NICE National Institute for Health and Care Excellence

Part 1 slides for public - redacted

Betibeglogene autotemcel (Zynteglo) for treating transfusion-dependent beta-thalassaemia

Lead team presentation

Lead team: Robert Hodgson, Soo Fon Lim, Malcolm Oswald

ERG: Centre for Reviews and Dissemination and Centre for Health Economics, University of York

Technical team: Gary McVeigh, Amy Crossley, Caron Jones, Linda Landells

Company: bluebird bio

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Key issues unresolved

Issue 1: Should 3.5% or 1.5% be used as the discount rate for costs and QALYs in this appraisal?

Issue 2: Should the company or ERG approach to utilities for people who are transfusion-dependent be used?

Issue 3: Should evidence from full UK chart review be used in the model, or should it be limited to match the efficacy population?

Issue 4: Should the proportion of the modelled patient population with a severe non-β^0/β^0 mutation be adjusted to better match the TDT population in England?

Issue 5: - What should the cardiac iron normalisation period after transfusion independence be in the model?

- What approach to complications from iron overload should be taken in the model?

Issue 6: Should potential for late graft failure/relapse be taken into account?

Issue 10: Should the number of profiles be increased until the ICER becomes stable?

ERG: Evidence Review Group; QALYs: quality-adjusted life years; TDT: transfusion-dependent beta-thalassaemia

Disease overview

- Beta-thalassaemia is an inherited blood disorder caused by a genetic mutation of β-globin (HBB) gene. Leads to reduced production of healthy red blood cells and haemoglobin
- Several different possible genotypes seen in the condition. β^0 = absence of production of β-globin on affected allele, β^+ allele has some residual production. Homozygous genotype (β^0/β^0) results in severe anaemia that requires regular blood transfusion.

1,033 people with TDT in UK

- In transfusion-dependent beta-thalassaemia (TDT), haemoglobin production is so reduced that normal growth and development only achieved by regular red cell transfusions from infancy, leading to excess iron build up in the body
- Iron build up typically treated with ongoing iron chelation therapy (oral and/or subcutaneous)
- 'Iron overload', associated with endocrine conditions (such as hypogonadism, growth delay, infertility), cardiac complications, liver disease
- Some people with TDT eligible for allogeneic haematopoietic stem cell transplantation (HSCT), depends on availability of matched donor, typically only an option for younger patients
- Improvements in iron chelation therapy over recent years means people with TDT have an increased life expectancy

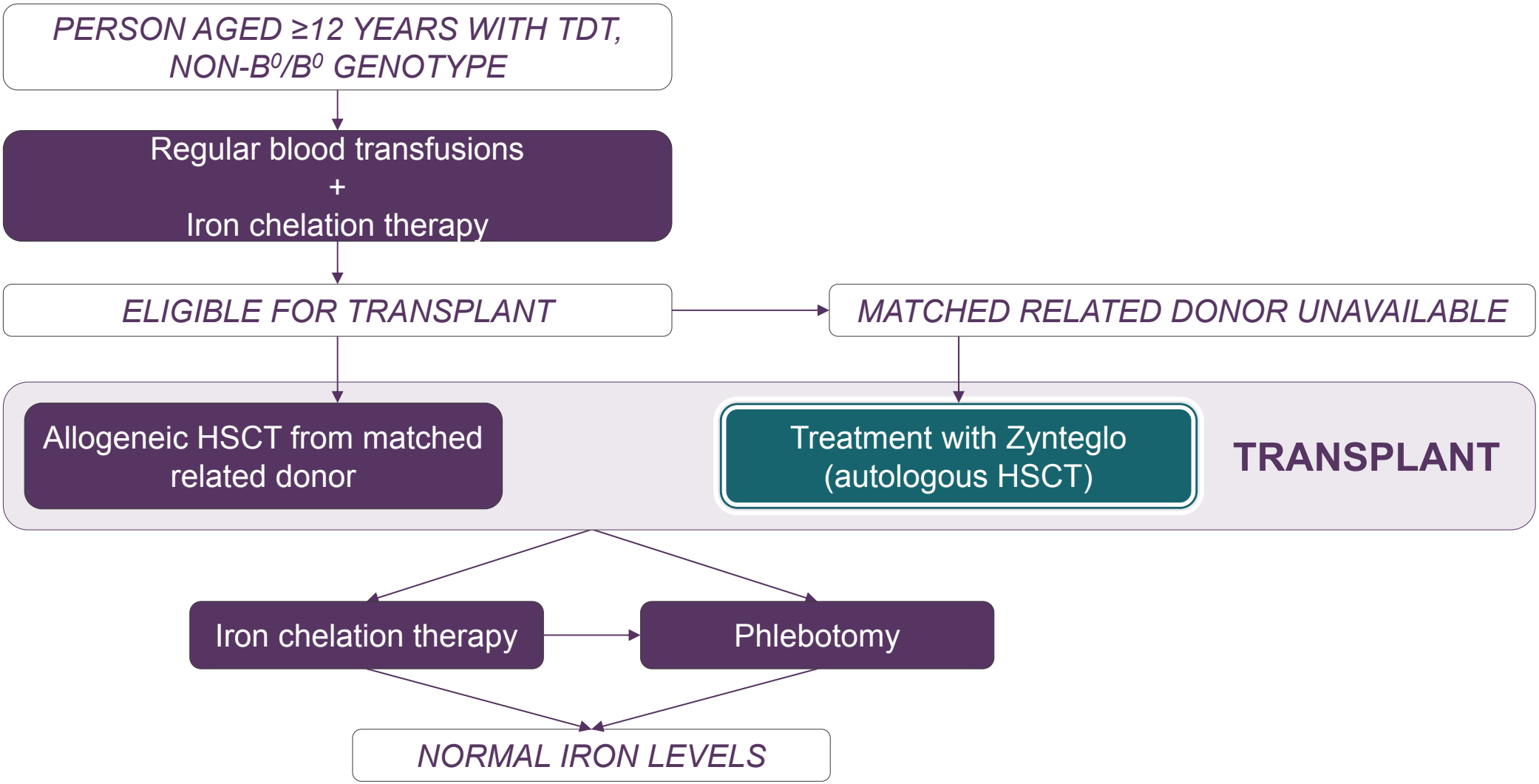
Patient and carer perspectives

- Views presented by United Kingdom Thalassaemia Society, gathered information from 200 patient and carer focus group participants
- ‘Become fully dependent on blood transfusions’, every 2 to 4 weeks, ‘in order to have a normal chance of life’. ‘Unpredictable nature’ of condition, can’t plan for future
- Time off education/work (patient, carer) to meet to daily treatment demands – ‘keeping up with vigorous treatment plans extremely difficult and time consuming’, ‘never-ending’, impacts family life
- ‘Extreme fatigue, exhaustion, breathlessness, palpitations, bone pain, cognitive disturbances, low mood when due for transfusion’
- Iron chelation can result in growth delay, eye and hearing issues, and kidney toxicity if not managed well long term. Difficulty keeping up with daily subcutaneous pump use, ‘quickly run out of injection sites’
- ‘Develop a myriad of secondary conditions’ including cardiac dysfunction, liver and gall bladder disease
- ‘Presently in England only TDT patients <9 years are usually considered for bone marrow transplant’. Unmet need - 90% of patients do not meet current criteria for bone marrow transplants due to not having a suitable match, or age

Clinical perspectives

- Views from 3 consultant haematologists
- Clinically significant response would be ‘correction of anaemia to a level which prevents symptoms and complications and is associated with transfusion independence’, which is the ‘most important outcome’
- ‘Allogeneic HSCT, while curative, has significant risks of morbidity and mortality and is limited by donor availability for people 12-18 years’. ‘Not currently offered to people >18 years in UK’
- ‘Innovative therapy’, ‘potentially curative’, ‘potentially lifesaving’. Would remove risk of graft versus host disease. Potential to be ‘cured from need for regular transfusions and downstream treatments’
- Removal of burden of hospital attendances every 3-4 weeks and constant medication would have significant impact on quality of life. ‘Ongoing outpatient follow up would need to be maintained for monitoring for ongoing efficacy of the treatment and any late effects’
- Some contraindications to Zynteglo treatment e.g. significant cardiac or iron loading. National Haemoglobinopathy Panel recently set up, to consider patient suitability for new treatments and ensure consistency across the country
- Will require a period of intensive inpatient based treatment and increased hospital visits, likely need time off work/education and increased family support. May deter some people, e.g. those in higher education

Treatment pathway



HSCT: haematopoietic stem cell transplantation; TDT: transfusion-dependent beta-thalassaemia

Autologous CD34+ cells encoding βA-T87Q-globin gene (Zynteglo, bluebird bio)

(Conditional) marketing authorisation	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.
Administration	Minimum recommended dose 5.0 $\times 10^6$ CD34+ cells/kg. Should only be administered once. Process: • Administration of mobilising agents, then apheresis to harvest patient's HSCs (≥1 cycles). Back-up collection required. • Pre-treatment myeloablative conditioning with chemotherapy (typically busulfan). • Autologous HSCT - modified stem cells given back to patient via intravenous infusion. Complete treatment process, from mobilisation to end of inpatient stay, lasts 13 to 19 weeks.

Background

Comparator	Supportive care (red cell transfusions, iron chelation)
Clinical trials	3 single arm, single dose studies (HGB-204, HGB-205, HGB-207), approx. 2 years follow up. 24 transfusion-evaluable patients overall, max age 34 years. Evaluable data for patients with non-β^0/β^0 genotypes from HGB-212 became available after original submission. Long term follow up study (LTF-303) ongoing.
Key results	Primary: transfusion independence Secondary: transfusion reduction
Comparison with supportive care	None - patients with TDT receiving supportive care do not spontaneously achieve transfusion independence/significant reductions in transfusion requirements.
Model	Discretely integrated condition event (DICE) simulation
Company ICER	Company base case [redacted]/QALY gained (with 1.5% discount rate and 600 profiles)
Technical team preferred ICER	[redacted]/QALY gained (5,000 profiles)
ERG base case ICER and plausible ERG scenarios	[redacted]/QALY gained (ERG base case, 600 profiles), [redacted]/QALY gained (ERG base case, 5,000 profiles), with scenarios up to [redacted]/QALY gained (5,000 profiles)

Key clinical evidence

At time of company submission, transfusion independence (TI) 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 packed red blood cell transfusion was [redacted]. Median (min, max) time to reach the definition of TI was 15.70 (14.9, 20.9) months.

Later data cut now available (presented at ASH December 2020) appears to show a lower proportion of patients achieving TI, rather than 20/24 (83%) that is applied in the model.

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
2 (partially)	• Utility impact of infertility resulting from myeloablative conditioning ahead of Zynteglo treatment not well understood and poorly captured with EQ-5D • Utility decrement for subcutaneous chelation therapy during iron normalisation period should be taken into account • Disagreement over dataset to use when adjusted utilities for natural decline in HRQoL over time	Company agreed with NICE and ERG, limited data to support modelled decrement, have removed. Has incorporated utility decrement for subcutaneous chelation. Has implemented whole population utility dataset in revised analysis (rather than subset excluding people with existing health problems)	Removing disutility associated with infertility from myeloablative conditioning increases company's base case ICER by a small amount. With lifetime time horizon and resulting implausible utility values in company's analysis compared to people of the same age in general population without TDT, the whole-population dataset from Ara and Brazier should be used for age-adjusting utilities (particularly as this approach has been used in other NICE appraisals)	Company ✓ ERG ✓
3 (partially)	• Hypogonadism is common in people with TDT, iron build up and resulting complications may have occurred before Zynteglo could be given • Using same weight for all patients may be inappropriate in terms of resource use	Company incorporated 20% figure as baseline population value for proportion of people in UK with TDT who have hypogonadism. Company have implemented category-specific body weight approach	Using age category-specific body weight may better reflect the resource use in both arms of the model, particularly in light of the long time horizon, and patients will usually spend the majority of their time in the model as an adult rather than paediatric patient	Company ✓ ERG ✓

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HRQoL: health-related quality of life

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
5 (partially)	Chelation practices have changed over time, regimens used in patients treated currently may not match historic practices, particularly when it comes to the proportion of patients receiving a combination of oral treatments in the UK	After expert consultation, company agree with ERG, updated model to reflect current iron chelation practices in UK, where a proportion of patients receive two oral agents	Modelling better matches both company's and ERG's clinical experts' views, and the distribution of chelation treatments in the UK	Company ✓ ERG ✓
6 (partially)	Due to lack of available data, company had used standardised mortality ratios (SMRs) derived from US-specific studies which were considered out of date and not applicable to the UK setting due to changes in chelation practices (leading to more favourable mortality rates for people with TDT)	Company have updated base case with ERG's preferred SMR value for transfusion-dependent patients in the model	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	Company ✓ ERG ✓
7	Company used BNF for some generic drug acquisition costs, ERG thought eMIT should be used instead (more representative of nationally available discounts)	Company agreed to use eMIT-sourced prices for 3 affected drugs	eMIT prices should be used for the 3 generic drugs affected, to better match prices NHS actually pays	Company ✓ ERG ✓

BNF: British National Formulary; eMIT: drugs and pharmaceutical electronic market information tool

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
8	Unclear whether thalassaemia genotyping and tests pre-transplant and post-transplant (of Zynteglo) would be paid for by the company (submission had indicated that this was the case) 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.	Commissioning: • Will not be additional genetic testing required for incident population Company: • Genotype testing not an additional cost relating to the introduction of Zynteglo in the NHS • Model amended to include one consultant-led appointment for every patient annually for 15 years, potentially over estimating follow up costs for patients receiving Zynteglo • For additional blood tests specific to this treatment conducted in bluebird bio labs, no charge made to NHS	• Expert submissions to NICE state that not all prevalent cases are tested routinely, so there will be some prevalent cases of TDT who may require genotyping • Due to uncertainty in whether genotyping is already widespread for prevalent patients, ERG implemented a scenario where these costs are incurred by the NHS. Found costs of testing are low, and would form a very small proportion of total costs associated with this new treatment, so it is unlikely that inclusion of this cost will have a substantial impact on cost-effectiveness results	Company – partially (follow up costs)
9	Unclear if non-busulfan conditioning regimens are used in the UK, if there is mortality associated with myeloablative conditioning, and what the impact on the cost-effectiveness would be if these were included in the modelling	Company consulted UK transplant physicians, no evidence to support use of other conditioning regimens. No mortality from conditioning observed in Zynteglo trials to date	Aligned upon during engagement teleconference – safety profile of intravenous busulfan well established, pharmacokinetic drug monitoring required, mortality risk associated with busulfan conditioning at dose ranges described in SmPC expected to be negligible	N/A

Outstanding issues unresolved post technical engagement	Status	Impact	Slide
Issue 1: Non-reference case discount rate	For discussion		14-16
Issue 2 (partial): Source of utilities data and utility decrement for transfusion-dependent patients	For discussion		17-18
Issue 3 (partial): Baseline characteristics of modelled population	For discussion		19-20
Issue 4: Underrepresentation of population with severe non-β^0/β^0 genotypes	For discussion		21-22
Issue 5: Iron normalisation and residual risk of developing iron-overload complications	For discussion		23-26
Issue 6: Unknown long-term outcomes – relapse (late graft failure), initial (primary) engraftment failure and mortality	For discussion		27-28
Issue 10: Number of patient profiles modelled	For discussion		29-30

 Model driver

 Unknown impact

 Small/Moderate impact

NICE

Issue 1: Non-reference case discount rate

NICE reference case uses 3.5% discount rate for both costs and benefits

'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.'
Criteria in methods guide for cases where 1.5% may be considered (all need to be met):

- treatment restores people who would otherwise die or have a very severely impaired life to full or near full health;
- this effect sustained over a very long period (normally ≥30 years);
- introduction of technology does not commit NHS to significant irrecoverable costs

Background

- Company used 1.5% for costs and benefits
- ERG and technical team thought reference case 3.5% should apply – evidence does not show people would otherwise die/have severely impaired life
- Company included 3.5% scenario at technical engagement
- Methods update ongoing, but methods in place at time of this appraisal are being used.

Stakeholder comments (Cell and Gene Therapy Catapult):

- Treasury Green Book recommends a discount rate of 1.5% per annum on health outcomes.
- Discounting disproportionately impacts benefits of therapies with high upfront costs but longer-term benefits.
- Long-term evidence on sustainability of effect very difficult to generate in time for launch (without delaying patient access significantly), traditional assessment frameworks could penalise lack of such evidence at time of appraisal.

Issue 1: Non-reference case discount rate

ERG concerns include:

- UK Thalassaemia Society (UKTS) state that '*the expectation is that well monitored and chelated patients will have a near normal life expectancy*'
- Company's mortality figures 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

Company comments at technical engagement:

- Zynteglo restores people who would otherwise die or have a very severely impaired life to full or near full health - based this on unpublished analysis of Health Episode Statistics database and company's UK chart review. Found median age at death for people with TDT in England was [redacted] years (2007-2016), mean utility of 0.69 for those receiving blood transfusions and chelation.
- As Zynteglo is a gene therapy, there is rationale for benefits being sustained over a long period, and growing evidence base shows it is highly likely the outcomes will be achieved. Gave example of highly specialised technologies appraisal of Strimvelis (HST7, different gene therapy, different condition), 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'
- Zynteglo has demonstrated durable clinical efficacy up to 61.3 months. EMA has recognised expected life-long benefit. SmPC: "Following successful engraftment and achievement of transfusion independence, the effects of the product are expected to be life-long."

Issue 1: Non-reference case discount rate

Technical team:

- Due to the high cost of the technology and the immaturity of the evidence base, the introduction of the technology may commit NHS to significant irrecoverable costs (e.g. if effect isn't lifelong in all patients who achieve TI)
- Company model assumes no engraftment failure in its model. The high acquisition cost could not be recovered by the NHS if the engraftment fails, with affected patients going back to transfusions and chelation

Scenario (affects costs and benefits)	ICER
Company base case (1.5%)	[redacted]
3.5%	[redacted]

Should a discount rate of 3.5% or 1.5% be used for costs and benefits?

ERG firm on 3.5% post technical engagement:

- May be a reduction in life expectancy of TDT patients treated optimally with current management strategies and therapies, but evidence presented is not convincing -impossible to quantify amount of reduction in life expectancy
- Assertion that TDT patients would otherwise die without this new treatment is not based on appropriate evidence
- Royal College of Pathologists and British Society for Haematology stated that they expect no impact on length of life compared to current care
- Eligible patients will need to be in good enough health to withstand conditioning; trials excluded people with cardiac T2* < 10 msec by MRI and those with evidence of liver disease. So treated patients are likely to be suffering less from TDT complications than general TDT population.
- Recognise there is some impact of TDT on patients' lives, but evidence that their lives are "severely impaired" has not been presented
- No outcomes-based scheme, NHS could face significant irrecoverable costs should treatment fail to achieve and maintain TI

Issue 2: Source of utilities data and utility decrement for transfusion-dependent patients

Background

- Company did not use the utility values collected from the trials in model - thought baseline values collected were 'artificially high' possibly due to an 'adjustment bias', so it would be hard to detect a utility benefit after treatment with Zynteglo.
- Company used mean utility of all people with TDT ≥16 years in their UK chart review to generate utility decrement associated with being transfusion-dependent (utility of 0.69, decrement of 0.27). Utility decrement applied to general population utilities.

ERG view:

- Demographics in chart review very different from those in trials, particularly age distribution - model may have double counted effects of ageing (HRQoL data derived from older population, while also adjusting utilities over time to account for ageing).
- Using a mean utility score for transfusion-dependent patients based on older population in chart review might be inappropriate - HRQoL may be lower than for younger patients due to changing chelation practices and more optimal management in recent years.
- In re-analysis of chart review data (aged 12 to 35 years) excluding those with existing co-morbidities that were already separately considered in the modelling, mean utility of re-analysis population was higher, [redacted]. Prefer to use this utility for the transfusion-dependent state in the model, as more comparable to baseline value for patients in the Zynteglo trials, and to population who might be eligible for treatment in practice.

Issue 2: Source of utilities data and utility decrement for transfusion-dependent patients

Company comments at technical engagement:

- Utility scores from published UK vignette study are credibly estimated and can provide more reliable values (versus trial data) for the acute post-transplant period in the model.
- 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.
- EQ-5D questions are not sensitive to quality-of-life issues for TDT patients.

ERG view after technical engagement:

- Utilities from vignette study are not the most appropriate representation of HRQoL associated with TDT at baseline, given the two sources of EQ-5D data available which are collected directly from people with TDT.
- Given similarity of HRQoL of trial population at baseline ([redacted]) with equivalent population in the chart review ([redacted]), it does not appear reasonable for company to dismiss both these patient-derived values as unrealistic. Already represent a utility decrement of ~ 0.1 compared to general population values for age group. Not insubstantial decrement, may already encompass reduced baseline HRQoL compared to general population. As patients and their families will be fully aware of the natural history and potential impact on future quality of life, this is likely to be a motivating factor for seeking gene therapy, rather than being indicative of current burden of the disease on their health.

Should the company or ERG approach to utilities for people who are transfusion-dependent be used?

Issue 3: Baseline characteristics of modelled population

The marketing authorisation includes people ≥ 12 years, but the company's UK chart review included people younger than this, while the transfusion-independence (TI)-evaluable population in the clinical studies only included people aged ≥12 years and <35 years

ERG:

- In company's UK 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)

Company submission:

- Only patients up to the age of 34 are included in efficacy population (patients evaluable for TI from clinical studies HGB-204, 205 and 207 [n=24]).
- Population was chosen for the base case to reflect a cohort of patients wishing to receive a gene therapy.

Patient Age Distribution (Years)	Company base-case (clinical studies HGB-204, 205, 207) (n=24)	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]

Technical team:

- Unclear whether clinical study data is generalisable to potential UK population, and whether data used from UK chart review should be limited to match the age restrictions in the marketing authorisation.
- Committee may wish to consider whether company's inclusion of an upper age of 34 years for Zynteglo treatment in their base case constitutes an equalities issue.

Issue 3: Baseline characteristics of modelled population

Company comments at technical engagement:

- Age is not a variable that determines a patient's eligibility for treatment. Zynteglo indication does not stipulate an upper age limit for treatment, so eligibility should 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. Have analysed correlations between age and HbAT87Q expression at month 6 (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 [redacted]. So based on the available data, extrapolation of results to patients older than the subjects treated to date is plausible.
- 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.

ERG view after technical engagement:

- Full chart review includes people who would not be eligible for Zynteglo. Company resubmitted their analysis using distribution of chelation therapies that has been age-matched to clinical trials (which results in lower ICER), while maintaining their previous position on the estimation of utilities (changing would result in higher ICER).
- No patients in clinical studies >35 years, so quality of life and chelation treatment more likely to reflect those of younger population of chart review, rather than older population of chart review (>35 years less likely to be sufficiently fit to be eligible for Zynteglo in clinical practice).

Should evidence from full UK chart review should be used in the model, or should it be limited to match the efficacy population?

Issue 4: Underrepresentation of population with severe non-β^0/β^0 genotypes

Severe non-β^0/β^0 genetic 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.

Company submission

- 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]).

ERG view:

- Proportion may be too low. In beta-thalassemia carriers in the UK, IVS-I-5 and IVS-I-110 are the most common and fourth most common mutation, respectively (22.5% and 5.5% of carriers), 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.
- Exploratory analysis, where the proportion of the modelled population is increased to 28% instead of the company's [redacted], showed resulting probability of transplant success decreased from [redacted] to [redacted].

Issue 4: Underrepresentation of population with severe non-β^0/β^0 genotypes

Company evidence and comments at technical engagement:

- Commissioned genotyping studies at Oxford Reference Laboratory, Manchester Molecular Haematology Service and sourced data from Royal London Hospital to inform approximate genotype breakdown in England. Data suggest approximately [redacted] of UK patients have a non-β^0/β^0 genotype based on [redacted] non-β^0/β^0 genotype patients out of a total of [redacted].
- 2019 Manchester Molecular Haematology Service genotype data ([redacted]) 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.
- Proportion of 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-β^0/β^0 genotypes versus non-severe non-β^0/β^0 genotypes and ranges were [redacted] between these groups.

ERG view after technical engagement:

- Company's data provided in response to this issue shows there may be [redacted] of severe genotype patients in the UK – even higher than assumption explored in ERG's scenarios, so modelled probability of transplant success may be less than [redacted].

Should the proportion of the modelled patient population with a severe non-β^0/β^0 mutation be adjusted to better match the TDT population in England?

Issue 5: Iron normalisation and residual risk of developing iron-overload complications

Iron normalisation period

Company

- Assumed iron levels normalised after 4 years in all patients who became transfusion-independent, with reduced iron levels in transfusion-reduced patients assumed to be achieved in model 1 year after Zynteglo treatment. Due to limited data availability, assumption for transfusion-independent patients was based on published data from 2 sources on iron levels in patients that received allogeneic-HSCT

ERG:

- 4-year time to normalisation assumption might be too optimistic, studies company found did not support this assumption in all patients. Data from the Zynteglo trials did not support assumption, as levels of some transfusion-independent patients were elevated even after 48 months of follow up, and many patients remained on iron removal treatments at latest follow up.
- Exploratory scenarios with iron normalisation period of 5, 7 or 10 years instead of 4 years, 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.

Company at technical engagement:

- Latest data cut June 2019 with [redacted] TI subjects across trials, [redacted] with cardiac data available had normal cardiac T2* values at 12 months – so have used 1 year time to cardiac iron normalisation.
- Also at 12 months, [redacted] of subjects had reached a normal liver iron level ([redacted] by month 60), so agree with ERG scenario of 5 years to achieve normal liver iron level.

Issue 5: Iron normalisation and residual risk of developing iron-overload complications

Complications due to iron overload in transfusion-independent patients, long term cardiac iron levels

Company

- Assumed that patients who have normalised iron levels are no longer at risk of developing complications from iron overload.
- Of 11 non-β^0/β^0 patients that have achieved TI from studies HGB-204 and HGB-205 (data available at submission), all continue to have normal cardiac T2* values through their last follow-up, with [redacted] demonstrating a cardiac T2* value at last follow-up that was higher than pre-treatment baseline.

ERG:

- Clinical adviser suggested there may be pre-existing irreversible damage caused by iron overload in many patients who would be eligible for Zynteglo (not high enough to rule out treatment), so these patients could potentially develop complications from pre-existing iron overload damage in the long-term.
- Explored potential impact of this, by applying 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).

Issue 5: Iron normalisation and residual risk of developing iron-overload complications

Complications due to iron overload in transfusion-independent patients, long term cardiac iron levels

Company at technical engagement:

- Uniformly applying annual cardiac complication rate ([redacted]) for TDT individuals with 'low' cardiac iron to all transfusion-independent patients who have had their iron normalised would markedly overstate the risk associated with the 'potential irreversible cardiac iron damage' scenario.
- 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 HES data indicate that irreversible damage is minimal in this population.
- As model applies cardiac risk on an annual basis to all patients who achieve TI status, 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).

Issue 5: Iron normalisation and residual risk of developing iron-overload complications

ERG views after technical engagement:

- Possible that patients in the trials 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
- Possible that the patients in the trials represented a more favourable population than would be eligible for treatment. Eligibility criteria is T2* > 10 ms; but lowest T2* value for a patient enrolled in the trials was reported as 27, with at least one patient already within the “normal” range.
- For liver iron normalisation, company agreed with the ERG value of 5 years to normalisation
- Further clinical input would be valuable to confirm whether arrythmias are attributable to irreversible damage, and whether there are other cardiac issues that should also be considered.
- Company presented results for cardiac iron based on a cut-off for normal levels of 20 ms, rather than 40 ms. Data is required (possibly from latest data cut) for the proportion reaching the 40ms threshold and the change from baseline.

What should the cardiac iron normalisation period after transfusion independence be in the model?

What approach to complications from iron overload should be taken in the model?

Issue 6: Unknown long-term outcomes

Limited trial follow up in a small number of patients so far (24 TI evaluable patients, maximum follow up presented in the company submission is 61.3 months), and the long-term follow up study is planned to give a total maximum follow up of 15 years.

Only a small number of people with TDT with a non-β^0/β^0 genotype have received Zynteglo so far in clinical trials, in non-UK centres. It is not known if a percentage of patients would experience engraftment failure (initial or late) in UK clinical practice.

Company

- Assumed engraftment procedure successful for all patients in model, because there were no engraftment failures in Zynteglo trials.
- Assumed 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.

ERG

- Clinical adviser thought assumption of permanent engraftment for all patients treated with Zynteglo could be too optimistic.
- Currently insufficient trial follow-up and patient numbers to determine whether long-term permanent engraftment occurs in some patients.
- The need to collect back-up cells for rescue treatment indicates that risk of engraftment failure exists.

Issue 6: Unknown long-term outcomes

ERG (continued)

- Exploratory scenarios of late graft failure - 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 to [redacted] For scenario where 10% of these patients relapse at every 10 years instead, company's base case ICER instead rises to [redacted]

Company do not accept ERG's exploratory relapse scenarios, as no evidence to support idea that effect of Zynteglo may not be lifelong.

ERG after technical engagement:

- Treatment effect longevity issue will only become clearer after longer-term follow up of the full cohort of recruited patients
- Assumptions of no relapse for TI patients and no engraftment failure unreasonable as they both remain highly uncertain, and that the impact of each assumption on cost-effectiveness should be explored

Should potential for late graft failure/relapse be taken into account?

Issue 10: Number of patient profiles modelled

Economic model structure runs a number of 'profiles' - 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, estimates results generated by 600 samples of profiles based on gender and 3 age bands (child, young adult, adult).

ERG:

- Stochastic models like discrete event simulation often need large number of iterations in order to give stable results, as some variation will occur due to 'random noise' or first order uncertainty.
- Re-ran the model with different numbers of profiles (100 to 50,000), and found a lot of variation in the resulting ICERs, 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.

Technical team:

- ICER appeared to stabilise around 5,000 profiles. ERG scenario analysis with combination of larger number of profiles (5,000) and SMR of 2.0 for transfusion-dependent patients increased ERG's base case ICER by more than [redacted] (increase of more than [redacted] compared to company's base case with 600 profiles).
- Committee may wish to consider scenarios with >600 simulated patients, as this could help stabilise the ICER - may be important given the level of uncertainty for this topic.

Issue 10: Number of patient profiles modelled

Company at technical engagement:

- Defined stability in terms of the purpose of analyses - reaching binary decision based on where ICER lies relative to NICE thresholds.
- Considered model stable at 600 profiles. Increasing number of profiles to 10,000 increases stability as defined by ERG, but also increases 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 ICER but in terms of the decision relevant range. To put it in terms of "first-order uncertainty", stochastic uncertainty is sufficiently minimised with 600 profiles.

Results of 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]

ERG after technical engagement:

- A longer model runtime is not a sufficient reason for producing a less robust analysis. Runtime for DICE models was acknowledged prior to this appraisal, and should have been factored into company's decision to use this modelling approach
- No explanation was provided as to why the company's analysis (600 simulated profiles), generated a lower ICER than analyses run with a higher number of iterations
- ICERs for company's base-case analysis are on boundaries of cost-effectiveness, any fluctuations in the estimate of ICER may cause it to go over threshold

Should the number of profiles be increased until the ICER becomes stable?

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Data limitations for comparison to other therapies	• Zynteglo trials all single arm, issues with literature reviews to fill in data gaps • Uncertainty in values used for clinical inputs for comparator arm in model	Unknown
Small patient numbers, immature evidence base	• Uncertainty over longevity of Zynteglo treatment effect, and possibility of adverse events in medium-to-long term	Cost-effectiveness estimates likely to optimistic.
Trial population representativeness, lack of evidence in key severe genotype sub-group	• Ethnicity distribution of Zynteglo trial population does not appear to well represent UK TDT population • Trial population might under-represent certain genotypes prevalent in UK • Primary outcome measure of HGB-212* is transfusion reduction (in HGB-207 it was TI), with TI as a secondary outcome measure - may suggest possible lower expectations of a TI response in people with more severe genotypes	Cost-effectiveness estimates likely optimistic. Increasing baseline proportion of population with severe non-β^0/β^0 mutation increases ICER, reduces probability of transplant success.
Heterogeneity of effect	• Heterogeneity based on genotype and evolving manufacturing process not addressed in evidence	Unknown

*v12, Dec 2020, https://clinicaltrials.gov/ct2/show/NCT03207009

TI: Transfusion independence

Equalities consideration

- In the UK, transfusion-dependent beta-thalassaemia is mostly seen in ethnic minority populations, the largest groups being Pakistani, Indian and Bangladeshi
- Some patients/parents/carers noted the stigma still associated with the condition in particular 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
- One of the experts involved in the appraisal explained that there is a cultural element that is important for this topic, as the UK TDT population is increasingly of Asian origin, and the stigma burden for some patients and their families may be uncaptured, therefore some treatment benefit is not being captured in the QALYs
- NHS England
  - ‘National Haemoglobinopathies Panel would oversee all referrals to identify any inequalities seen in the patients referred for or accepted into treatment with this technology.’ ‘Current care pathways are not genotype specific and therefore applicable to all patients with the condition.’ ‘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.’
  - ‘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.’

Cost effectiveness

Scenario	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company base case (1.5% discount rate, 600 profiles)	[redacted]	11.16	[redacted]
ERG base case *Including 3.5% discount rate, ERG's preferred approach for calculating the utility decrement for the transfusion-dependent state, 5-year 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*			
Run with 600 profiles	[redacted]	3.05	[redacted]
Run with 5,000 profiles	[redacted]	2.93	[redacted]
Scenario analysis on the ERG base case analysis, using 1.5% discount rate, run with 600 profiles	[redacted]	6.71	[redacted]
Scenario analysis on the ERG base case analysis, using 1.5% discount rate, run with 5,000 profiles	[redacted]	6.47	[redacted]
Technical team preferred assumptions (at time of technical report, [redacted]) *Including 3.5% discount rate, ERG's preferred approach for calculating the utility decrement for the transfusion-dependent state, 7-year 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*			
Run with 600 profiles	[redacted]	0.68	[redacted]
Run with 5,000 profiles	[redacted]	0.61	[redacted]

Key issues

Issue 1: Should 3.5% or 1.5% be used as the discount rate for costs and QALYs in this appraisal?

Issue 2: Should the company or ERG approach to utilities for people who are transfusion-dependent be used?

Issue 3: Should evidence from full UK chart review be used in the model, or should it be limited to match the efficacy population?

Issue 4: Should the proportion of the modelled patient population with a severe non-β^0/β^0 mutation be adjusted to better match the TDT population in England?

Issue 5: - What should the cardiac iron normalisation period after transfusion independence be in the model?

- What approach to complications from iron overload should be taken in the model?

Issue 6: Should potential for late graft failure/relapse be taken into account?

Issue 10: Should the number of profiles be increased until the ICER becomes stable?

Model driver

Unknown impact

Small/Moderate impact

NICE