating agents which involve weight-based dosing.

Patient age

In the company's original response to the technical report, they asserted that evidence from the full UK chart review should be used in the model, rather than being limited to match the age range treated to date within clinical trials. This has an impact on how utility values are estimated (see Issue 2) and the distribution of chelation agents. As previously stated, the full chart review includes a number of

patients who would not be eligible for treatment with betibeglogene autotemcel, including those with high levels of cardiac iron. However, the company then amended their response and resubmitted their analysis using the distribution of chelation therapies that has been age-matched to the clinical trials, while maintaining their previous position on the estimation of utilities (discussed in Issue 2). The acceptance of the rationale for one assumption but not the other creates an inconsistency in the approach to modelling the patient population. Moreover, the inclusion of the age-matched utilities in the analysis results in a higher ICER, while the inclusion of age-matched distribution of chelation agents results in a lower ICER for betibeglogene autotemcel.

While the marketing authorisation of betibeglogene autotemcel allows for patients over the age of 35 to be potentially eligible for treatment if they are sufficiently well, there are no patients in the clinical studies over the age of 35. The eligibility criteria for HGB-204 and HGB-205 excluded patients over 35 years, suggesting that it was felt to be unlikely that there would many eligible patients over 35 years old. In addition, while patients over 35 may receive betibeglogene autotemcel, they would be eligible only if they are sufficiently fit. Therefore, their quality of life and chelation treatment is more likely to reflect those of the younger population of the chart review, rather than the older population of the chart review who would be less likely to be sufficiently fit to be eligible for betibeglogene autotemcel. Therefore, the outcomes in patients over 35 years of age remains an unresolved issue.

2.4 Issue 4: Underrepresentation of population with severe non-β^0/β^0 genotypes

The ERG notes the more recent trial data submitted by the company, particularly with respect to the issue of transfusion independent effects across non-severe and severe subjects. Although the use of a more recent manufacturing process *may* improve results in subjects with severe genotypes – when compared to the results seen in similar patients in the earlier HGB-204 trial (see ERG report p37) – there is nevertheless still much uncertainty about this. This is primarily because:

- The new data are very limited: so far, only two subjects with severe non-β^0/β^0 genotypes and with mature enough data to evaluate TI, have been recruited to HGB-212.
- Optimisation of the drug product manufacturing process may not yet be fully resolved i.e. the optimum process may have not been reached yet, as indicated in the CS when describing the manufacturing processes used in the two ongoing trials (see p38, CS): [redacted].

It is also worth remembering that the primary outcome of study HGB-212 is transfusion reduction (in HGB-207 it was transfusion independence), suggesting lower expectations of a TI response in patients with severe genotypes. In light of these points, the ERG does not agree with the company's statement

that *"The proportion of the modelled patient population with a severe non-β0/β0 mutation should not be adjusted because TI effects are assumed to be the same across non-severe and severe subjects"*.

Additionally, the company's data provided in response to this issue shows there may be [redacted] of severe genotype patients in the UK. This value is higher than the assumption explored in the ERG's scenarios, where the proportion with severe non-β^0/β^0 mutations is [redacted] to 28%, which had the effect of decreasing the modelled probability of transplant success from [redacted] to [redacted].

2.5 Issue 5: Iron overload treatment, iron normalisation and residual risk of developing iron-overload complications

Iron overload treatment

After expert consultation, the Company agree with the ERG and have updated the model to reflect current iron chelation practices in the UK, where a proportion of patients receive two oral agents as well as a combination of oral and parenteral therapy.

Iron normalisation

The company presented a summary of the values of iron parameters over time in patients who had achieved TI (Table 3 of TE response). This summary assesses [redacted] patients, whereas [redacted] patients (n=[redacted] from studies HGB-204, and n=[redacted] from HGB-205) had been assessed in the original CS. The ERG assumes this discrepancy is due to the addition of TI patients from study HGB-207 (n=[redacted]), who at the time of submission did not have data mature enough to allow for their inclusion. However, this is not clear. Additionally, the population of patients with available assessments decreases after the initial follow-up at 12 months. The company does not provide an explanation for this, but the ERG assumes this could be attributed to either a loss of patients to follow-up or patients not having reached the later follow-up times.

The company reports the proportion of patients who have T2* > 20 ms. The company's definition of "normal" cardiac iron levels is inconsistent through their submission, with a cut-off of T2* > 40 ms originally stated as normal, while elsewhere, "normal" levels of T2* are described as being above 20 ms. Clinically, patients are at a lower risk of developing cardiac complications relating to iron overload when T2* > 20 ms, but this risk is non-zero, as acknowledged by the company with the implementation of a low risk of developing cardiac complications for those with T2* > 20. In order to determine how iron levels may have normalised over the trial period, it would be necessary to estimate the proportion who achieved T2* > 40 ms, and their change from baseline. Notably, there was one patient who had a poorer T2* at 48 months compared to baseline (pg 105 of CS).

Further, it is possible that the patients in the trials represented a more favourable population than would be eligible for treatment with betibeglogene autotemcel. The eligibility criteria is T2* > 10 ms;

however, the lowest T2* value for a patient enrolled in the trials was reported as 27 (Table 32 of CS), with at least one patient already within the "normal" range. However, it does appear that there would be existing patients with a T2* value of between 10 ms and 20 ms (i.e. "medium" iron risk) who would be sufficiently fit to be eligible for betibeglogene autotemcel. From the company's analysis of their Chart Review data, [redacted] of individuals aged 12 to 35 and without comorbidities that would preclude treatment with betibeglogene autotemcel, had a T2* value > 10 ms, so would be eligible for treatment based on these parameters. As such, it is possible that patients in the trials for betibeglogene autotemcel are not typical of the eligible population and may achieve cardiac iron normalisation more quickly than a typical patient, due to their reduced levels at baseline.

For liver iron normalisation, the company showed that of the [redacted] TI patients, [redacted] had reached LIC < 7mg/g at 12 months but patients with longer follow-up ([redacted]) maintained this at 5 years. Therefore, the company agreed with the ERG value of 5 years to normalisation.

The company state that the serum ferritin normalisation is of limited clinical relevance, but agree with the ERG value of 5 years to normalisation as well. The impact of iron overload in serum ferritin remains in the economic model.

Residual risk of iron overload complications

The company adjusted the model to account for the underlying risk due to irreversible damage caused by iron overload prior to "normalisation" by lowering the annual cardiac complication rate for TI patients with 'normalised' iron by a factor of [redacted]. It is unclear how this factor was estimated. The company undertook an analysis of HES data for TDT patients and estimated the 10-year rate of cardiac disease. For those aged 10 to 34, [redacted] had 'any' cardiac disease, and [redacted] had arrhythmias which the company considered to be attributable to irreversible damage from cardiac iron overload. The ERG considers that further clinical input would be valuable to confirm whether arrythmias are attributable to irreversible damage, and whether there are any other cardiac issues that should also be considered.

2.6 Issue 6: Unknown long-term outcomes – relapse (late graft failure), initial (primary) engraftment failure and mortality

Possibility of relapse and late graft failure

The Company assert that there is no evidence to support the idea that the therapeutic effect of betibeglogene autotemcel may not be lifelong, and that primary engraftment failure should not be implemented in the model.

The ERG considers that there is uncertainty about the longevity of the effect of betibeglogene autotemcel, despite the fact that, so far, no TI patients have relapsed. This uncertainty is based both on the small numbers of patients treated to date, and the results for the HGB-207 patient who [redacted]

[redacted] The implication of this is that there exists some degree of clinical heterogeneity of response in patients who achieve many consecutive transfusion-free months. The ERG therefore considers that the treatment effect longevity issue will only become clearer after longer-term follow up of the full cohort of recruited patients (two trials are still ongoing).

Primary engraftment failure

With regard to primary engraftment failure, the ERG note that uncertainty may arise from the relatively small numbers used to assert 100% engraftment success (n=86 across all trials). The ERG also notes that the SmPC states that the collection of back-up cells may be needed for rescue treatment if there is: 1) compromise of betibeglogene autotemcel after initiation of myeloablative conditioning and before betibeglogene autotemcel infusion, 2) primary engraftment failure, or 3) loss of engraftment after infusion with betibeglogene autotemcel. The fact that back-up cells are stored for the possibility of 2) or 3) occurring would suggest that the perceived risk of these events is not zero.

Mortality

The ERG considered the source the company used for SMR rates for people who have TDT to be outdated, of limited generalisability, and not relevant to current NHS practice due to improved iron chelation and patient monitoring. In their response, the company accepted the ERG and NICE's preferred SMR of 2.

The ERG considers the assumptions of no relapse for TI patients and no engraftment failure to be unreasonable as they both remain highly uncertain, and that the impact of each assumption on the cost-effectiveness of betibeglogene autotemcel should be explored.

2.7 Issue 7: Generic drug acquisition costs

The company accepted the use of eMIT prices in the economic analysis and implemented the most recent (4th March 2020) eMIT database prices in their updated analyses.

2.8 Issue 8: Genotyping, other testing the company will pay for, and impact on the NHS

In their original submission, the company noted that the cost of genotype testing would be incurred by the company. However, in their response to the technical report, the company responded that this was

in fact an error, and that genotyping for patients with TDT is funded by the NHS. The company considered that genotype testing is currently part of routine practice, and so it does not constitute an additional cost relating to the introduction of betibeglogene autotemcel in the NHS.

The ERG agrees that there will not be additional genetic testing required for the incident population as this is now routinely undertaken as part of the initial diagnosis process, but there will be a requirement for genetic testing of the prevalent population who have not previously been tested to enable access to this technology.

The UK Thalassemia Society's Standards (2016) note that globin genotyping should be done at diagnosis, as well as at diagnosis of patients who arrive in the UK after being treated abroad.[5] Expert submissions to NICE state that not all prevalent cases are tested routinely, and so there will be some prevalent cases of TDT who may require genotyping. However, it is unclear whether the genotyping of already diagnosed patients is widespread in standard of care, or whether these patients would only be genotyped when being assessed for eligibility for betibeglogene autotemcel.

Due to the uncertainty in whether genotyping is already widespread for prevalent patients, the ERG implemented a scenario where these costs are incurred by the NHS, i.e. the cost of genotyping all prevalent patients who are considered for betibeglogene autotemcel treatment (Table 1).

Data provided by the company indicates that there are currently [redacted] prevalent patients with TDT in the UK, of which [redacted] are over the age of 12. The company estimates that [redacted] of adolescent patients do not have access to a matched donor, and that 10% of patients are expected to be unfit to undergo myeloablative conditioning given the risk for short and long-term toxicity. Recent market research conducted with TDT patients in England, suggests [redacted]% of patients would accept a referral to a transplant physician and wish to move forward with betibeglogene autotemcel. This results in approximately [redacted] prevalent patients with TDT of unknown genotype who are eligible and willing to receive treatment with betibeglogene autotemcel. Estimates from NHS England place this figure at around [redacted] patients. The cost of testing has been reported by one UK laboratory as £250 per test,[9] which results in a total cost of screening all prevalent patients ranging from [redacted] to [redacted]. These costs represent an upper limit of the potential screening costs, as there may be some patients who were already genotyped.

The proportion of TDT patients who had the non-β^0/β^0 genotype was reported by the company as being 51%, which means that approximately two TDT patients would need to be screened in order to identify one with the non-β^0/β^0 genotype. This estimate results in approximately 107 total identified patients within the prevalent population, equivalent to approximately £490 per identified prevalent patient.

Table 1 Cost of screening prevalent patients

	Parameter	Source
Prevalent patients over the age of 12	[redacted]	bluebird bio (HES analysis)
Access to matched donor (adolescents)	[redacted]	bluebird bio (HES analysis)
Willingness for treatment	[redacted]	bluebird bio
Fitness for treatment	90%	bluebird bio
Total eligible and willing prevalent population	[redacted]	-
Unit cost of screening	£250	Oxford Molecular Diagnostics Centre[9]
Total cost of screening	[redacted]	-
Proportion of TDT who are non-β^0/β^0	51%	bluebird bio (pg 19 of CS)
Total identified prevalent patients	[redacted]	-
Cost per identified prevalent patient	[redacted]	-

Regarding the potential cost of screening incident patients, the ERG has estimated the additional cost per patient should the cost of screening be incurred as a result of the introduction of betibeglogene autotemcel (Table 2). Assuming that patients born in the UK receive routine screening at birth, it is only necessary to apply this cost to incident patients who were not screened at birth e.g. they were born outside the UK where screening is not routine practice. There is very little available data on the incidence of TDT in the UK, and it is particularly difficult to determine the proportion of incident patients each year who were not born in the UK and may not have received genotype testing at birth, or who were born in the UK before genetic testing at birth became widespread. National screening report data provided by the company indicate that there are [redacted] incident TDT patients each year, but these figures do not account for immigration cases and European patients traveling to England for treatment. Presumably they also do not capture patients born within the UK who were not screened. The ERG has assumed that 10% of the total incident patients eligible for betibeglogene autotemcel would not have a known β^0/β^0 genotype, which captures those who are incident to the UK but not diagnosed at birth and are otherwise fit for betibeglogene autotemcel, or are immigration cases and European patients. Further clinical input on this proportion is required. However, it is worth noting that the costs of testing are low, and would form a very small proportion of total costs associated with betibeglogene autotemcel, so it is unlikely that this inclusion of this cost will have a substantial impact to the cost-effectiveness results.

Table 2 Screening costs for incident patients

	Parameter	Source
Incident patients per year*	[redacted]	bluebird bio (NHS screening data)
Willing and eligible incident patients per year*	[redacted]	See assumptions above

Proportion of incident patients not captured in screening data (i.e. of unknown genotype)	10%	Assumption
Incident patients of unknown genotype (per year)	[redacted]	
Unit cost of screening	£250	Oxford Molecular Diagnostics Centre[9]
Total cost of screening incident TDT patients of unknown genotype	[redacted]	
Proportion of TDT who are non-β^0/β^0	51%	bluebird bio (pg 19 of CS)
Cost per identified patient	£[redacted]	

*Excluding immigration cases and European patients

As such, the need for testing would result in an additional £[redacted] per incident patient of unknown genotype, or an additional £[redacted] per incident patient of all those eligible and willing for betibeglogene autotemcel treatment each year. The impact to the results of the addition of this cost is negligible.

Regarding the infrastructure and training costs, the company's response to technical engagement highlights the NHS's pre-existing expertise and the company's work with NHSE's Commissioning Teams. Despite this, the submission from NHS England states that there may be significant impact on specific services that would be part of the pathway for the delivery of this technology, including *"the preparation of patients, the transfer of the medicine from the manufacturer"*. There will likely also be some training and infrastructure costs borne by the NHS to accommodate genotyping. The magnitude of such costs, however, are unknown, particularly since the level of uptake remains uncertain. The omission of these costs from the economic model likely results in the underestimation of the true ICER. Yet, since the number of patients eligible for betibeglogene autotemcel is expected to be small (between [redacted] and [redacted] prevalent patients, and [redacted] annual incident patients), the ERG does not consider the magnitude of the bias on the ICER to be substantial.

In response to the question of how much NHS staff involvement there will be in the testing costs incurred by the company, it was stated that those wishing to be included in the registry will require one additional blood test per year for 15 years. To allow for this, the company's newly submitted economic model includes the cost of one consultant-led appointment per year for 15 years.

The ERG considers this a reasonable addition to the model to capture the additional cost, although they were unable to identify the addition of the unit cost in the model itself. However, the ERG agrees with the company that this cost is likely a conservative estimate of the additional cost, potentially overestimating the actual cost of testing.

2.9 Issue 9: Myeloablative conditioning

In the NICE technical report, the issue was raised as to the use of pre-transplant conditioning with a busulfan regimen and whether it was standard practice for the UK. The company consulted with

transplant physicians in the UK who concur that single-agent busulfan will be used for conditioning in UK clinical practice, given that there is no evidence to support use of an alternative conditioning regimen. Therefore, no other drugs for myeloablative conditioning need to be considered in the model.

The NICE technical team also questioned whether there was a mortality risk associated with myeloablative conditioning. The company noted that no treatment-related mortality has been observed in the betibeglogene autotemcel clinical studies to date and that the mortality risk associated with busulfan conditioning at the dose ranges described in the SmPC is expected to be negligible. The ERG noted that the SMR for patients achieving transfusion independence after betibeglogene autotemcel treatment was greater than 1 to reflect the potential mortality impact of busulfan conditioning (page 176 of CS).

2.10 Issue 10: Number of patient profiles modelled

The economic model runs a number of 'profiles', which are hypothetical patients defined by age and gender, with each profile weighted to reflect the distribution of patients in the eligible treatment population. The company's model estimated results generated by 600 simulated profiles based on gender and three age bands. The ERG observed that the ICER only appeared to stabilise between 5,000 and 10,000 profiles. The ERG remained unclear on why the model estimated a higher ICER with a greater number of profiles, and which was the most appropriate method to generate results. It may be more appropriate to generate many more hypothetical patient profiles than this, in order to 'smooth out' variation in the ICER arising from random noise.

The reasons provided by the company for selecting the number of iterations is a pragmatic decision based on computation time. The ERG noted that the time taken to generate 5,000 iterations was approximately 15 minutes, which the ERG does not regard as prohibitive (although not ideal). Further, the ERG does not consider a longer model runtime as a sufficient reason for producing a less robust analysis. The runtime for DICE models was acknowledged prior to this appraisal, and this should have been factored into the decision to use this modelling approach.[10] After 5,000 iterations the ICER increased by 7.7%, and if betibeglogene autotemcel is costed to meet the threshold, this 7.7% is important.

In their response, the company stated that stability was defined *"in terms of the purpose of the analyses, that is, reaching a binary decision based on where the ICER lies relative to NICE thresholds"*, and *"should not be defined in terms of a small change in the ICER but in terms of the decision relevant range"*. That is, although the ICER values may be numerically different, the change in ICER would not lead to a different decision. However, the ICERs for the company's presented base-case analysis are on the

boundaries of cost-effectiveness (Table 3), and any fluctuations in the estimate of the ICER may indeed cause it to go over the cost-effectiveness threshold.

The company maintains that the stochastic uncertainty is sufficiently minimised with 600 profiles. However, no explanation was provided as to why the company's analysis, based on simulated 600 profiles, generated a lower ICER than analyses run with a higher number of iterations.

A potential solution is to run the base case scenario using a higher number of iterations, and any analyses to explore the impact of changing key parameter values can be taken on the model with 600 iterations. However, this assumes that the relative impact of the new scenario relative to the baseline scenario is constant and does not vary when the number of iterations is changed, which may not be the case.

3 Results

3.1 Company analysis

Modelling assumptions

In response to the NICE Technical Report and following the technical engagement teleconference, the company updated their base case cost-effectiveness analyses.

The following ERG and/or NICE preferred assumptions are incorporated within the revised model:

- Whole population set from Ara and Brazier for age-adjusting utilities,
- HRQoL impact of subcutaneous chelation therapy for transfusion-independent patients in iron normalization period,
- 20% hypogonadism in baseline population,
- Age category-specific (paediatric and adult) mean body weights used in the model,
- Chelation therapy distribution adjusted to match change in clinical practice including proportion of patients being treated with two oral chelation agents (i.e. both deferasirox and deferiprone),
- SMR of 2.0 applied for patients in the model who are transfusion-dependent and don't develop cardiac complications,
- eMIT-sourced prices used for bulsulfan, ursodeoxycholic acid and desferrioxamine (updated to March 2020 eMIT prices),
- Removal of the disutility for infertility.

In addition, the following assumptions have been altered in the revised model:

- Iron normalisation period for people who become transfusion independent after betibeglogene autotemcel,
- Cardiac complications from iron overload damage prior to betibeglogene autotemcel modelled for people who become transfusion-independent.

The company maintain their original position on the following assumptions, which differ to the ERG and NICE's preferred assumptions:

- 1.5% discount rate in the base case analyses,
- Company's preferred approach for calculating the utility decrement for the transfusion-dependent state, using the analysis from the full Chart Review population.

Deterministic results

The updated base case results for betibeglogene autotemcel versus transfusions and iron chelation therapy (SoC) are shown in Table 3, which includes the updated patient access scheme (PAS). The PAS comprised a simple discount, resulting in a list price of [redacted].

In the company's analysis, betibeglogene autotemcel is associated with 11.16 incremental QALYs and incremental costs of [redacted] per patient, compared to chronic transfusions and iron chelation. The resulting ICER is [redacted] per additional QALY gained.

Table 3 Company base case results with PAS (based on 600 iterations of the model)

Technologies	Total			Incremental			ICER
	Costs	LYs*	QALYs	Costs	LYs*	QALYs	
SoC	[redacted]	42.41	17.40	-	-	-	-
Betibeglogene autotemcel	[redacted]	55.00	28.56	[redacted]	12.59	11.16	[redacted]
Abbreviations: PAS, patient access scheme; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care							

* undiscounted life years

Due to the uncertainty in the modelling sampling procedure and its impact on the ICER, the results of the company base case in which results are based on 5,000 modelled profiles, rather than 600 as in the company base-case analysis are presented in Table 4.

Increasing the number of 5,000 profiles increases the ICER of the company base case from £[redacted] per QALY to [redacted]. While this is a relatively small increase in the ICER, it has the impact of moving it above the cost-effectiveness threshold.

Table 4 Company base case results with PAS (based on 5,000 iterations of the model)

Technologies	Total			Incremental			ICER
	Costs	LYs*	QALYs	Costs	LYs*	QALYs	
SoC	[redacted]	41.97	17.20	-	-	-	-
Betibeglogene autotemcel	[redacted]	54.48	28.19	[redacted]	12.51	10.98	[redacted]
Abbreviations: PAS, patient access scheme, ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

* undiscounted life years

Probabilistic results

PSA was conducted using 300 patient profiles and 1,000 iterations. The results of the PSA are presented in Table 5, Figure 1 and Figure 2. Under the company's preferred assumptions, the likelihood of betibeglogene autotemcel being cost-effective is [redacted] and [redacted] at thresholds of £20,000 and £30,000 per QALY respectively.

Table 5. Results of the company's probabilistic sensitivity analysis results (with PAS)

	Total		Incremental		ICER
Technologies	**Costs**	**QALYs**	**Costs**	**QALYs**	
SoC	[redacted]	17.60	-	-	-
Betibeglogene autotemcel	[redacted]	28.27	[redacted]	10.56	[redacted]

Figure 1 Cost-effectiveness plane (company base case analysis, with PAS)

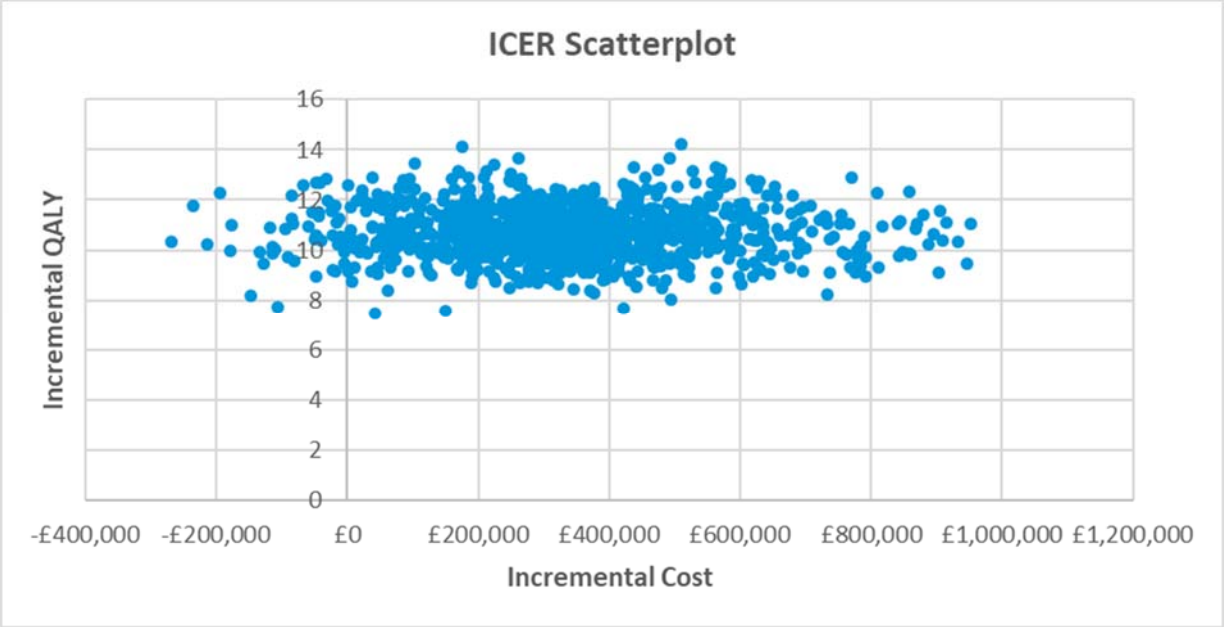
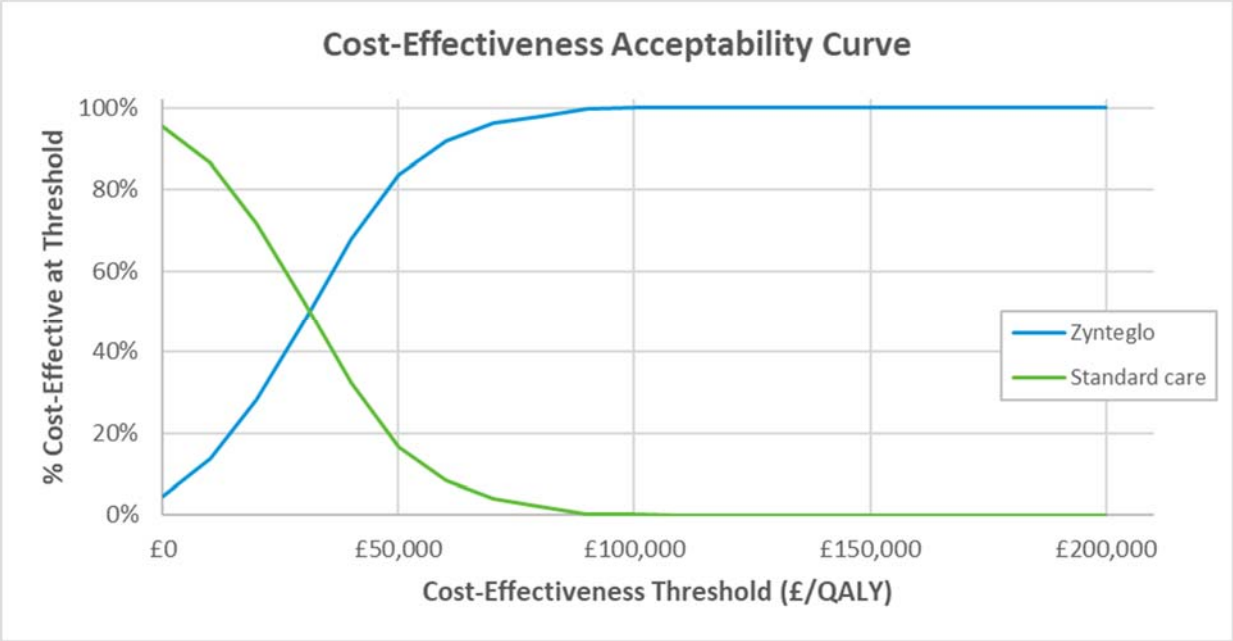


Figure 2 Cost-effectiveness acceptability curve (company base case analysis, with PAS)



3.2 ERG analysis

Deterministic results

The results of the ERG alternative base case analysis are presented in Table 6, which includes the updated PAS for betibeglogene autotemcel.

In the ERG's analysis, betibeglogene autotemcel is associated with 3.05 incremental QALYs and incremental costs of [redacted] per patient, compared to chronic transfusions and iron chelation. The resulting ICER is [redacted] per additional QALY gained.

Table 6 ERG base case results, using 600 profiles (with PAS)

Technologies	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
SoC	[redacted]	37.79	15.48	-	-	-	-
Betibeglogene autotemcel	[redacted]	53.40	18.53	[redacted]	3.05	[redacted]	[redacted]
Abbreviations: PAS, patient access scheme, ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

* undiscounted life years

The results of the ERG's scenarios on their base case are in Table 7. Notably, with the application of the company's preferred discount rate of 1.5%, betibeglogene autotemcel cannot be considered cost-effective, with an ICER of [redacted]. With the application of a lower value for the SMR for transfusion dependent patients, the ICER increased to [redacted] and in a scenario where both assumptions were incorporated the ICER rose to [redacted].

Table 7 Scenario analyses on the ERG base case analysis, using 600 profiles (with PAS)

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
Scenario: 1.5% discount rate							
SoC	[redacted]	37.79	21.07				
Betibeglogene autotemcel	[redacted]	53.40	27.78	[redacted]	6.71	[redacted]	[redacted]
Scenario: SMR of 2 for transfusion dependent patients							
SoC	[redacted]	42.41	16.14				
Betibeglogene autotemcel	[redacted]	53.89	18.62	[redacted]	2.48	[redacted]	[redacted]
Scenario: 1.5% discount rate and SMR of 2 for transfusion dependent patients							
SoC	[redacted]	42.41	22.54				
Betibeglogene autotemcel	[redacted]	53.89	27.96	[redacted]	5.42	[redacted]	[redacted]

* undiscounted life years

The results of the scenario analyses on the ERG base case, based on 5,000 patient profiles, are presented in Table 8.

Table 8 Scenario analyses on the ERG alternative base case analysis, using 5,000 profiles (with PAS)

Intervention	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
ERG base case analysis, based on 5,000 model profiles							
SoC	[redacted]	37.34	15.32				
Betibeglogene autotemcel	[redacted]	52.60	18.25	[redacted]	2.93	[redacted]	[redacted]
Scenario: ERG base-case analysis with 1.5% discount rate, based on 5,000 model profiles							
SoC	[redacted]	37.34	20.81				
Betibeglogene autotemcel	[redacted]	52.60	27.28	[redacted]	6.47	[redacted]	[redacted]
Scenario: ERG base-case analysis with SMR of 2 for transfusion dependent patients, based on 5,000 model profiles							
SoC	[redacted]	41.97	15.99				
Betibeglogene autotemcel	[redacted]	53.13	18.35	[redacted]	2.35	[redacted]	[redacted]
Scenario: ERG base-case analysis with 1.5% discount rate and SMR of 2 for transfusion dependent patients, based on 5,000 model profiles							
SoC	[redacted]	41.97	22.30				
Betibeglogene autotemcel	[redacted]	53.13	27.47	[redacted]	5.17	[redacted]	[redacted]

* undiscounted life years

Probabilistic results

PSA was conducted on the ERG's preferred base case analysis, using 300 patient profiles and 1,000 iterations. The results of the PSA are presented in Table 9, Figure 3 and Figure 4. Betibeglogene autotemcel has a [redacted] probability of being cost-effective at a threshold of £30,000 per QALY, and standard care is associated with a higher probability of cost-effectiveness than betibeglogene autotemcel for all thresholds up to [redacted] per QALY.

Table 9 Results of the ERG's probabilistic sensitivity analysis results (with PAS)

	Total		Incremental		ICER
Technologies	**Costs**	**QALYs**	**Costs**	**QALYs**	
SoC	[redacted]	15.77	-	-	-
Betibeglogene autotemcel	[redacted]	18.57	[redacted]	2.80	[redacted]

Figure 3 Cost-effectiveness plane (ERG base case analysis, with PAS)

Figure 4 Cost-effectiveness acceptability curve (ERG base case analysis, with PAS)

3.3 NICE preferred base case analysis

Deterministic analysis

The results of the analysis under the NICE-preferred assumptions, including the new PAS discount, are in Table 10.

Table 10 Results of the analysis under NICE preferred assumptions (with PAS)

Technologies	Total			Incremental			Change from company base case ICER
	Costs	LYs*	QALYs	Costs	QALYs	ICER	
Scenario with 600 profiles							
SoC	[redacted]	42.41	16.14	-	-	-	-
Betibeglogene autotemcel	[redacted]	45.39	16.82	[redacted]	0.68	[redacted]	[redacted]
Scenario with 5,000 profiles							
SoC	[redacted]	41.97	15.99	-	-	-	
Betibeglogene autotemcel	[redacted]	44.84	16.60	[redacted]	0.61	[redacted]	[redacted]
Abbreviations: PAS, patient access scheme, ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

* undiscounted life years

Probabilistic analysis

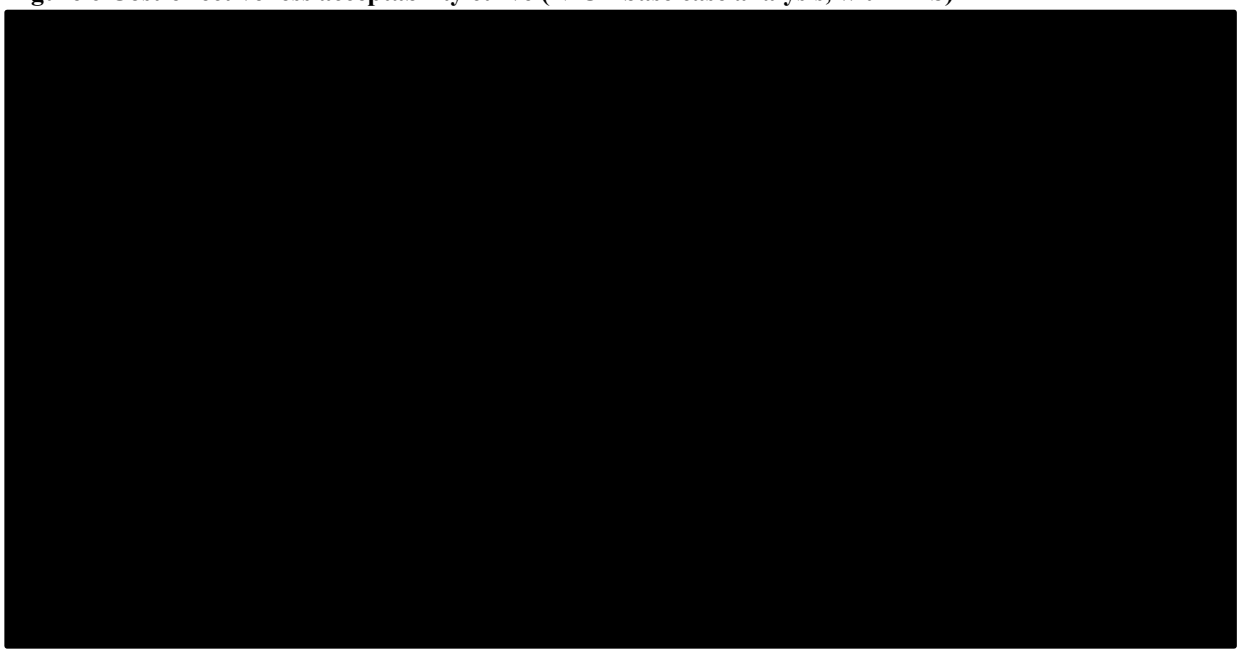
PSA was conducted on NICE's preferred base case analysis, using 300 patient profiles and 1,000 iterations. The results of the PSA are presented in Table 11, Figure 5 and Figure 6. In NICE's preferred scenario, betibeglogene autotemcel [redacted].

Table 11 Results of NICE's probabilistic sensitivity analysis results (with PAS)

	Total		Incremental		ICER
Technologies	Costs	QALYs	Costs	QALYs	
SoC	[redacted]	16.32	-	-	-
Betibeglogene autotemcel	[redacted]	16.99	[redacted]	0.67	[redacted]

Figure 5 Cost-effectiveness plane (NICE base case analysis, with PAS)

Figure 6 Cost-effectiveness acceptability curve (NICE base case analysis, with PAS)



References

1. Jobanputra M, Paramore C, Laird SG, McGahan M, Telfer P. Co-morbidities and mortality associated with Transfusion Dependent Beta-thalassaemia Patients in England: A 10-Year Retrospective Cohort Analysis - Draft manuscript. Draft manuscript.

2. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2008;**10**:42.

3. Weidlich D, Kefalas P, Guest JF. Healthcare costs and outcomes of managing β-thalassemia major over 50 years in the United Kingdom. *Transfusion* 2016;**56**:1038-45.

4. National Institute of Health and Care Excellence (NICE). *Guide to the methods of technology appraisal 2013*. London: NICE; 2013.

5. United Kingdom Thalassaemia Society. *Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK, 3rd Edition*. London: United Kingdom Thalassaemia Society; 2016.

6. Javanbakht M, Keshtkaran A, Shabaninejad H, Karami H, Zakerinia M, Delavari S. Comparison of Blood Transfusion Plus Chelation Therapy and Bone Marrow Transplantation in Patients with β-Thalassemia: Application of SF-36, EQ-5D, and Visual Analogue Scale Measures. *Int J Health Policy Manag* 2015;**4**:733-40.

7. Seyedifar M, Dorkoosh FA, Hamidieh AA, Naderi M, Karami H, Karimi M, et al. Health-Related Quality of Life and Health Utility Values in Beta Thalassemia Major Patients Receiving Different Types of Iron Chelators in Iran. *Int J Hematol Oncol Stem Cell Res* 2016;**10**:224-31.

8. Zynteglo SmPC. bluebird bio, Zynteglo 1.2 20 × 106 cells/mL dispersion for infusion. Draft Summary of Product Characteristics. 2019.

9. Oxford Molecular Diagnostics Centre, Oxford University Hospitals NHS Foundation Trust. *National Haemoglobinopathy Reference Laboratory. Information for users*. Oxford: Oxford Molecular Diagnostics Centre; 2020.

10. Moller J, Davis S, Stevenson M, Caro JJ. Validation of a DICE simulation against a discrete event simulation implemented entirely in code. *Pharmacoeconomics* 2017;**35**:1103-9.

-Author name in bold denotes the presenting author
-Asterisk * with author name denotes a Non-ASH member
denotes an abstract that is clinically relevant.

denotes that this is a recommended PHD Trainee Session.

denotes that this is a ticketed session.

153 Long-Term Efficacy and Safety of Betibeglogene Autotemcel Gene Therapy for the Treatment of Transfusion-Dependent β-Thalassemia: Results in Patients with up to 6 Years of Follow-up

Program: Oral and Poster Abstracts
Type: Oral
Session: 112. Thalassemia and Globin Gene Regulation
Hematology Disease Topics & Pathways:
Biological, Diseases, thalassemia, Therapies, Hemoglobinopathies, gene therapy, stem cells

Saturday, December 5, 2020: 12:00 PM

Janet L. Kwiatkowski, MD, MSCE[1,2], Mark C. Walters, MD[3], Suradej Hongeng, MD[4], Franco Locatelli, MD, PhD[5], John E.J. Rasko, BSc, MBBS, PhD[6,7,8*], Marina Cavazzana, MD, PhD[9,10,11], Ying Chen, PhD[12*], Richard A. Colvin, MD, PhD[12*] and Alexis A. Thompson, MD[13,14]

[1]Division of Hematology, Children's Hospital of Philadephia, Philadelphia, PA
[2]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA
[3]UCSF Benioff Children's Hospital Oakland, Oakland, CA
[4]Mahidol University, Ramathibodi Hospital, Bangkok, Thailand
[5]Department of Pediatric Hematology/Oncology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy
[6]Royal Prince Alfred Hospital, Camperdown, Australia
[7]Sydney Medical School, University of Sydney, Sydney, Australia
[8]Gene and Stem Cell Therapy Program, Centenary Institute, Camperdown, Australia
[9]Necker Children's Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France
[10]IMAGINE Institute, Université Paris Descartes, Sorbonne Paris Cité, Paris, France
[11]Biotherapy Clinical Investigation Center, Groupe Hospitalier Universitaire Ouest, Paris, France
[12]bluebird bio, Inc., Cambridge, MA
[13]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL
[14]Northwestern University Feinberg School of Medicine, Chicago, IL

Introduction

The goal of betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) gene therapy in patients with transfusion-dependent β-thalassemia (TDT) is lifelong, stable production of functional adult hemoglobin (Hb) sufficient for transfusion independence (TI) and reduction in ineffective erythropoiesis. 60 patients with TDT have been treated with beti-cel across 2 completed phase 1/2 studies (HGB-204, HGB-205) and in 2 ongoing phase 3 studies (HGB-207, HGB-212). After 2-yrs of follow-up in these 4 parent studies, patients were invited to enroll in a 13-yr long-term follow-up study, LTF-303 (NCT02633943). Interim results of patients enrolled in LTF-303 with follow-up as long as 6 years are reported.

Methods

Autologous CD34+ cells were transduced with BB305 lentiviral vector and infused into patients following single-agent, pharmacokinetic-adjusted busulfan myeloablation. Transduction in the phase 3 studies used a refined manufacturing process compared to the phase 1/2 studies. LTF-303 assessments include Hb, peripheral blood vector copy number (PB VCN), assessment of erythropoiesis and iron overload, quality of life, adverse events (AEs), replication-competent lentivirus (RCL), and insertion site analysis. Data are analyzed as median (min – max).

Results

As of 3 March 2020, all 32 patients who completed the parent studies (age at enrollment in parent study: 20 [12 – 35] yrs) enrolled in LTF-303 (22 treated in phase 1/2 studies, 10 treated in phase 3 studies). Follow-up post-infusion was 49.1 (23.3 – 71.8) months. PB VCN was detected in all patients at last follow-up (Phase 1/2: 0.4 [0.07 – 4.0] c/dg; Phase 3: 2.0 [0.13 – 3.0] c/dg). Gene therapy-derived Hb, HbA^{T87Q}, in patients treated in the phase 1/2 studies was stable over time: 6.4 (0.5 – 10.1), 6.7 (0.4 – 10.1), 6.6 (0.5 – 10.7), and 7.1 (2.8 – 11.2) g/dL at months 24 (n=22), 36 (n=22), 48 (n=22), and 60 (n=10). Median HbA^{T87Q} at month 24 in patients treated in the phase 3 studies was 9.5 (0.9 – 12.4) g/dL (n=10)

Median HbA at month 24 in patients treated in the phase 3 studies was 9.9 (8.9 – 12.4) g/dL (n=10).

Of the 32 patients enrolled in LTF-303, TI (defined as a weighted average Hb ≥9 g/dL without packed red blood cell transfusions for ≥12 months) was achieved in 14/22 (64%) patients treated in phase 1/2 (12 achieved TI during parent study, 2 during LTF-303) and in 9/10 (90%) patients treated in phase 3 (all achieved TI in parent study). All patients remain TI at last follow-up for 39.4 (19.4 – 69.4) months. Weighted average Hb during TI was 10.4 (9.4 – 13.3) and 12.5 (11.9 – 13.5) g/dL in patients treated in the phase 1/2 and phase 3 studies, respectively. In patients who achieved TI in the phase 3 studies, soluble transferrin receptor decreased from 144.1 (65.9 – 235.3) nmol/L at baseline to 54.1 (24.7 – 67.1) nmol/L at Month 24. Patients who achieved TI in HGB-207 had an improved health state today score from 65 – 96 at baseline to 90 – 100 at month 24 (n=8) on the EQ-5D-3L or EQ-5D-Y instrument.

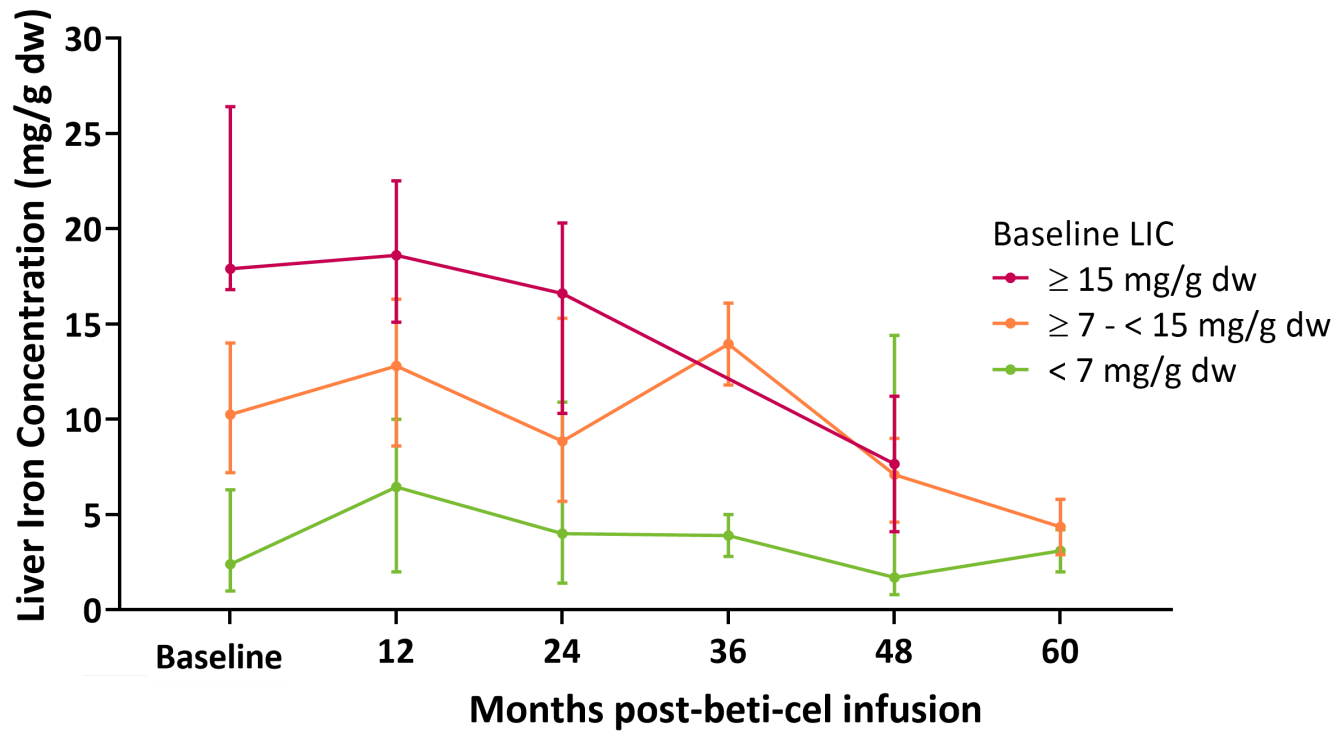
All patients were on iron chelation before beti-cel infusion, but post-infusion, only 26/32 (81%) patients restarted iron chelation; of these, 11 have since discontinued chelation. Phlebotomy was used for iron removal in 7/32 patients (22%; 3 patients treated in phase 1/2, 4 patients treated in phase 3) including 3 patients who also used iron chelation. Following an initial increase in liver iron concentration (LIC) after infusion, LIC in patients who achieved TI decreased, particularly in patients with an elevated baseline LIC (Figure). The median decrease in LIC from baseline to month 48 in patients who achieved TI was a 38% reduction (85% reduction to 269% increase; n=13).

No drug-product-related AEs were reported >2 years post-infusion. Serious AEs during LTF-303 included gonadotropic insufficiency, ectopic pregnancy, gall bladder wall thickening/polyp, bacteremia with neutropenia. and major depression (all n=1). No deaths, RCL, or insertional oncogenesis were reported. Insertion site analysis as assessed every 6 months until month 60 showed unique insertions accounted for <30% of all insertions indicating polyclonal hematopoiesis.

Summary

These results demonstrate the durability and stability of response after beti-cel gene therapy in patients with TDT. Sustained levels of HbA^{T87Q} and effective iron reduction with phlebotomy and/or iron chelation have resulted in improved hematologic parameters and iron burden. The paucity of gene therapy-related AEs observed beyond 2 years post-infusion study suggests a favorable long-term safety profile.

Figure. Liver iron concentration (LIC) over time by baseline value in patients who achieved transfusion independence and enrolled in LTF-303



N	4	4	4	0	2	0
N	6	4	6	2	5	2
N	13	12	13	2	6	2

Disclosures: Kwiatkowski: bluebird bio,Inc.: Consultancy, Research Funding; Terumo Co: Research Funding; Novartis: Research Funding; Sangamo: Research Funding; Celgene: Consultancy; Apopharma: Research Funding; Imara: Consultancy; Agios: Consultancy; BMS: Consultancy. Walters: Editas: Consultancy; AllCells, Inc: Consultancy; Veevo Biomedicine: Consultancy. Locatelli: Bellicum Pharmaceutical: Membership on an entity's Board of Directors or advisory committees; Miltenyi: Speakers Bureau; Medac: Speakers Bureau; Jazz Pharmaceeutical: Speakers Bureau; Novartis: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Amgen: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. Rasko: Novartis: Honoraria; Genea: Other; Imago: Consultancy; Rarecyte: Consultancy, Other; Gene Technology Technical Advisory, OGTR, Australian Government: Other; Advisory Committee on Biologics, Therapeutics Goods Administration, Australian Government: Other; NHMRC Mitochondrial Donation Expert Working Committee: Membership on an entity's Board of Directors or advisory committees; Cure The Future Foundation: Other; FSHD Global Research Foundation; Australian Cancer Research Foundation SAB: Membership on an entity's Board of Directors or advisory committees; bluebird bio, Inc.: Honoraria; Celgene: Honoraria; Pfizer: Honoraria; Cynata: Honoraria; Gilead: Honoraria; Takeda: Honoraria; GSK: Honoraria; CRISPR Therapeutics: Consultancy; Spark: Honoraria. Chen: bluebird bio, Inc.: Current Employment. Colvin: bluebird bio, Inc.: Current Employment, Current equity holder in publicly-traded company. Thompson: Novartis: Consultancy, Honoraria, Research Funding; bluebird bio, Inc.: Consultancy, Research Funding; Biomarin: Research Funding; BMS: Consultancy, Research Funding; Beam: Consultancy; Baxalta: Research Funding; Agios: Consultancy.

See more of: 112. Thalassemia and Globin Gene Regulation
See more of: Oral and Poster Abstracts

Previous Abstract | Next Abstract >>

*signifies non-member of ASH