Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Contents:

The following documents are made available to stakeholders:

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

Pre-technical engagement documents

1. **Company submission summary** from Vertex Pharmaceuticals

2. **Company summary of information for patients (**SIP) from Vertex Pharmaceuticals

3. **Clarification questions and company responses**
   a. Main response
   b. Additional data cut clinical summary
   c. Additional data cut updated model parameters

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Anthony Nolan
   b. NHS England
   c. Joint submission from The Royal College of Pathologists and General Haematology Guidelines Task Force for British Society of Haematology
   d. United Kingdom Forum on Haemoglobin Disorders (UKFHD)
   e. United Kingdom Thalassaemia Society

5. **External Assessment Report** prepared by Centre for Reviews and Dissemination, University of York:
   a. Main report
   b. Addendum on additional data
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6. **External Assessment Report – factual accuracy check**
   a. Response to factual accuracy check on main report
   b. Response to factual accuracy check on addendum on additional data

Post-technical engagement documents

7. Technical engagement response from company

8. Technical engagement responses and statements from experts:

a. Ben Carpenter, Consultant Haematologist – clinical expert, nominated by Vertex Pharmaceuticals Ltd
b. Roanna Maharaj, Vice Chair of United Kingdom Thalassaemia Society – patient expert, nominated by United Kingdom Thalassaemia Society
c. Gabriel Theophanous, Chair of United Kingdom Thalassaemia Society – patient expert, nominated by United Kingdom Thalassaemia Society
d. Emma Drasar, Consultant Haematologist – clinical expert, nominated by Athony Nolan
e. Subarna Chakravorty, Consultant Paediatric Haematologist – clinical expert, nominated by NHS England
f. Clare Samuelson, Consultant haematologist – clinical expert, nominated by UK Thalassaemia Society

9. Technical engagement responses from stakeholders:

a. British Society of Haematology General Haematology Task Force
b. Cell and Gene Therapy Catapult
c. NHS England
d. UK Forum on Haemoglobin disorders
e. United Kingdom Thalassaemia Society

10. External Assessment Group critique of the company's response to technical engagement

11. NICE Managed Access Feasibility Assessment

12. NICE position statement on using distributional cost-effectiveness analyses in NICE's technology appraisal and highly specialised technologies programmes

13. External Assessment Group post-appraisal committee meeting 1 (ACM1) analyses

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

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Document B

Company evidence submission

June 2023

File name	Version	Contains confidential information	Date
ID4015_Exa-cel_TDT_Document B_FINAL [CON]	1.0	Yes	29/06/2023

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Tables and figures

Tables

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Abbreviations

Abbreviation	Definition
A&E	Accident and emergency
AE	Adverse event
Allo	Allogeneic
ALT	Alanine aminotransferase
AUC	Area under curve
Beti-cel	Betibeglogene autotemcel
BMTS	Bone marrow transplantation scale
BoI	Burden of illness
BSBMTCT	British Society of Blood and Marrow Transplantation and Cellular Therapy
BSC	Best supportive care
BSH	British Society of Haematology
CAR-T	Chimeric antigen receptor-T cell therapy
CI	Confidence interval
CIC	Cardiac iron content
CPRD-HES	Clinical Practice Research Datalink-Hospital Episode Statistics
CRG	Clinical reference group
CRISPR	Clustered regularly interspaced short palindromic repeats
CSR	Clinical study report
DFO	Deferoxamine / desferrioxamine
DFP	Deferiprone
DFX	Deferasirox
DICE	Discretely integrated condition event
DNA	Deoxyribonucleic acid
DS	Descriptive system
DSA	Deterministic sensitivity analyses
EAC	Endpoint Adjudication Committee
EHA	European Haematology Association
EMA	European Medicines Agency
EMBT	European Society for Blood and Marrow Transplantation
EQ-5D-5L	EuroQol Questionnaire 5 Dimensions-5 Levels of Severity
EQ-VAS	EuroQol-Visual Analogue Score
ERG	Evidence Review Group

ESS	Effective sample size
EWB	Emotional wellbeing
Exa-cel	Exagamglogene autotemcel
FACT-BMT	Functional Assessment of Cancer Therapy-Bone Marrow Transplant
FACT-G	Functional Assessment of Cancer Therapy-General
FAS	Full Analysis Set
FBC	Full blood count
FDA	Food and Drug Administration
FWS	Functional wellbeing
G-CSF	Granulocyte-colony stimulating factor
GP	General practitioner
GvHD	Graft versus host disease
Hb	Haemoglobin
HbA	Adult haemoglobin
HbA2	Haemoglobin A2
HbC	Haemoglobin C
HbE	Haemoglobin E
HbF	Fetal haemoglobin
HCC	Hepatocellular carcinoma
HCRU	Healthcare resource utilisation
HLA	Human leukocyte antigen
HPFH	Hereditary persistence of fetal haemoglobin
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSC	Haematopoietic stem cell
HTA	Health technology assessment
hHSPC	Human haematopoietic stem and progenitor cells
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
ICT	Iron chelation therapy
IM	Intramuscular
IMD	Index of Multiple Deprivation
IPD	Individual patient data
IQR	Interquartile range
ITC	Indirect treatment comparison

IV	Intravenous
LIC	Liver iron content
LoS	Length of stay
LY	Life-year
MAIC	Matching-adjusted indirect comparison
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRD	Matched related donor
MRI	Magnetic resonance imaging
NHR	National Haemoglobinopathy Registry
NHS	National Health Service
NHSE	NHS England
NICE	National Institute for Health and Care Excellence
NTDT	Non-transfusion-dependent β-thalassaemia
OWSA	One-way deterministic sensitivity analysis
PASS	Post-autorisation safety study
PES	Primary Efficacy Set
PPPY	Per patient per year
RBC	Red blood cell
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PWB	Physical wellbeing
QALY	Quality-adjusted life year
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Safety Analysis Set
SC	Subcutaneously
SD	Standard deviation
SCT	Stem cell transplantation
SF	Serum ferritin
SF-36	Short Form-36
SLR	Systematic literature review
SmPC	Summary of Product Characteristics

SMR	Standardised mortality ratio
SoC	Standard of care
SWB	Social/family wellbeing
TA	Technology appraisal
TD	Transfusion dependence
TDT	Transfusion-dependent β-thalassaemia
TI	Transfusion independence
TI3	Transfusion independence for at least 3 consecutive months
TI6	Transfusion independence for at least 6 consecutive months
TI12	Transfusion independence for at least 12 consecutive months
TIF	Thalassaemia International Federation
TR	Transfusion reduced
TranQoL	Transfusion-dependent quality of life
TTO	Time trade-off
UK	United Kingdom
UKTS	UK Thalassaemia Society
VBA	Visual Basic for Applications
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's anticipated Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation, namely, for the treatment of transfusion-dependent β-thalassaemia in patients 12 years of age and older for whom a human leukocyte antigen (HLA)-matched related haematopoietic stem cell (HSC) donor is not available.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Transfusion-dependent β-thalassaemia (TDT) where there is no human leukocyte antigen (HLA)-matched related donor	Patients with TDT 12 years of age or older for whom an HLA-matched related haematopoietic stem cell donor is not available	This population better aligns with the proposed Medicines and Healthcare products Regulatory Agency marketing authorisation.
Intervention	Exagamglogene autotemcel (exa-cel)	Exa-cel	N/A
Comparator(s)	Established clinical management of beta-thalassaemia without exagamglogene autotemcel including: • Blood transfusions and iron chelating agents • Best supportive care	• Best supportive care (including blood transfusions and chelating agents)	N/A
Outcomes	The outcome measures to be considered include: • Reduction in transfusions • Change to haematological parameters (haemoglobin levels) • Reduction in the use of iron chelating agents • Proportion with and time to engraftment	The outcome measures to be considered include: • Reduction in transfusions • Changes to haematological parameters (haemoglobin levels) • Proportion with and time to engraftment • Mortality • Adverse effects of treatment • Health-related quality of life	The outcome 'reduction in the use of iron chelating agents' was not stated *a priori* as an endpoint in the pivotal CLIMB THAL-111 trial. The outcome 'new or worsening haematologic disorders' was not an endpoint in the pivotal CLIMB THAL-111 trial.

	• New or worsening haematologic disorders • Mortality • 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. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a National Health Service and Personal Social Services perspective.	Exa-cel qualifies for the non-reference discount rate and the severity modifier	Exa-cel meets the criteria for a non-reference case discount rate of 1.5% as laid out in the NICE methods guide: The technology is for people who would otherwise die or have a very severely impaired life. • As described in Section B.1.3.2, patients with TDT not only have poor daily health-related quality of life (HRQoL) compared with the general population but are also at risk of developing severe complications over the course of their lifetime. The complications of TDT, including cardiac and liver complications, bring with them not only substantial morbidity but also mortality. In a retrospective cohort analysis of UK TDT patients, 76% had at least one co-morbidity, 54% suffered from two of more, and 37% suffered from three or more (1). In a UK burden of illness study conducted by Vertex, the crude mortality rate in the TDT cohort was more than 5 times that of the matched general population (7.2% v. 1.2%) (2, 3), in line with findings from a previous UK study (1). • In summary, TDT patients on standard of care have a limited life span and a high risk of co-

			morbidities affecting many organs in their body. They also have to manage the huge impact of regular transfusion and iron chelation, including fatigue and pain, as shown in our HRQoL study (4). It is likely to restore them to full or near-full health: • Patients treated with exa-cel will experience improved survival, reduced risk of co-morbidities (both thalassaemia/anaemia-related and iron overload related) and they will no longer need transfusion or iron chelation, which are hugely burdensome treatments. They will have improved HRQoL akin to the general UK population and reduced fatigue, pain, plus more time released, more likely to return to work (see Section B.2.6.2.8). The benefits are likely to be sustained over a very long period: • The expected benefits of exa-cel as a one-time gene editing therapy include ameliorating a life-long disease indefinitely (see section B.2.12.1). There is no biological plausibility to lose treatment effect, and experts are aligned that if there is sustained effect at 2 years there is no reason to believe the effect would wane (given past experience with stem cell transplantation in this indication (5)).
Subgroups to be considered	If the evidence allows, the following subgroups will be considered:	None	β-thalassaemia can be broadly categorised clinically into β-thalassaemia major and β-thalassaemia intermedia. In β-thalassaemia major haemoglobin (production is so reduced

	• People with beta thalassaemia major • People with beta thalassaemia intermedia		that normal growth, development and health related quality of life can only be achieved with regular red blood cell (RBC) transfusion from infancy. In β-thalassaemia intermedia in which a reduced amount of Hb is produced, sufficient for growth and development without the absolute requirement for regular transfusions. There is a continuum of clinical severity with no absolute cut-off between the two phenotypes and transfusion independence can vary over time within the same individual and some patients with β-thalassaemia may require regular transfusions at some point in their lives. An alternative diagnosis/classification concept has been used in the Thalassaemia International Federation guidelines which divides β-thalassaemia in two groups depending on clinical severity and blood transfusion requirements: transfusion dependent β-thalassaemia and non-transfusion dependent β-thalassaemia (6). In the CLIMB THAL-111 trial only patients with TDT were included, defined as patients with homozygous β-thalassaemia or compound heterozygous β-thalassaemia (including β-thalassaemia/HbE) and with a history of at least 100ml/kg/year or 10 units/year of packed RBC transfusion in the prior 2 years before trial entry (7, 8). The sub-groups of β-thalassaemia major and β-thalassaemia intermedia were not used in the trial.
Special considerations including issues related to equity or equality	NR	People with thalassaemia are largely from non-white backgrounds, including South Asian, Southeast Asian and Middle Eastern heritage. Therefore, they	Principle 9 of NICE's charter aims to reduce health inequalities. Thus, NICE considers inequality or unfairness in the distribution of health to be an important factor in decision-making (9).

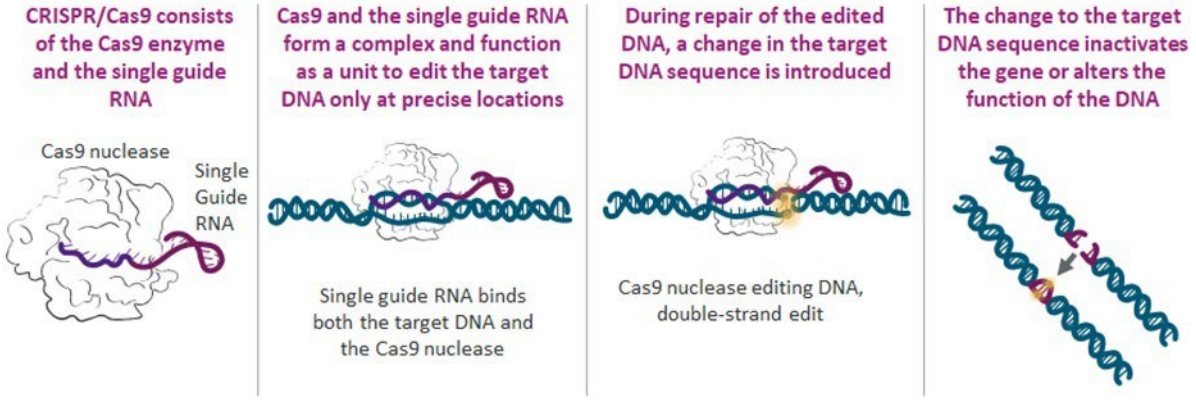
		are subject to a number of challenges related to their condition which manifest as health inequalities. NICE should take account of issues relating to health inequalities faced by patients with TDT.	As part of this submission, Vertex has conducted a DCEA as a framework for incorporating health inequality concerns into the economic evaluation of exa-cel.

Key: Exagamglogene autotemcel: exa-cel; HLA: human leukocyte antigen; HRQoL: health-related quality of life; N/A: not applicable; NR: not reported; RBC: red blood cell; TDT: transfusion-dependent β-thalassaemia.

B.1.2 Description of the technology being appraised

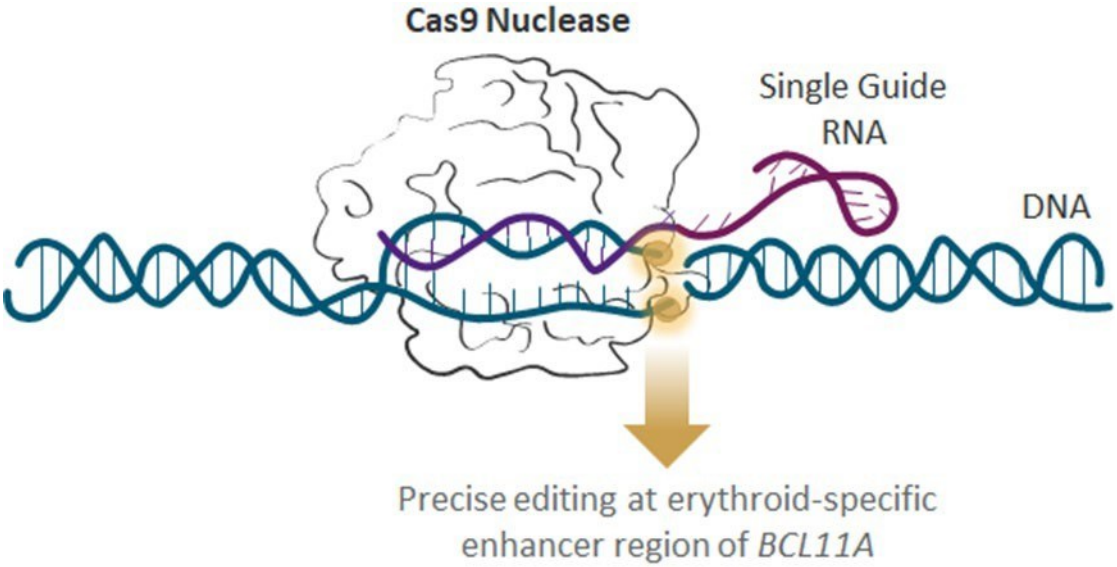
Exagamglogene autotemcel (exa-cel, formerly known as CTX001), is a cellular product consisting of autologous CD34+ haematopoietic stem and progenitor cells (hHSPCs) which uses non-viral, *ex vivo* CRISPR/Cas9-mediated gene editing to restore fetal haemoglobin (HbF) production through the editing of a non-coding region in the *BCL11A* gene (see Figure 1 and Figure 2) (10). Through reactivating the production of HbF, exa-cel mimics hereditary persistence of fetal haemoglobin (HPFH), a naturally occurring genetic variation that causes continued expression of HbF into adulthood, which leads to a reduction in the clinical severity of β-thalassaemia (10-12).

Figure 1: CRISPR/Cas9 gene-editing



Key: DNA: deoxyribonucleic acid; RNA: ribonucleic acid.
Source: Modified from Adli *et al.* (2018) and Barman *et al*., (2020) (13, 14).

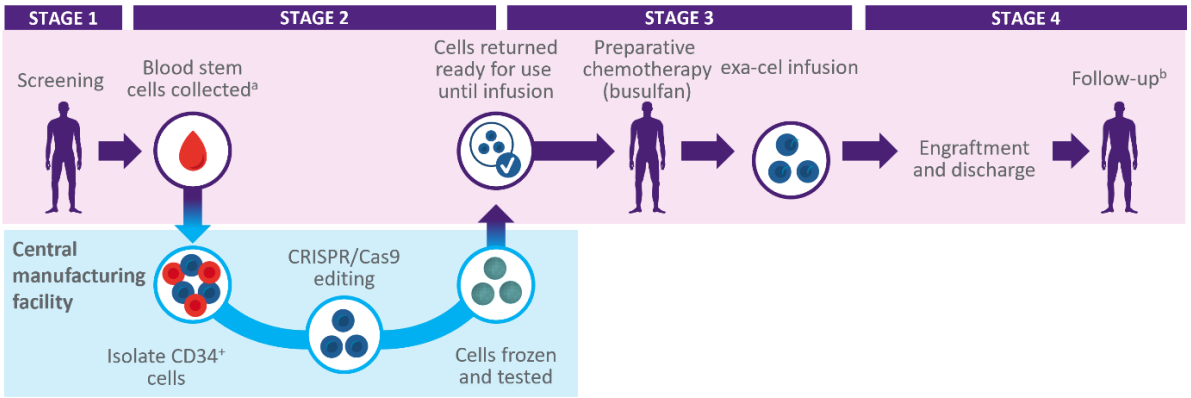
Figure 2: Exa-cel mechanism of action



Key: DNA: deoxyribonucleic acid; HbF: fetal haemoglobin; RNA: ribonucleic acid.
Notes: In exa-cel, CRISPR/Cas9 mediated gene editing only occurs at the erythroid lineage-specific enhancer region of the *BCL11A* gene using a specific single-guide RNA and Cas9 nuclease, thereby conferring lineage specificity and avoiding pleiotropic effects. The goal of this genetic modification is to reactivate the expression of γ-globin mRNA in erythroid precursors, which results in an increase in HbF protein levels in adult erythroid cells.
Source: Frangoul *et al*., (2020) (10).

Exa-cel is manufactured from the patient's own HSPCs after they have been mobilised and collected via apheresis. The HSPCs are then used to manufacture exa-cel using the CRISPR/Cas9 gene-editing technology which is delivered inside the cell using electroporation. Collected cells are edited *ex vivo* to target the erythroid-specific enhancer region of *BCL11A* (Figure 3) (10). Using a patient's own HSPCs for the editing process removes the need for a suitable matched donor (generally a sibling), as well as the risk of graft versus host disease (GvHD) and graft rejection that is associated with allogeneic stem cell transplantation (hereafter referred to as allo-SCT) (15, 16).

Figure 3: Exa-cel treatment process schematic



Key: CRISPR: clustered regularly interspaced short palindromic repeats; HSPCs: haematopoietic stem and progenitor cells
[a] Patients enrolled in CLIMB THAL-111 received a combination of plerixafor and filgrastim for mobilisation; cells were collected by apheresis.
[b]All patients will receive routine long-term follow-up by treating clinicians.
Source: Frangoul *et al*., (2021) (10).

In contrast with other gene therapies (e.g. betibeglogene autotemcel [beti-cel]), which typically use a viral vector for gene insertion, exa-cel does not rely on the insertion of a functional gene and subsequent transgene overexpression which may result in an imbalanced production of haemoglobin (Hb) α and β chains (17). In addition, due to the non-viral gene editing approach, exa-cel eliminates the risk of insertional mutagenesis, transcriptional deregulation or loss of response (17).

Table 2 provides an overview of the technology being evaluated. The draft Summary of Product Characteristics (SmPC) is located in Appendix C1.1 SmPC (18).

Table 2: Technology being evaluated

UK approved name and brand name	Exagamglogene autotemcel (exa-cel) Casgevy®
Mechanism of action	Exa-cel acts by reactivating the expression of γ-globin mRNA, which in turn leads to an increase in HbF protein levels in erythroid precursors and circulating RBCs, thereby potentially ameliorating effects of decreased or absent β-globin in TDT. Thus, exa-cel addresses the underlying cause of the disease and allows TDT patients to achieve a disease-free state.
Marketing authorisation/CE mark status	A marketing authorisation application was submitted to the MHRA on 29th December 2022, with regulatory approval anticipated in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Exa-cel is indicated for the treatment of TDT in patients 12 years of age and older and for whom a HLA-matched related HSC donor is not available.

Method of administration and dosage	Exa-cel is administered as a one-time, single dose IV infusion. • The minimum recommended dose of exa-cel is 3 × 10^6 CD34+ cells/kg. Treatment consists of a single dose for infusion containing a dispersion of viable CD34+ cells in one or more vials. • A back-up collection of ≥2 × 10^6 CD34+ cells/kg is required. These cells must be collected from the patient and be cryopreserved prior to myeloablative conditioning and infusion with exa-cel.
Additional tests or investigations	No additional tests or investigations are anticipated, beyond what is already performed in clinical practice, to identify the patients eligible to receive exa-cel.
List price and average cost of a course of treatment	[redacted]
Patient access scheme (if applicable)	N/A

Key: HbF: fetal haemoglobin; HLA: human leukocyte antigen; IV: intravenous; HSC: haematopoetic stem cell; RBC: red blood cell; TDT: transfusion-dependent β-thalassaemia.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

β-thalassaemia, one of the most prevalent autosomal recessive disorders worldwide, is an inherited blood disease characterised by mutations in the β-globin gene resulting in reduced (β^+) or absent (β^0) synthesis of the β-globin chains of Hb (19, 20). Limited or absent synthesis of β-globin leads to a diminished production of adult haemoglobin (HbA) and an accumulation of excess unpaired α-globin chains which form intracellular aggregates in RBC precursors, causing mechanic and oxidative damage (19-21).

The clinical severity of β-thalassaemia depends on the type of mutation in the β-globin gene (6, 22, 23). These mutations are assigned a severity index: β^0 refers to mutations that result in a complete absence of β-globin production by the affected allele, whereas β^+ refers to a mild reduction in the β-globin production, although the reduction can vary in magnitude by patient. Individuals with β-thalassaemia are either homozygous or compound heterozygous for the β^0 or β^+ genes, resulting in variable phenotypes ranging from clinically asymptomatic to life-threatening anaemia (6, 22). The β-thalassaemia gene can also be co-inherited with the gene for haemoglobin E (HbE), resulting in a HbE/ β-thalassaemia genotype which behaves like a mild form of β-thalassaemia similar to a β^+ mutation (24). Overall, β-thalassaemia can be broadly categorised clinically as (6):

- β-thalassaemia major, in which Hb production is so reduced that normal growth, development, and health-related quality of life (HRQoL) can only be achieved by regular RBC transfusion from infancy.

- β-thalassaemia intermedia, in which a reduced amount of Hb is produced, sufficient for growth and development without the absolute requirement for regular transfusions. Growth may fail, and other complications may develop in later childhood and adulthood, requiring regular transfusions.

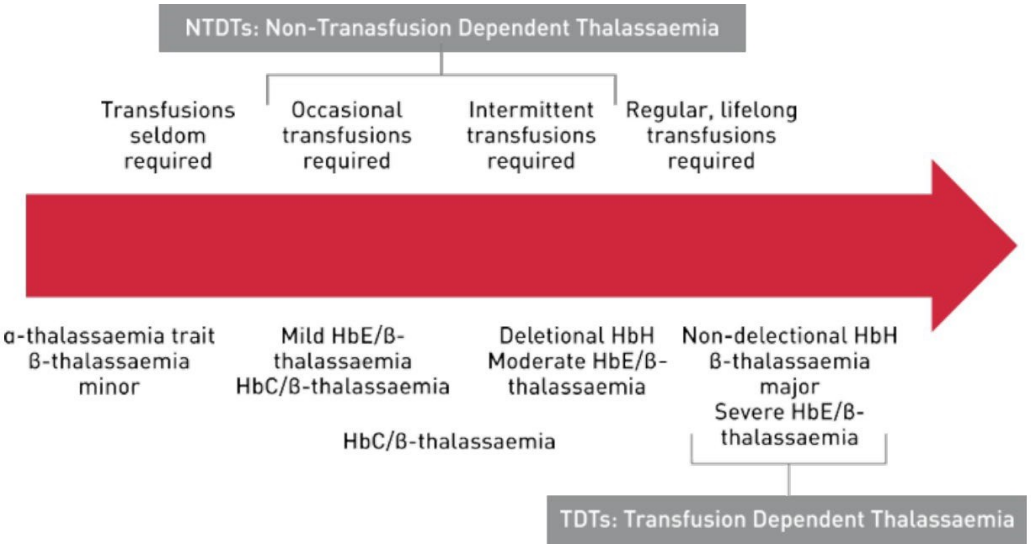
However, there is a continuum of clinical severity, with no absolute cut-off between the two phenotypes, and transfusion independence (TI) can vary over time within the

same individual (25). An alternative diagnosis and classification concept is described in the Thalassaemia International Federation (TIF) guidelines which divides β-thalassaemia into two main phenotypic groups based on clinical severity and blood transfusion requirements (Figure 4) (26, 27):

- Non-transfusion dependent β-thalassaemia (NTDT)
- Transfusion-dependent β-thalassaemia (TDT)

TDT is the most serious form of β-thalassaemia, characterised by severe anaemia requiring regular lifetime transfusions of RBCs, without which approximately 85% of patients with TDT would die within the first 5 years of life (6, 28). While regular red blood cell (RBC) transfusions address anaemia and associated symptoms, they lead to progressive iron accumulation and overload, requiring a life-time administration of iron chelation therapy (ICT) (6).

Figure 4: Phenotypic classification of thalassaemia syndromes based on clinical severity and transfusion requirement



Key: Hb: haemoglobin; NTDT: non-transfusion dependent thalassaemia: TDT: transfusion dependent β-thalassaemia.
Notes: HbC and HbE are abnormal versions of β-globin that behave like a β^+ mutations.
Source: Cappellini *et al*., 2021 (6).

In England, there are approximately 1,210 patients with β-thalassaemia who are aged 12 years or older based on NHS data from 2019/20 (29). Of the cohort aged 12 years and above, 76% are estimated to have TDT (30), defined as patients with ≥ 8 RBC transfusions per year, resulting in a prevalent population of 920 TDT patients in the UK (see Figure 10; Section B.1.3.3.5).

B.1.3.2. Burden of disease

B.1.3.2.1. Clinical burden

a. Morbidity

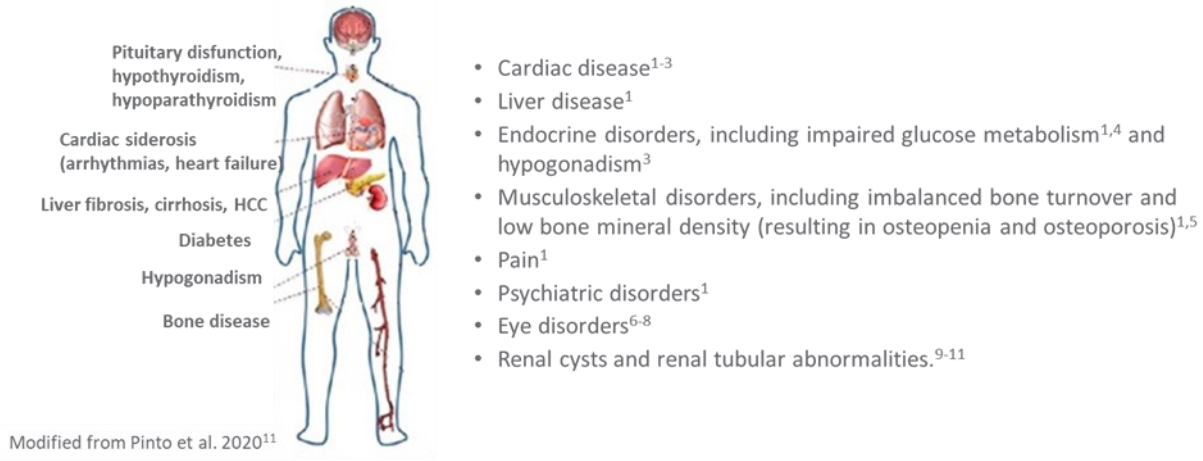
In the UK, TDT is usually diagnosed from antenatal or neonatal screening programmes (31). Without treatment, disease manifestations will typically present within the first 2 years of life, with affected infants failing to thrive and becoming progressively pale (28, 32, 33). Feeding problems, diarrhoea, irritability, recurrent bouts of fever, and progressive enlargement of the abdomen caused by spleen and liver enlargement may occur (33).

Patients with TDT who are not adequately transfused have seriously reduced erythropoiesis resulting in severe chronic anaemia with inadequate oxygen delivery to organs and tissues (34, 35). Chronic complications of anaemia include abnormalities of the lung parenchyma, vasculature and cardiac function that can lead to pulmonary hypertension, thrombosis and cardiovascular issues (34, 35), while the consequences of inadequate oxygen delivery include cerebral ischaemia and myocardial ischaemia (36). The chronic complications of anaemia outlined above, and consequences of inadequate oxygen delivery have the potential to be life threatening (34-37). Affected infants with inadequate blood transfusions may also experience growth retardation, pallor, jaundice, poor musculature, hepatosplenomegaly, leg ulcers, and skeletal changes resulting from the expansion of bone marrow (33). Once a diagnosis of TDT is confirmed, a regular transfusion programme is initiated (6). This will typically involve life-long regular packed RBC transfusions every 2-5 weeks (6, 27).

Frequent transfusions are associated with a variety of additional complications. A systematic literature review (SLR) on this topic found that adverse transfusion-related reactions were reported in ~50% of patients with β-thalassaemia mutations with regular transfusions across several markets, including the UK (19). Among these, unspecified allergic (52.0%) and febrile (16.0%) reactions were most common, while anaphylactic (0.6%), hypotensive (0.6%) and haemolytic reactions (4.7%) all occurred in a small proportion of patients (19).

Regular RBC transfusions are also the cause of progressive iron accumulation and overload, leading to complications such as heart failure, cirrhosis, liver cancer, growth retardation and multiple endocrine abnormalities (6). The substantial impact of iron overload on almost all organ systems leads to several comorbidities/complications in patients with TDT (Figure 5). Consequently, patients with TDT require continuous and rigorous monitoring of iron burden, and treatment with ICT is required to prevent iron accumulation in affected organs by removing excess iron from plasma and cells (32, 38). ICT regimens are usually initiated at an early age, with Shah *et al*., (2021) reporting a median age at initiation of ICT at 2.9 years (interquartile range [IQR] 1.8-12.1) (39).

Figure 5: Organ systems affected by iron overload in patients with TDT



Key: HCC: hepatocellular carcinoma; TDT: transfusion-dependent β-thalassaemia.
Sources: [1]Betts *et al*. (2020) (19); [2]Koohi *et al*. (2019) (40); [3]Turner *et al*., (2019) (41); [4]He *et al*., (2019) (42); [5]Gaudio *et al*., (2019) (43); [6]Liaska *et al*., (2016) (44); [7]Dunaief *et al*., (2016) (45); [8]Jafari *et al*., (2017) (46); [9]Ricchi *et al*., (41); [4]He *et al*., (2019) (42); [5]Gaudio *et al*., (2019) (43); [6]Liaska *et al*., (2016) (44); [7]Dunaief *et al*., (2016) (45); [8]Jafari *et al*., (2017) (46); [9]Ricchi *et al*., (2019) (47); [10]Tanous *et al*, (2018) (48); [11]Demosthenous *et al*., (2019) (49).

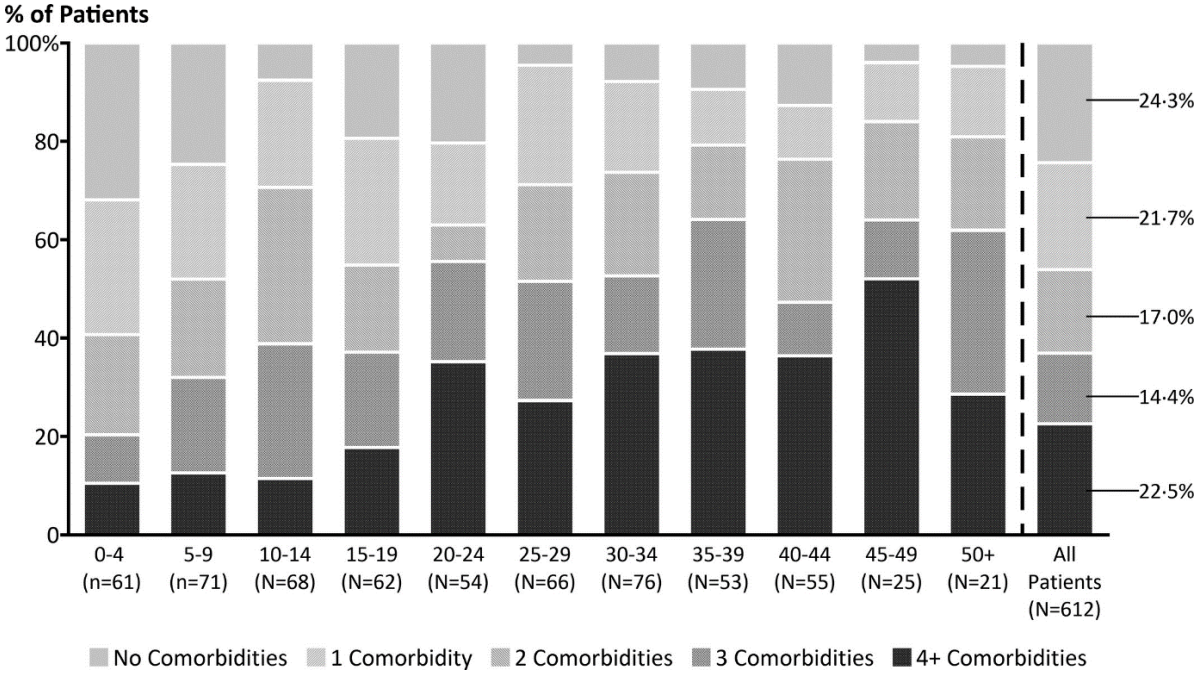
However, despite advances with ICT and monitoring in recent years, chronic iron overload remains one of the most challenging aspects in the management of patients with TDT as it is associated with a range of adverse events (AEs), including kidney toxicity, growth delay, and problems with hearing and vision (32, 50). In a series of focus groups conducted by the UK Thalassaemia Society (UKTS), all thalassaemia patients and caregivers reported the difficulty of keeping up or administering ICT as part of their daily routine (51). For instance, patients receiving ICT subcutaneously highlighted that they would often run out of injection sites because the medication caused large painful bumps. In addition, despite offering a more convenient route of administration, oral ICTs were reported to be responsible for numerous side effects,

with patients noting negative impacts of medication on their stomach, immune system, and overall health (51).

Clinical experts consulted by Vertex as part of this submission highlighted that a major aspect of TDT management in UK clinical practice is the management of AEs from iron chelation and adjustment of ICT prescription (52). In a UK study by Shah *et al*., (2021), 40.2% of AEs associated with ICT resulted in switching of therapy, with a majority (58.5%) leading to ICT discontinuation, 39.0% leading to ICT dose decrease, and 2.5% requiring an increase in ICT dosage. Furthermore, 35.3% of AEs associated with ICT required treatment (39). Due to the nature of ICT, patients must be constantly monitored and managed, which increases the burden of treatment on clinicians, patients and caregivers (52).

Both the disease itself and the consequences of iron overload lead to specific TDT-associated comorbidities (1). According to a retrospective cohort analysis of 612 patients with TDT in England, conducted between 2009 and 2018, 76% of patients with TDT had at least one comorbidity, 54% had two or more comorbidities, and 37% had three or more comorbidities (Figure 6). The most common comorbidities were endocrine disorders (excluding diabetes) affecting 40% of patients, osteoporosis affecting 40% of patients, and diabetes affecting 34% of patients (1). Another UK study of 156 patients with TDT identified hypogonadism and cardiac disease (in addition to splenectomy and vitamin D deficiency) as the most common comorbidities, each affecting >15% of patients (39). Cardiac disease represents a major cause of mortality in regularly transfused patients (6).

Figure 6: 10-year comorbidity rates by age range (Jobanputra *et al*., 2020)



Source: Jobanputra *et al*., (2020) (1).

To further understand the clinical and economic burden of TDT in a UK setting, a retrospective Clinical Practice Research Database Hospital Episode Statistics (CPRD-HES) study of the Burden of Illness (BoI) in a TDT cohort (n=237, ~25% of the overall TDT population in the UK) was conducted, with a 10 year eligibility period (1st July 2008 – 30th June 2019), and end date for the overall study period on 30th June 2019. The study population comprised β-thalassaemia patients who had experienced ≥ 8 annual transfusion events per year in at least 2 consecutive years prior to the index date. This report is referred to as the BoI study, providing data on a population aligned to the pivotal CLIMB THAL-111 study eligibility criteria (2, 3).

Over the course of the BoI study, where patients were followed-up for a mean (SD) of [redacted] years, the prevalence of complications was substantially greater in patients with TDT compared to the matched general population (Table 3). The most prevalent complications in patients were endocrine complications and bone disorders (58%), as well as urinary tract (18%), mental health (15%), cardiopulmonary (14%), and liver complications (14%) (2, 3). Table 3 outlines the most prevalent disease complications of TDT in UK patients.

Table 3: Common disease complications in TDT patients reported in the UK BoI study

	Patients with TDT (n=237)		Matched general population (n=1,184)	
	Rate (per 100 Person-Years)	Prevalence, n (%)	Rate (per 100 Person-Years)	Prevalence, n (%)
Endocrine complications and bone disorders	**5.77**	**138 (58.23)**	**1.11**	**150 (12.67)**
Diabetes	2.06	67 (28.27)	0.45	56 (4.73)
Hypogonadotropic hypogonadism	1.55	31 (13.08)	0	-
Hypoparathyroidism	0.29	-	0	-
Hypopituitarism	2.94	67 (28.27)	0	-
Hypothyroidism	1.18	34 (14.35)	0.28	39 (3.29)
Infertility	1.67	45 (18.99)	0.13	29 (2.45)
Insulin resistance or prediabetes	0.79	59 (24.89)	0.39	61 (5.15)
Osteopenia	1.46	44 (18.57)	0.06	-
Osteoporosis	3.54	69 (29.11)	0.13	-
Cardiac and cardiopulmonary complications	**1.36**	**34 (14.35)**	**0.26**	**-**
Arrythmia	0.36	-	0.1	-
Atrial fibrillation	0.57	-	0.09	-
Heart failure	0.81	24 (10.13)	0.12	-
Pericarditis	0.07	-	0	-
Pulmonary hypertension	0.64	-	0.01	-
Liver complications	**0.95**	**32 (13.50)**	**0.06**	**-**
Mental health complications	**0.88**	**35 (14.77)**	**1.02**	**201 (16.98)**
Splenomegaly	**0.82**	**25 (10.55)**	**0**	**-**
Urinary tract complications	**2.02**	**42 (17.72)**	**0.42**	**57 (4.81)**

Key: BoI: burden of illness; TDT: transfusion-dependent β-thalassaemia.
Notes: Acute complications can be repeated events per patient. Chronic complications are one-off events per patient. Patient numbers less than five were masked as '*. Patients were followed-up for a mean (SD) of [redacted] years.
Source: Li *et al,* (2023) (2).

Some of the most common disease complications are elaborated below.

i. Endocrine complications

Endocrine deficiencies are frequent, yet avoidable, manifestations in patients with TDT. Iron toxicity is the most common cause of these disorders and can be responsible for pituitary damage even in well-chelated individuals (25).

In children, hypogonadotropic hypogonadism, short stature, and delayed puberty are most commonly reported. As patients progress to adolescence and adulthood, further endocrine complications may evolve. These include the development of additional pituitary failure in addition to secondary gonadal failure and growth hormone deficiency, development of secondary hypothyroidism and secondary adrenal failure. The development of any of the aforementioned endocrine disturbances can lead to significant symptoms, adverse effects on cardiac function and a significant impact on bone development, limiting the attainment and maintenance of peak bone mineral density if not adequately treated (25).

ii. Impaired glucose tolerance and diabetes mellitus

Impaired glucose regulation and diabetes mellitus are common and significant complications of TDT. A retrospective analysis of 92 adult patients with TDT (median age: 36 years) by researchers at The Whittington Hospital, London found around 20% of patients have impaired glucose regulation and up to 41% have diabetes (37). Transfusional iron overload is the key aetiological factor which damages pancreatic β-cells, reducing insulin secretion. Other risk factors for diabetes include increasing patient age, average serum ferritin (SF) over 10 years > 1,250 µg/l, and myocardial T2 < 20ms (37).

Complications of diabetes, including macrovascular complications (cardiovascular disease, cerebrovascular disease, peripheral vascular disease) and microvascular complications (diabetic retinopathy, nephropathy, neuropathy and erectile dysfunction), can cause major patient morbidity and mortality and account in general for 80% of direct patient care costs in the UK (25). Further, diabetes significantly increases the risk for cardiac complications, heart failure, hyperkinetic arrythmias and myocardial fibrosis in patients with TDT (53).

iii. Cardiovascular disease

Cardiovascular disease represents the leading cause of mortality in patients with TDT (6), and includes a wide spectrum of complications such as iron overload cardiomyopathy, ventricular dysfunction, pulmonary hypertension, arrhythmias, valvular disease, pericarditis, and myocarditis (6). An SLR investigating the burden of disease for TDT patients reported a diagnosis of iron overload associated heart failure in approximately 10% of patients (19).

iv. Bone disease

Skeletal changes, which manifest as facial deformities, bone masses, and/or osteoporosis, can appear in patients with TDT because of ineffective bone marrow expansion and extramedullary haematopoiesis (6). Osteoporosis is a prominent skeletal manifestation in patients with TDT. The pathogenesis includes genetic factors as well as endocrine complications (mainly hypogonadism), iron overload, bone marrow expansion, vitamin deficiencies, and lack of physical activity (54).

v. Liver disease

Liver disease, which arises from iron overload and viral hepatitis, leads to chronic inflammation, fibrosis, cirrhosis, and increased risk of hepatocellular carcinoma (HCC); hepatomegaly and splenomegaly develop as a result of chronic haemolysis within the first few years of life (6). The SLR by Betts *et al*., (2020) found the prevalence of liver damage (i.e., cirrhosis and HCC) varied between 2.1-7.0% in patients with TDT (19). HCC is increasingly reported, particularly in older patients (mean age: 48 years). HCC was not a common cause of death in survival studies published over the last 20 years, however it is now becoming a more important cause of mortality (55).

b. Mortality

Life expectancy for patients with TDT has significantly improved over the last 50 years due to improvements in patient care (25). However, the life expectancy of TDT patients still lags far behind population norms even with optimal care, with approximately 40% of patients dying before the age of 50 years in the UK (56).

Despite advances in ICT and iron monitoring, patients with TDT remain at an early risk of death. Over a 10-year period in England, patients with TDT had a significantly higher

mortality rate than matched controls, which was six times higher than the age and sex-adjusted mortality rate of the general population (7.2% vs 1.2%, p<0.05) (2, 3). A retrospective cohort analysis of UK TDT patients by Jobanputra *et al.,* (2020) reported a slightly lower crude 10-year mortality rate of 6.2% (five times greater than the age and sex-adjusted mortality of the general UK population) (1). The mortality rate (per 100 person-years) was reported at 1.19 for the cohort of patients with TDT, compared with just 0.2 in matched controls. When the TDT cohort was stratified by age (<18 years and ≥18 years), older patients with TDT (aged ≥18 years) had a higher mortality rate (1.68 per 100 person-years) compared to younger patients <18 years of age (0.5), indicating that mortality rate increases substantially with age.

In the BoI study, the mean age of death (SD) for patients with TDT was 55.0 years (29.01) (2, 3), which is <30 years lower than the modal age of death for the general population in the UK (females: 89.3 years; males: 87.1 years) (57). In the study by Jobanputra *et al*., (2020), a lower mean age of death was reported at 43.9 years (1).

B.1.3.2.2. Humanistic burden

TDT is a multifaceted condition with a negative impact on HRQoL and activities of daily living for patients living with the condition, as well as their caregivers and families. All symptoms, along with treatments for TDT, including RBC transfusions and ICT, have an impact on all domains of life, including the ability to plan, work, leisure and social activities, relationships, and emotional wellbeing. The severity of these symptoms and functional issues, and the subsequent impact, may fluctuate according to where the individual is in their RBC transfusion cycle. Symptoms and functional issues are most severe prior to transfusions, and are considered to be better during the period after transfusion (4).

Patients with TDT have significant HRQoL impairment when using generic (EuroQol Questionnaire 5 Dimensions-5 Levels of Severity [EQ-5D-5L], Functional Assessment of Cancer Therapy – General [FACT-G]) as well as disease specific (transfusion-dependent quality of life [TranQoL]) instruments (39, 58).

For instance, a multi-national prospective longitudinal study evaluating HRQoL and work productivity among adult patients with TDT (n=155), reported that, according to

the EQ-5D-5L questionnaire, most patients experienced problems with pain (73%), anxiety or depression (61%), and the ability to conduct daily activities (59%) (59, 60).

Despite this evidence showing HRQoL impairment in TDT, other studies suggests that the derived utility index scores may not fully represent and underestimate the burden of TDT in affected patients. For instance, a study of 30 patients with TDT from the UK, France, and the US found that EQ-5D-5L does not fully capture important symptoms/functional impacts and therefore lacks face validity in a TDT population given that these patients undergo frequent RBC transfusions and require treatment with ICT, which is associated with poor tolerability (4, 6). Given that these patients have an inherited condition and have experienced chronic symptoms of TDT and therefore treatment since early childhood, one reason for the high baseline utility values is adaptation, an issue which has been observed with chronic conditions (61).

In addition, further support for the negative impact of TDT on HRQoL comes from a UK based study which examined health state utilities for patients with TDT, using a composite time-trade-off approach (62, 63). Eleven TDT-related health states were examined from the general population perspective with the resulting utility values ranging from 0.30 to 0.75. The highest utility value (i.e., the lowest impact) was the health state characterised by low RBC transfusion burden and oral or subcutaneous ICT (0.75, SD 0.30), while the lowest utility value (i.e., the greatest impact) was the health state with high RBC transfusion burden and subcutaneous ICT (0.37, SD 0.50) (62, 63).

HRQoL impairment is also supported by a low mean score of the TranQoL questionnaire. The TranQoL overall score ranges from 0 (worst thalassaemia-related HRQoL) to 100 (best thalassaemia-related HRQoL). A prospective longitudinal study conducted by Li *et al*., (2022) noted substantial impairments across all domains of the TranQoL questionnaire (physical health, emotional health, family functioning, and school and career functioning (Table 4) (59, 60). Similar results were reported in an observational study by Shah *et al*., (2021), which reported a mean TranQoL score of 58.6 ± 18.4 (n=94) (39).

Table 4: Mean scores for the individual domains of the TranQoL among patients with TDT in the UK

TranQoL domain	Adults with TDT, mean (SD) (n=155)
Overall score	53.9 (18.5)
Physical health	53.8 (22.6)
Emotional health	57.0 (19.9)
Family functioning	53.6 (18.1)
School and career functioning	62.5 (28.5)

Key: SD: standard deviation; TranQoL: transfusion-dependent quality of life questionnaire; TDT: transfusion-dependent β-thalassaemia.
Notes: TranQoL overall score ranges from 0 (worst thalassaemia-related QoL) to 100 (best thalassaemia-related QoL).
Source: Li *et al*., (2022) (59).

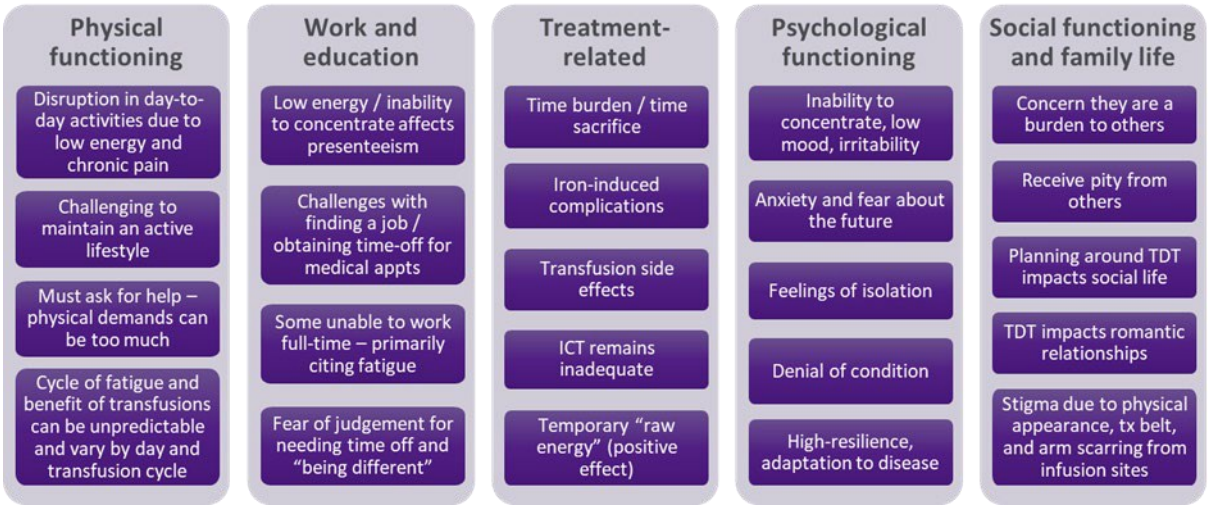
Many patients with TDT also experience impairments in mental health. A series of patient interviews and focus groups conducted in the UK and US provides evidence of the psychological impact TDT can have on patients and caregivers. They found that the limited ability to carry out activities of daily living and contribute to family life can lead to a profound psychological impact on morale and self-esteem of patients with TDT. Other commonly reported psychological symptoms include depression, anxiety, stress and worries about the future (64).

In addition to psychological functioning, the study by Martin (2022) also reported that TDT negatively impacted many aspects of patients' lives including physical functioning and daily activities, psychological functioning, social and family life, relationships, and education and work (Figure 7) (64). With regards to the latter, patients with TDT need a considerable amount of time off education and work to manage their condition. A global longitudinal patient-reported outcome (PRO) survey study conducted by Vertex found TDT patients spent a median time of 7.0 hours (IQR: 2.0-7.0) at medical appointments and 2.0 hours (IQR: 1.6-4.5) travelling to and from medical appointments within the past month. A vast majority of patients reported the time burden imposed to manage their condition impacts their ability to travel (88%) and spend time with family and friends (80%) (59, 60).

A prospective longitudinal survey conducted by Li *et al*., (2022) showed that work productivity was reduced by 41.7%, while the ability to do non-work related activities was impaired by 44.2% (59, 60). Similar values were reported in an observational

study by Shah *et al*., (2021) (42% and 48% respectively) (39). Furthermore, only 32.3% of TDT patients were in full-time work (≥32 hours/week), while 17.7% were employed part-time (<32 hours per week) (59, 60). The studies conducted by Li *et al*., (2022) and Shah *et al*., (2021) reported similar rates of absenteeism (amount of work time missed [19.5% versus 10.0%]) and presenteeism (impaired productivity at the workplace [34.0% versus 34.0%]) (39, 59, 60).

Figure 7: Summary of the impact of TDT on patient lives



Source: Martin 2022 QC Medica focus groups and interviews (64).

It is important to note that the impact of TDT on HRQoL may be under-reported as patients typically exhibit high resiliency and adaptation to their condition despite the disruption of their daily lives, including suffering debilitating fatigue and managing time-intensive treatments (52). Clinical experts highlighted that patients with TDT have never known anything different, and as such self-reported HRQoL is typically overestimated (4, 52).

B.1.3.2.3. Societal and economic burden

The management of TDT is associated with significant healthcare resource use (HCRU). The UK BoI study found that patients with TDT had significantly higher HCRU compared to a cohort of matched patient controls. Patients with TDT averaged (all per patient per year [PPPY]) 17.4 inpatient hospitalisations, of which 16.6 were for <1 day, 16.7 outpatient visits, and 24.1 prescriptions. Inpatient hospitalisations were driven by attendances for RBC transfusion (2, 3). The mean annual number of hospitalisations recorded in the BoI study is similar to that estimated in a UK-based study of 612 TDT

patients by Jobanputra *et al*., (2020) (18.2 hospitalisations PPPY) (1-3). A full list of results from the BoI study can be found below in Table 5 (2, 3).

Table 5: HCRU associated with managing TDT in the UK

Rate, PPPY, Mean (SD)	TDT (n=237)	Matched controls (n=1,184)
Primary care visits*[1]	7.0	4.2
GP visits*[1]	4.0 (5.5)	3.0 (3.8)
Nurse visits*[1]	3.0 (8.1)	1.2 (2.0)
Prescriptions*[1,2]	24.1 (58.7)	8.6 (26.6)
Hospitalisations*[2]	34.8 (13.9)	1.9 (3.5)
A&E hospitalisations*[2]	0.7 (1.0)	0.4 (0.9)
Outpatient visits*[2]	16.7 (10.7)	1.3 (2.6)
Inpatient hospitalisations*[2]	17.4 (7.7)	0.2 (0.9)
Inpatient hospitalisation < 1 day*[2]	16.6 (7.5)	0.1 (0.7)
Inpatient hospitalisation ≥ 1 day*[2]	0.8 (1.8)	0.1 (0.4)

Key: A&E: accident and emergency; GP: general practitioner; PPPY: per patient per year; SD: standard deviation; TDT: transfusion-dependent thalassaemia.
Notes: *P<0.05 between SCD patients and matched controls (z-test). [1]Captured from CPRD. [2]Captured from HES.
Source: Li *et al*., (2023); Vertex BoI report (2, 3).

B.1.3.3. Clinical care pathway

Current guidance for the clinical care of children and adults with TDT in the UK is provided by the UKTS (25). The National Institute for Health and Care Excellence (NICE) does not provide guidelines on the treatment of TDT. Three technology appraisals (TAs) have been initiated by NICE, two of which are in relation to recent therapies, as summarised in Table 6 below. However, neither of these therapies were recommended by NICE.

Table 6: Summary of NICE guidance in TDT

Title	Outcome	Rationale
TAG423: Chronic iron overload (in people with thalassaemia)	Suspended since 2011	One reason for the suspension of TAG423 was the lack of confidence by regulatory authorities about the safety of combination therapies.
TA10506: Luspatercept for treating β-thalassaemia	Terminated	The company considered that there was not enough evidence to provide a submission for an appraisal.

Title	Outcome	Rationale
TA10334: Betibeglogene autotemcel for treating transfusion-dependent β-thalassaemia	Discontinued	Following an appraisal committee meeting, the preliminary decision was not to recommend betibeglogene autotemcel for reimbursement due to lack of cost-effectiveness and high levels of uncertainty relating to longer-term clinical effectiveness data. The company has since decided not to commercialise beti-cel in Europe.

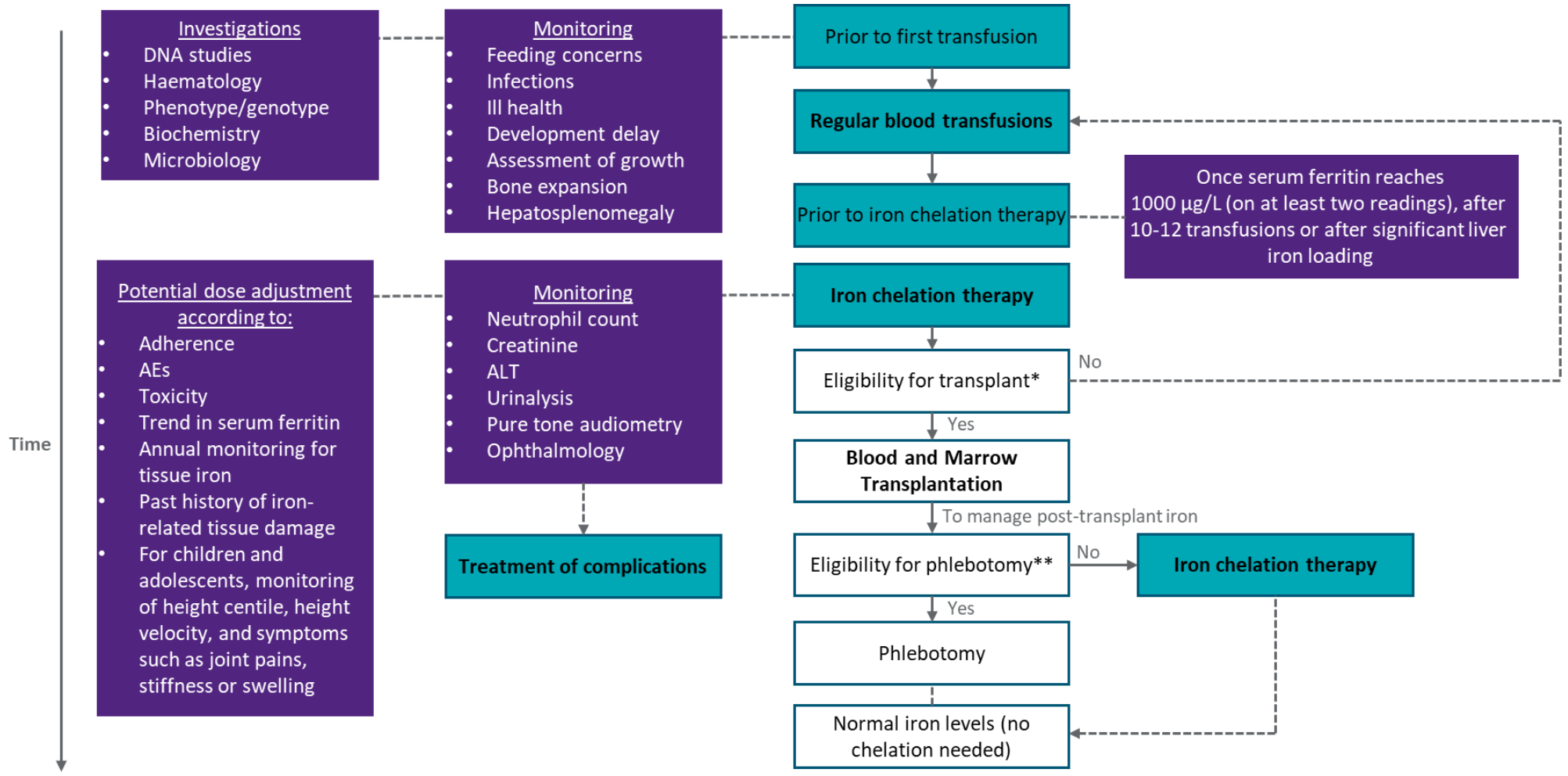
Key: TA: technology appraisal.
Sources: NICE TAG423 (65); NICE TA10506 (66); NICE TA10334 (67).

In addition, the British Society of Haematology (BSH) provides guidance on the screening and diagnosis of haemoglobinopathies (68), while both the BSH and NHS England (NHSE) provide guidance on the treatment of iron overload in patients with haemoglobinopathies and rare anaemias (69-71).

B.1.3.3.1. UKTS guidelines

The third edition of the Standards for the Clinical Care of Children and Adults with Thalassaemia by UKTS was issued in 2016 (25), although publication of an updated guideline is anticipated in the coming months. The current clinical pathway for patients with TDT in the UK, as described in the current UKTS guidance, is depicted in Figure 8.

Figure 8: UK TDT treatment pathway (adapted from UKTS guidelines)



Key: ALT: alanine aminotransferase; DNA: deoxyribonucleic acid; Hb: haemoglobin; UKTS: UK Thalassaemia Society.
Notes: *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 Hb levels are sustained above 11 g/dL.
Source: Third edition of the Standards for the Clinical Care of Children and Adults with Thalassaemia (25).

RBC transfusions are essential in children with TDT, enabling normal growth and development, while in adults, regular RBC transfusions remain necessary to treat anaemia. A trough (pre-transfusion) Hb level maintained above 9.0-10.5 g/dL is considered sufficient to inhibit bone marrow expansion and minimise transfusion iron loading in most patients. RBC transfusions are usually given regularly every 2-4 weeks, although intervals vary from patient to patient and should be agreed between the clinician and patient depending on the clinical response to anaemia/RBC transfusions and pragmatic lifestyle decisions (25).

In the medium- and long-term, iron overload is a significant risk associated with RBC transfusion and can be fatal in the second or third decade of life if not managed appropriately. ICT should be initiated once SF reaches 1,000 µg/l (on at least two readings), after 10 to 12 RBC transfusions, or after significant liver iron loading. All licensed ICTs can be effective in reducing iron stores in overloaded patients. However, in practice, there is variability in individual response to each agent, and differing susceptibility and tolerance to their AEs. Decisions about initiating and changing ICT should be made by a thalassaemia specialist, taking into account the preferences of the patient and caregivers, and the views of other involved healthcare workers (25).

In UK clinical practice, three ICTs are currently available: deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX). The choice of the specific ICT agent is based on the patient's age, comorbidities, patient preference (taking into account potential adherence challenges), and AE profile (Table 7). A UK study by Shah *et al*., (2021) reported that DFX was the most commonly used chelating agent in the UK (58%), followed by DFO (14%) and DFP (7%), with the remainder of patients treated using combination therapy (21%) (39).

Table 7: Comparison of UK licensed indications for iron chelation therapies

	DFO	DFP	DFX
Children aged < 2	First line	Unlicensed indication	Second line if DFO contraindicated or inadequate (unlicensed indication)

Children aged 2 – 6	First line	Unlicensed indication	Second line if DFO contraindicated or inadequate
Children aged > 6 and adults	First line	Second line: if DFO contraindicated of inadequate	First line
Route	SC, IM or IV injection	Oral, tablet or liquid	Oral, dispersible tablet
Dosage	20-60 mg/kg 3-7 times per week. Children's dose up to 30 mg/kg per week.	75-100 mg/kg/day	10-40 mg/kg/day
Contraindications	Hyper-sensitivity	Previous agranulocytosis, pregnancy – teratogenic risk	Hyper-sensitivity, estimated creatinine clearance < 60ml/min, and pregnancy
Effectiveness removing cardiac iron	Not effective	Effective	Mildly effective
Effectiveness removing liver iron	Effective	Not effective	Effective
Monitoring	Hearing and vision test Growth assessment Pulmonary, renal, and liver function	FBC with differential zinc Liver function	FBC with differential Platelet count Liver and renal function

Key: DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; FBC: full blood count; IM: intramuscular; IV: intravenous; SC: subcutaneous.
Sources: Table adapted from UKTS Standards Version 3 (25). Additional information supplemented from Bayanzay *et al*., (2016) (72), Rachmilewitz *et al.,* (2011) (28), Allali *et al.*, (2017) (73), Shah *et al*. (2022) (71), and Saliba *et al*., (2015) (74).

At present, allo-SCT is the only proven treatment modality that can establish long-term haemopoiesis, avoiding the need for RBC transfusions and ICT, with the best results achieved with HLA-matched sibling donors (75). Referral to a transplant centre for discussion about blood and stem cell transplantation should be offered to parents when the child is 1-2 years of age. The benefits of transplantation must be carefully balanced with the risks and difficulties of the procedure. The discussion must weigh the benefit risk of allo-SCT and include highlighting the improved outcomes for children and adults managed conventionally with transfusion and chelation (25).

The UK Paediatric Bone Marrow Transplant (BMT) Group have produced guidelines for eligibility for allo-SCT in children with thalassaemia. They recommend that this is

standard of care (SoC) for suitable patients with a fully HLA-matched sibling donor (76).

B.1.3.3.2. BSH guidelines

BSH has developed two clinical practice guidelines on the management of haemoglobinopathies, including screening and diagnosis (68), and for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias (71). Key points of the guidelines are summarised below:

- Antenatal screening/testing of pregnant women should be carried out according to the guidelines of the National Health Service (NHS) Sickle Cell and Thalassaemia Screening programme (68).
- TDT patients on regular transfusions (at least every three months) should be assessed for iron overload and the associated complications at least annually as part of their annual review (71).
- TDT patients should be commenced on ICT after 10–12 transfusions or when SF >1 000 µg/l on two occasions (71).

B.1.3.3.3. NHSE commissioning policy

In the UK, haemoglobinopathies are recognised as a specialised service commissioned by NHSE and covered by the Clinical Reference Group (CRG) for Haemoglobinopathies. The CRG for Haemoglobinopathies has produced one clinical commissioning policy with relevance to the treatment of TDT in the UK, namely for the treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias, which was recently updated in October 2022 (70). Key points of the clinical commissioning policy are summarised below:

- DFO, DFP, DFX or combination therapy (DFO and DFP) should be offered to treat transfusional iron overload in patients with inherited haemoglobinopathies or rare anaemias who either are on or have previously been transfused either regularly or intermittently (69, 70).

- The sequence of treatment selection should be determined by the individual patient assessment for toxicity, tolerability and adherence to manage iron loading (69, 70).

B.1.3.3.4. Unmet needs with current treatment

Whilst the ultimate goal of treatment is to achieve TI, currently available options are only able to provide symptomatic management, rather than addressing the underlying pathophysiology. RBC transfusions are the current SoC in the UK and provide a temporary relief of anaemia symptoms (77). However, they also lead to progressive iron accumulation and overload, requiring a lifetime administration of ICT (6). Unfortunately, even with present-day ICT, iron overload is often inadequately controlled in TDT patients, who continue to suffer from the significant morbidity associated with a high iron burden (1). Challenges also persist around the tolerability of ICT regimens, as iron overload management with ICT is also often associated with AEs, including abdominal pain, nausea, and diarrhoea (6, 64).

Despite currently available care, patients with TDT in the UK experience significant clinical complications associated with the disease, with complication rates increasing with age (2, 3). These are driven by iron overload, ineffective erythropoiesis, haemolysis, hypercoagulability and anaemia. Endocrine and bone disorders are among the most common complications observed in patients with TDT in the UK, with osteoporosis (29.1%), diabetes (28.3%), and hypopituitarism (28.3%) showing the highest prevalence in this category. Heart failure, pulmonary hypertension, and atrial fibrillation were the most common cardiac and cardiopulmonary complications recorded (2, 3).

Even with an optimised transfusion and ICT schedule, the mortality rate of patients with TDT is significantly higher compared to the general population, with UK-based studies reporting that TDT patients experience a minimal five-fold greater risk of mortality compared to those without the disease (1-3). A recent BoI study reported that patients with TDT had a significantly higher mortality rate than matched controls (7.17% vs 1.18%; $p<0.05$) with a mean age of death in the TDT cohort of 55 years (2, 3). This compares with previous data showing a crude 10-year mortality rate of 6.2%,

significantly greater than the 1.2% age/sex-adjusted mortality rate of the general population (1).

Allo-SCT is the only curative therapy currently available for patients with TDT, however it is only recommended for patients with an available HLA-matched sibling donor, limiting the number of patients who can benefit. At present, allo-SCT is only an option for children in the UK, with clinical experts noting that this is typically reserved for children nine years of age or younger (78). The mean age at date of transplant in a UK study of TDT patients by Jobanputra *et al*., (2020) was 6.4 years (1). In addition, less than 30% of TDT patients have a matched sibling donor (79), and even fewer patients undergo the transplant procedure due to suboptimal organ function and/or age restrictions (15).

Furthermore, allo-SCT carries significant risks including infections, GvHD, and increased mortality (15). Jobanputra *et al*., (2020) reported a mortality rate of 9.7% for a cohort of TDT patients who underwent allo-SCT, with a mean age at death of 7.6 years (1). Considering the risks, transplants are infrequently performed for patients with TDT (12 transplants were performed for thalassaemia in 2021 according to the British Society of Blood and Marrow Transplantation and Cellular Therapy [BSBMTCT]) (80). Notably, allo-SCT is not currently available for adult TDT patients in the UK, although Vertex understands that a proposal is currently in development (52).

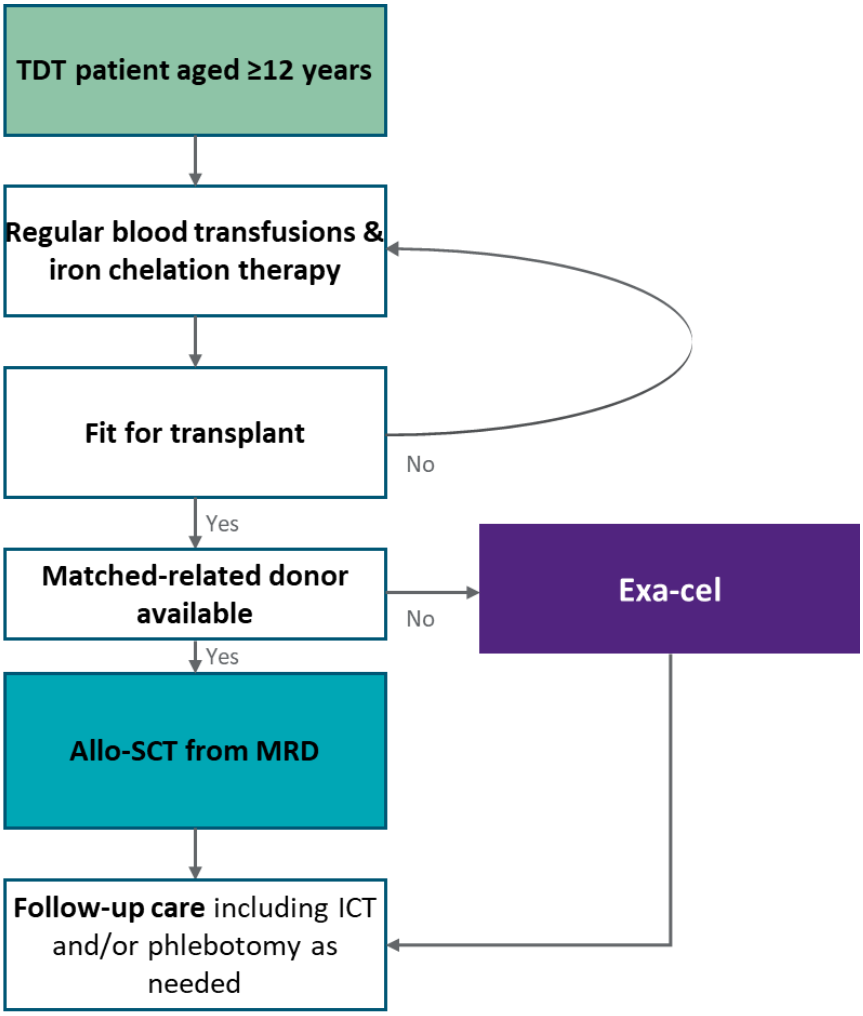
Considering all of the above, a substantial unmet medical need remains for treatment options that can provide transfusion independence, and eliminate complications associated with iron overload, thus improving morbidity, HRQoL and survival.

B.1.3.3.5. Proposed positioning of exa-cel in the TDT pathway

Exa-cel is positioned for the treatment of TDT in patients 12 years of age and older for whom an HLA-matched related HSC donor is not available.

The proposed positioning of exa-cel is displayed schematically below in Figure 9.

Figure 9: Proposed positioning for exa-cel in UK clinical practice

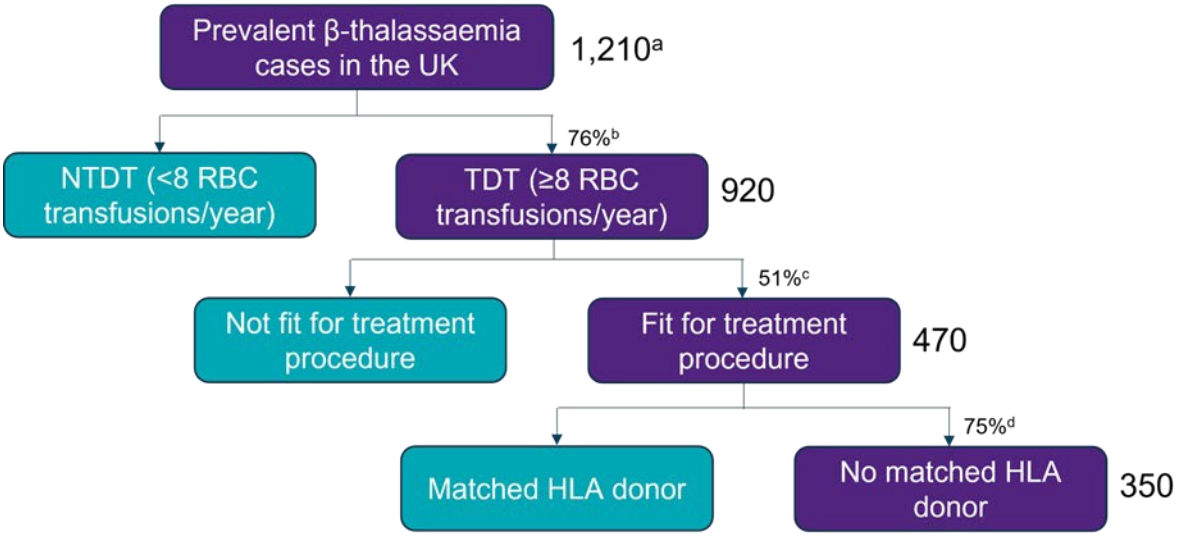


Key: Allo-SCT: allogeneic-stem cell transplant; exa-cel: exagamglogene autotemcel; ICT: iron chelation therapy; MRD: matched-related donor; TDT: transfusion dependent β-thalassaemia.

Figure 10 presents the epidemiology of the sub-populations of TDT relevant to this appraisal.

Of note, there are several additional clinical and real-world considerations for a gene therapy such as exa-cel (e.g., healthcare professional referral for cell and gene therapy, patient willingness to undergo gene therapy, bed capacity); when factors like these are applied, the likely exa-cel treated patients will only be a small fraction of eligible TDT patients.

Figure 10: Epidemiological cascade for TDT patients aged 12 and older in the UK



Key: HLA: human leukocyte antigen; RBC: red blood cells; NTDT: non-transfusion-dependent β-thalassaemia; TDT: transfusion-dependent β-thalassaemia; UK: United Kingdom.
[a]Based on data collected by the National Haemoglobinopathies Registry in 2019/20 (29). Age intervals to reflect <12 years, 12-17 years, and ≥18 years were estimated from most recent NHR data request.
[b]Estimated proportion transfusion dependent based UK NHR Monthly Status Report (August 2022), percent of patients with B-TM + transfusion dependent HbE B-thal
[c]Based on Vertex Sponsored Market Research Studies from 2022.
[d]Based on Vertex data on file.
Notes: In the current economic model, patients with TDT were defined as those with ≥8 RBC transfusions per year. Patients for treatment procedure include those who are fit for procedures requiring myeloablative conditioning. Patients treated with exa-cel include those who are fit for the treatment procedure but do not have a matched HLA donor.

B.1.4 Equality considerations

β-thalassaemia is most prevalent across the Mediterranean, the Middle East, India, East and Southeast Asia, and North and Central Africa (81). However, due to migration patterns from endemic regions, β-thalassaemia has become increasingly common in western Europe (6, 23, 82).

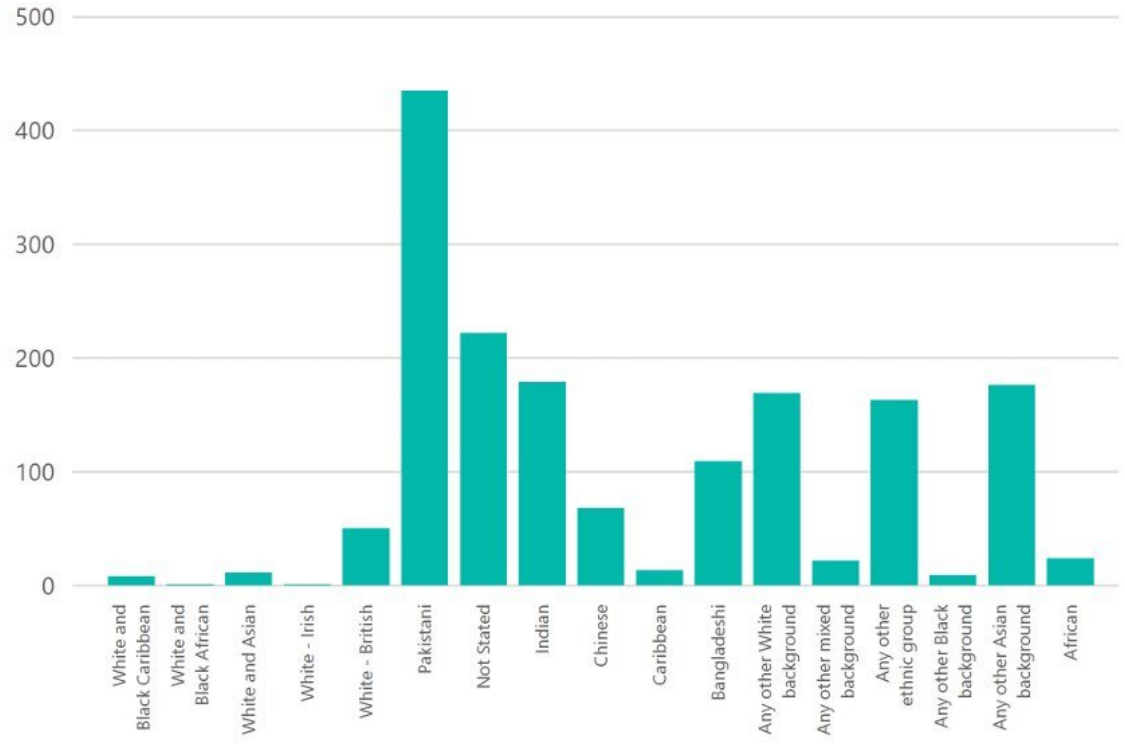
In the UK, TDT predominantly affects individuals of Pakistani and South Asian ethnicity. Data published by the National Haemoglobinopathy Registry (NHR) in 2021 indicates that almost half of thalassaemia patients in the UK are Pakistani (Figure 11) (83). In the UK BoI study, 53.6% of TDT patients were South Asian (2, 3). UKTS estimates that 79% of babies born with TDT each year in the UK are to Asian parents who originate from India, Pakistan and Bangladesh (84).

People of Asian and Southeast Asian descent living with TDT experience lower life expectancy and health related quality of life compared to other ethnicities due to development of secondary morbidities later in life. Patients report that the diagnosis and treatment process can be overwhelming because their clinicians often demonstrate a lack of support and understanding of their condition (85).

The medications and regular transfusions that constitute TDT disease management are burdensome and time-consuming, making it difficult for patients to socialise and to maintain regular employment. Consequently, patients experience social isolation and significant negative financial constraints, and a lack of access to funding support can often limit patients' ability to travel to treatment centres, which further contributes to worsening of their condition.

In addition, the availability of blood can be compromised by the chronic shortage of ethnically matched blood stocks available to treat patients of ethnic-minority heritage and ensure optimal treatment outcomes. Where any treatment can completely remove the need for chronic transfusions, or even significantly reduce the volumes of blood required, this will have a positive impact on the wider healthcare system.

Figure 11: Thalassaemia patients by ethnicity in the UK



Source: NHR Annual Report 2020/21 (83).

Furthermore, TDT patients are more likely to live in a more deprived area of the UK, with 56.2% of TDT patients identified in the BoI study living in the two most deprived quintiles according to the Index for Multiple Deprivation (IMD) (Table 8) (2, 3).

Table 8: Socio-economic status of TDT patients identified in the BoI study

Socio-economic status (IMD), N (%)*	TDT (n=237)
Q1 (least deprived)	23 (9.7%)
Q2	34 (14.4%)
Q3	47 (19.8%)
Q4	71 (30%)
Q5 (Most deprived)	62 (26.2%)

Key: IMD: Index of Multiple Deprivation.
Notes: IMD is a composite measure of material deprivation including income, employment, education and skills, health, housing, crime, access to services, and living environment.
Source: Li *et al*., (2023) and Vertex BoI report (2, 3).

As a result of the deprivation scores, and prevalence in ethnic minority groups, patients with TDT are subjected to health inequality concerns that could be addressed by exa-cel.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

An SLR was conducted to identify all relevant clinical trial evidence associated with the decision problem outlined in Section B.1.1. Full details are provided in Appendix D. As the manufacturer, Vertex is aware of all relevant clinical trials for exa-cel.

B.2.2 List of relevant clinical effectiveness evidence

The clinical SLR identified one trial that provides direct clinical evidence for the efficacy and safety of exa-cel in the treatment of TDT patients 12 years of age or older: CLIMB THAL-111 (NCT03655678). Seven records were retrieved relating to CLIMB THAL-111, including one publication, four conference abstracts, one oral presentation and one poster (Table 64). As described in Section B.2.11, CLIMB-131 is an ongoing, long-term follow-up study for TDT patients who received exa-cel in the parent CLIMB THAL-111. Only a small subset of patients (n=8) have completed CLIMB THAL-111 and enrolled onto CLIMB-131 (86), and as such there are no publications relating to this trial.

CLIMB THAL-111 is an ongoing Phase 1/2/3 single-arm, open-label, multicentre, single-dose study investigating the safety and efficacy of exa-cel in patients aged 12-35 years with TDT. The study protocol for CLIMB THAL-111 included three interim analyses that were to be performed following a group sequential testing procedure to allow for an early evaluation procedure. The first interim analysis (IA1) was not performed. The results of the second interim analysis (IA2) provide the most recent data cut-off for CLIMB THAL-111, taken on 06 September 2022. Evidence from this interim analysis can be found in the CLIMB THAL-111 and CLIMB-131 interim clinical study reports (CSRs), dated December 2022 (7, 86). Data from the IA2 data cut was recently presented at the European Haematology Association (EHA) Congress, 08-15 June, 2023, outside of the timeframe for the clinical SLR search (8). Where possible, data from the publicly available EHA presentation will be used as the primary source of information in this section, with the CSR used to supplement where additional detail is required.

At the time of the IA2 data cut-off, 59 patients were enrolled and 48 were infused with exa-cel (7, 8). The final analysis of CLIMB THAL-111 (IA3) is planned to be performed once 45 patients have reached ≥16 months of post-infusion follow-up, with an efficacy boundary of 31 respondents, corresponding to a 69% response rate (7). All patients who complete CLIMB THAL-111 (followed-up for approximately two years after exa-cel infusion) or discontinue from the study will be asked to participate in a long-term follow-up study (NCT04208529) (7).

CLIMB-131 is designed to evaluate the long-term safety and efficacy of exa-cel in patients who received exa-cel in CLIMB THAL-111 and CLIMB SCD-121 (for patients with severe sickle cell disease) for a total of up to 15 years after exa-cel infusion. As of the data cut-off of 06 September 2022, 8 patients who completed CLIMB THAL-111 rolled over to study CLIMB-131. Evidence from the recent data cut-off provides the longest duration of follow-up on the efficacy and safety of exa-cel (8, 86). Further details of the ongoing CLIMB-131 study can be found in Section B.2.11.

CLIMB-131 is a long-term follow-up study for patients previously enrolled in CLIMB THAL-111 so, for the sake of brevity, we report the study methodology for CLIMB THAL-111 in Sections B.2.3 and B.2.4 and provide details on CLIMB-131 when reporting clinical effectiveness and safety data.

Table 9: Clinical effectiveness evidence

Study	CLIMB THAL-111 (NCT03655678)
Study design	A Phase 1/2/3 Study of the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ hHSPCs in Patients With TDT
Population	Patients with TDT aged 12 to 35 years
Intervention(s)	Exa-cel
Comparator(s)	None (CLIMB THAL-111 is a single-arm trial)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	Not applicable.
Reported outcomes specified in the decision problem	• **Reduction in transfusions** • Changes to haematological parameters (haemoglobin levels) • **Proportion with and time to engraftment** • New or worsening haematologic disorders • **Mortality** • **Adverse effects of treatment** • **Health-related quality of life**
All other reported outcomes	N/A

Key: hHSPC: human haematopoietic stem cell; N/A: not applicable; TDT: transfusion-dependent β-thalassaemia
Notes: Outcomes in bold are those directly used in the economic modelling.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. Study methodology

Table 10: Summary of study methodology for CLIMB THAL-111

Study	**CLIMB THAL-111 (NCT03655678)**
Location	This study is being conducted at 13 sites in the United States (5 sites), Canada (2 sites), United Kingdom (2 sites), Germany (3 sites), and Italy (1 site)
Study design	A Phase 1/2/3 Study of the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ hHSPCs in Patients With TDT
Key eligibility criteria for participants	**Inclusion criteria:** • Diagnosis of TDT, defined by homozygous or compound heterozygous β-thalassaemia, including β-thalassaemia/HbE) and by history of ≥100 mL/kg/year or ≥10 units/year of packed RBC transfusions in the prior 2 years • Aged 12 to 35 years • Eligible for autologous HSCT **Exclusion criteria:** • Willing and healthy 10/10 HLA-matched related donor • Sickle cell β-thalassaemia variant • Clinically significant and active bacterial, viral, fungal, or parasitic infection • Prior allogeneic haematopoietic SCT • Associated α-thalassaemia and >1 α deletion or α multiplications • WBC count <$3x10^9$ /L or platelet count <$50x10^9$ /L
Settings and locations where the data were collected	• Patients are hospitalised to undergo myeloablative conditioning and for treatment with exa-cel. Patients remain in the transplant unit until confirmation of successful engraftment and stabilisation of major medical issues as per local hospital guidelines and/or investigator judgement. • Ongoing data post-discharge is collected by the transplant unit in the outpatient setting. • Patients who enrol in the long-term follow-up study, CLIMB-131, will have outpatient follow-up visits every three months for the first three years, every six months in years four and five, and annual visits thereafter for up to 15 years after exa-cel infusion in CLIMB THAL-111.

Study periods and trial drugs	Given CLIMB THAL-111 was a single-arm study, all enrolled participants were dosed with exa-cel. For each patient, the study is conducted in four stages: **Screening and pre-mobilisation period (Figure 3; Stage 1):** • Informed consent and determination of patient eligibility • Fertility preservation via cryopreservation of oocyte or sperm, or gonadal tissue for pre-pubescent patients • RBC transfusions to achieve the goal of Hb ≥11 g/dL before the start of apheresis **Mobilisation, autologous CD34+ stem cell collection, exa-cel manufacture and disposition (Figure 3; Stage 2):** • Patients receive a combination of G-CSF products (e.g., filgrastim, 5 µg/kg every 12 hours) and plerixafor (0.24 mg/kg) prior to apheresis. The apheresis procedure lasts for three consecutive days to collect CD34+ cells. • Stem cell mobilisation with plerixafor four days before apheresis (0.24 mg/kg) and filgrastim/granulocyte colony-stimulating factor (G-CSF, 5 µg/kg every 12 hours for 5 to 6 days) followed by apheresis for three consecutive days to collect peripheral blood mononuclear cells. • Target collection of CD34+ cells for manufacturing of exa-cel is ≥15x10^6 CD34+ cells/kg (minimum target dose of 3×10^6 CD34+ cells/kg). Up to three cycles of mobilisation and apheresis, separated by ≥14 days, are allowed to achieve target collection. An additional 2x10^6 CD34+ cells/kg are collected as backup for rescue therapy in an event of non-engraftment of exa-cel. • Shipment of collected cells intended for manufacturing on the same day at 2°C to 8°C to the manufacturing facility. Cryopreservation of back-up CD34+ stem cells at the site. • If sufficient numbers of cells for exa-cel manufacturing and backup were not obtained, up to two mobilisation and apheresis cycles were allowed to collect additional cells. • Manufacturing of exa-cel from collected CD34+ cells by editing ex-vivo at the erythroid-specific enhancer region of *BCL11A* with a specific single-guide ribonucleic acid and Cas9 nuclease, which is delivered inside the cell using electroporation. **Myeloablative conditioning (Figure 3; Stage 3A) and infusion of exa-cel (Figure 3; Stage 3B):** • Conditioning (Stage 3A): Daily IV administration of busulfan at a starting dose of 3.2 mg/kg/day once daily or 0.8 mg/kg every 6 hours for 4 consecutive days. Busulfan dose was adjusted to maintain appropriate levels for myeloablation. Target area under the curve (AUC) for participants receiving once daily and every 6-

	hour dosing was 5,000 μM*min and 1,125 μM*min, respectively. Chelation has to be discontinued at least 7 days prior to starting busulfan. • Infusion of exa-cel (Stage 3B): A single infusion of exa-cel through a central venous catheter given at least 48 hours and not later than 7 days after the last busulfan dose. **Follow-up through engraftment and up to two years after exa-cel infusion:** • Post-infusion in-hospital follow-up during engraftment (Figure 3; Stage 4A): Monitoring in the transplant unit and supportive care according to standard practices for patients undergoing HSCT, with supporting RBC transfusions (recommended for Hb<7.0 g/dL) and platelet transfusions when medically indicated and monitoring for AEs and engraftment. • Post-engraftment follow-up (Figure 3; Stage 4B): Follow-up for approximately 2 years from exa-cel infusion, with physical examinations, laboratory and imaging assessments, and evaluations for AEs. Patients were recommended not to restart iron chelation (if needed) until at least three months after exa-cel infusion. Bone marrow aspirates are obtained at 6, 12, and 24 months after exa-cel infusion and next-generation sequencing is used to measure the fraction of on-target allelic editing in CD34+ bone marrow cells. A total of 59 patients were enrolled at the time of the IA2 data cut-off date (06 September 2022). All patients who received exa-cel infusion who completed or discontinued CLIMB THAL-111 were asked to participate in study CLIMB-131. Patients will be followed up for a total of up to 15 years after exa-cel infusion, including the two-year follow-up period from CLIMB THAL-111 and up to 13 years of follow-up in CLIMB-131.
Prior and concomitant medication	• RBC transfusions required to achieve the goal of pre-transfusion Hb ≥11 g/dL prior to the start of the apheresis procedure for at least 60 days prior to planned initiation of busulfan conditioning. • All iron chelation drugs were discontinued at least 7 days prior to starting myeloablative conditioning with busulfan. • During hospitalisation for busulfan conditioning and exa-cel infusions, patients should be supported with packed RBC and platelet transfusions as per standard or institutional practices for patients undergoing haematopoietic SCT. • During the follow-up period, patients should receive packed RBCs for Hb ≤7 g/dL or for clinical symptoms. • There are no prohibited medications.

Primary efficacy endpoint	• Proportion of patients achieving TI12*
Secondary outcomes used in the model/specified in the scope	• Proportion of patients achieving TI6** • Duration transfusion free for patients who achieved TI12 • Reduction in volume, units, and episodes of RBC transfusions • Total Hb and HbF concentration • Proportion of alleles with intended genetic modification • Patient-reported outcomes
Pre-planned subgroups	• Age at screening (12-<18 and 18-35) • Severity defined by genotype (β^0/ β^0-like and non-β^0/ β^0-like) • Gender (male and female)

Key: AE: adverse event; AUC: area under curve; CRISPR: clustered regularly interspaced short palindromic repeats; G-CSF: granulocyte colony-stimulating factor; Hb: haemoglobin; HbE: haemoglobin E; HbF: fetal haemoglobin; hHSPC: human haematopoietic stem and progenitor cells; HLA: human leukocyte antigen; IA2, interim analysis 2; IV: intravenous; PRO: patient-reported outcome; RBC: red blood cell; SCT: stem cell transplantation; TDT: transfusion-dependent β-thalassaemia; TI6: transfusion independence for at least 6 consecutive months; TI12: transfusion independence for at least 12 consecutive months; WBC: white blood cell.
Notes: *TI12 is defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion. **TI6 is defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 6 consecutive months any time after exa-cel infusion. The evaluation of TI12 and TI6 starts 60 days after the last RBC transfusion for post-transplant support or TDT disease management.

B.2.3.2. Study design

CLIMB THAL-111 is a Phase 1/2/3 single-arm, open-label, multi-site, single-dose study investigating the safety and efficacy of exa-cel in patients aged 12 to 35 years with TDT. Transfusion dependence was defined as a history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the two years before signing the informed consent form (7).

Approximately 45 patients were planned to be dosed in the CLIMB THAL-111 pivotal study to assess the efficacy and safety of a single dose of exa-cel, with the proportion of TI for at least 12 consecutive months (TI12) as the primary endpoint. TI12 was defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after the RBC transfusion washout period (60 days after the last RBC transfusion for post-transplant support or TDT disease management) (7).

As described above in Table 10, and depicted in Figure 3, the study was conducted in four stages:

- **Stage 1**: Screening and pre-mobilisation period
- **Stage 2:** Mobilisation, autologous CD34+ stem cell collection, exa-cel manufacture and disposition
- **Stage 3A**: Myeloablative conditioning
- **Stage 3B:** Exa-cel infusion
- **Stage 4A**: Post-infusion in-hospital follow-up
- **Stage 4B**: Post-engraftment follow-up

At the time of IA2 data cut on 06 September 2022, 59 patients were enrolled in the pivotal CLIMB THAL-111 clinical study, of which 48 had received exa-cel infusion. Of these 48 patients, 44 had completed the initial RBC transfusion washout period (7, 8).

Upon the conclusion of CLIMB THAL-111 at Month 24, or upon the discontinuation of the study, all patients who received infusion with exa-cel were asked to participate in the long-term follow-up study, CLIMB-131. This study aims to evaluate the long-term efficacy and safety of exa-cel in patients who received exa-cel in a parent study (CLIMB THAL-111 or CLIMB SCD-121) for a total follow-up of 15 years after exa-cel infusion. Patients who roll over into the long-term follow-up study will have follow-up visits every three months for the first three years, every six months in years four and five, and annual visits thereafter for up to 15 years after infusion of exa-cel in CLIMB THAL-111 (86).

At the time of the most recent data cut-off, eight patients who completed CLIMB THAL-111 rolled over to study CLIMB-131 (8, 86).

B.2.3.3. Eligibility criteria

The key inclusion and exclusion criteria for CLIMB THAL-111 are described below in Table 11.

Table 11: Key eligibility criteria for CLIMB THAL-111

Key inclusion criteria	Key exclusion criteria
• Diagnosis of TDT, defined by homozygous or compound heterozygous β-thalassaemia, including β-thalassaemia/HbE) and by history of ≥100 mL/kg/year or ≥10 units/year of packed RBC transfusions in the prior 2 years • Aged 12 to 35 years • Eligible for autologous haematopoietic SCT	• 10/10 HLA-matched related donor • Sickle cell β-thalassaemia variant • Clinically significant and active bacterial, viral, fungal, or parasitic infection • Prior allo-SCT • Associated α-thalassaemia and >1 α deletion or α multiplications • WBC count <$3x10^9$ /L or platelet count <$50x10^9$ /L • LIC ≥15 mg/g dry weight on R2 MRI of liver, unless liver biopsy within 3 months before or at screening showed no evidence of bridging fibrosis or cirrhosis • Cardiac T2* <10 msec by MRI or LVEF <45% by echocardiogram

Key: Allo-SCT: allogeneic stem cell transplant; HbE: haemoglobin E; HLA: human leukocyte antigen; LIC: liver iron content; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; RBC: red blood cell; SCT: stem cell transplantation; TDT: transfusion-dependent β-thalassaemia; WBC: white blood cell.
Source: Section 9.3, CLIMB THAL-111 CSR (7).

For a full list of eligibility criteria, please refer to the CSR (7).

B.2.3.4. Settings and locations where the data were collected

CLIMB THAL-111 was conducted at a total of 13 study centres across the US, Canada, UK, Germany, and Italy. Patients were hospitalised to undergo myeloablative conditioning and exa-cel infusion (Stages 3A/3B) and remained in hospital post-infusion until successful neutrophil engraftment and stabilisation of major medical issues as per local hospital guidelines and/or investigator judgement. All remaining treatment and study procedures occurred on an outpatient basis (7).

B.2.3.5. Trial drugs and concomitant medications

B.2.3.5.1. Trial drugs

Mobilisation (Stage 2) consisted of a combination of G-CSF products (e.g., filgrastim) and plerixafor. Granulocyte-colony stimulating factor (G-CSF) was administered subcutaneously (SC) or intravenously (IV) at a dose of 5 µg/kg approximately every 12 hours for four days prior to apheresis. The dose was based on body weight taken within five days of the first day of mobilisation. Plerixafor was administered SC after

the patient had received G-CSF for four days; the recommended dose was 0.24mg/kg administered approximately four to six hours before planned apheresis. Like G-CSF, the dose was based on body weight taken within five days before the first day of mobilisation (87).

Patients underwent apheresis for two or three consecutive days to collect $CD34^+$ hHSPCs for exa-cel manufacturing and backup CD34+ cells for rescue therapy in the event of non-neutrophil engraftment with exa-cel (87). The targeted $CD34^+$ cell collection was at least 15 x 10^6 $CD34^+$ cells/kg in order to facilitate manufacturing of exa-cel (87).

Busulfan conditioning (Stage 3A) commenced once exa-cel was received at the patient's study site. Busulfan was administered IV through a central venous catheter daily at a starting dose of 3.2mg/kg/day for four consecutive days (based on body weight collected within three to seven days before the first day of busulfan administration). Once-daily dosing was the preferred schedule, but busulfan could be adjusted every six hours per study site's standard practice. The dose of busulfan was adjusted based upon the first dose busulfan pharmacokinetics to maintain appropriate levels for myeloablation. During busulfan conditioning, anti-seizure prophylaxis and other supportive measures were instituted as per hospital guidelines (87).

Patients received the entire dose of exa-cel at least 48 hours, and within seven days, after the last busulfan dose (Stage 3B) (87). To ensure engraftment in all patients, a conservative minimum dose of ≥3 × 10^6 CD34+ cells/kg, which is 20% to 50% higher than the typical minimum dose for autologous transplantation was assessed (7).

Following exa-cel infusion (Stage 4A), patients underwent infection surveillance and prophylaxis as per local guidelines for allo-SCT and investigator judgement. Broad spectrum antibiotic treatment for febrile neutropenia and other supportive measures were administered as per local hospital guidelines/investigator judgement. (87).

B.2.3.5.2. Concomitant medication

There were no prohibited medications in the CLIMB THAL-111 study (7). Further details on the use of transfusions and ICT are outlined below.

Transfusions

Prior to the start of apheresis, and for at least 60 days prior to the planned initiation of busulfan conditioning, patients were transfused to achieve the goal of pre-transfusion Hb ≥11 g/dL. This was done to suppress ineffective erythropoiesis and to allow for a more successful engraftment (87).

Furthermore, during hospitalisation for busulfan conditioning and exa-cel infusion, patients were supported with packed RBC and platelet transfusions as per standard or institutional practices for patients undergoing allo-SCT (87).

Post-exa-cel infusion, it was recommended that patients received packed RBCs for Hb ≤7 g/dL or for clinical symptoms (87).

Iron chelation therapy

All ICTs were required to be discontinued at least seven days prior to undergoing myeloablative conditioning with busulfan (87).

Patients were regularly evaluated to determine whether chelation post exa-cel infusion was required. If required, iron chelation with DFO or DFX was recommended not to be restarted until at least three months following exa-cel infusion to allow for stable haematopoietic recovery and avoid potential myelosuppressive effects. Iron chelation with DFP was not recommended until at least six months post exa-cel infusion, if needed (87).

B.2.3.5.3. Restricted medications

There were no restricted medications in CLIMB THAL-111 (87).

B.2.3.6. Outcomes used in the economic model or specified in the scope, including primary outcome

The primary efficacy endpoint of CLIMB THAL-111 is the proportion of patients achieving TI12, defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion. The evaluation of TI12 starts 60 days after the last RBC transfusion for post-transplant support or TDT disease management (washout period) (7).

Other secondary efficacy endpoints used to evaluate the clinical benefit of exa-cel are summarised in Table 12 below (7).

Table 12: CLIMB THAL-111 secondary endpoints

Endpoint	Definition
RBC transfusions	• Proportion of patients achieving transfusion independence for at least six consecutive months (TI6), defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions. Evaluation of TI6 starts 60 days after last RBC transfusion for post-transplant support or TDT disease management. • Proportion of patients achieving >95%, 90%, 85%, 75%, and 50% reduction from baseline in annualised transfusions up to 24 months starting 60 days after exa-cel infusion • Relative change from baseline in transfusions up to 24 months starting 60 days after exa-cel infusion • Duration of transfusion-free period in participants who have achieved TI12 up to 24 months starting 60 days after exa-cel infusion
Allelic editing	• Proportion of alleles with intended genetic modification present in peripheral blood leukocytes and $CD34^+$ bone marrow cells over time
HbF and Hb	• Change in HbF and Hb concentration over time from baseline through to Month 24 • Change in proportion of F-cells over time
PROs	• Changes in PROs over time from screening through to Month 24: o EQ-5D-5L o FACT-BMT
Iron overload markers	• Change in LIC, CIC, and ferritin parameters of iron overload from screening through to Month 24
ICT	• Proportion of patients receiving ICT after exa-cel infusion through to Month 24

Key: CIC: cardiac iron content; EQ-5D-5L: EuroQol Questionnaire 5 Dimensions-5 Levels of Severity; FACT-BMT: functional assessment of cancer therapy-bone marrow transplant; Hb: haemoglobin; HbF: fetal haemoglobin; ICT: iron chelation therapy; LIC: liver iron concentration; PedsQL: paediatric quality of life inventory; PRO: patient-reported outcome; RBC: red blood cell; TI6: transfusion independence for at least six consecutive months; TI12: transfusion independence for at least 12 consecutive months.
Source: CLIMB THAL-111 CSR (7).

Safety endpoints used to evaluate the safety of exa-cel include (7):

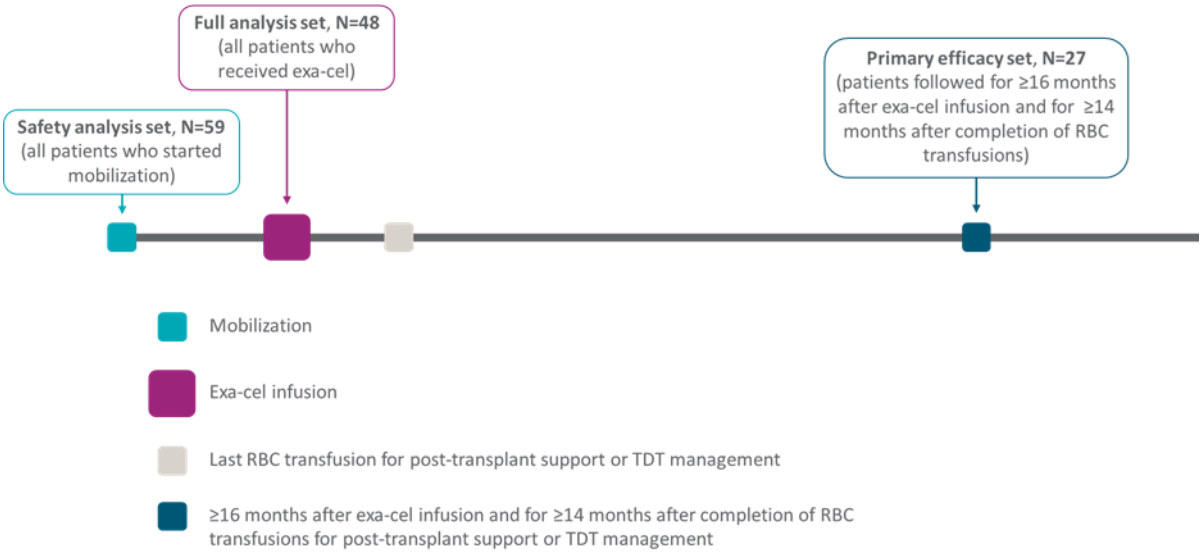
- Safety and tolerability assessments based on AEs, clinical laboratory values, and vital signs

- Successful neutrophil engraftment
- Successful platelet engraftment
- Incidence of transplant-related mortality within 100 days and within one year post-exa-cel infusion
- All-cause mortality

B.2.3.7. Patient datasets

All study analysis sets are summarised in Figure 12. Efficacy analyses were performed using the Primary Efficacy Set (PES), unless otherwise stated. The PES is a subset of the Full Analysis Set (FAS), and includes all patients who have been followed for at least 16 months after exa-cel infusion and for at least 14 months after completion of RBC transfusions for post-transplant support or TDT disease management. The analysis of safety was performed on the Safety Analysis Set (SAS), a subset of all enrolled patients who signed informed consent and met the eligibility criteria which included patients who started the mobilisation regimen (7).

Figure 12: CLIMB THAL-111 data collection points and analysis sets



Key: FAS: Full Analysis Set; PES: Primary Efficacy Set; RBC: red blood cell; SAS: Safety Analysis Aet; TDT: transfusion-dependent β-thalassaemia.
Notes: the number of patients in each analysis set was recorded at the time of IA2. A RBC transfusion washout period of 60 days after the last RBC transfusion for post-transplant support or TDT disease management was also required post exa-cel infusion. All patients who receive exa-cel will be eligible to enrol for 15 years in a long-term follow-up study (NCT04208529) after completion or withdrawal from CLIMB THAL-111.
Source: CLIMB THAL-111 CSR (7).

At the time of the IA2 data cut-off, all 59 patients started mobilisation and were included in the SAS, and 48 patients received exa-cel infusion and were included in the FAS (Table 13). Of note, 44 of 48 patients had completed the 60-day RBC transfusion washout period post exa-cel infusion, and as such were included in the analysis of the additional secondary efficacy endpoints. Twenty-seven patients were evaluable for the PES at the time of analysis (Table 13) (7, 8).

Table 13: Patient disposition (CLIMB THAL-111 and CLIMB-131)

Disposition/Reason	Total, n
Enrolled Set	59
SAS	59
Started the conditioning regimen	48
FAS	48
FAS beyond initial RBC transfusion washout period*	44
PES	27
Completed CLIMB THAL-111 and enrolled in CLIMB-131	8

Key: AE: adverse event; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; SAS: Safety Analysis Set; TDT: transfusion-dependent β-thalassaemia.
Notes: The Enrolled Set included all enrolled patients who signed informed consent and met eligibility criteria. The SAS included all patients who started the mobilisation regiment. The FAS included all patients who received exa-cel infusion. The PES included all patients who had been followed least 16 months after exa-cel infusion and for at least 14 months after completion of the RBC transfusions washout period.
*The RBC transfusion washout period refers to a 60-day period after the last RBC transfusion for post-transplant support or TDT disease management.
Source: Table 10-1, CLIMB THAL-111 CSR (7, 8).

The analysis of the primary endpoint, the proportion of patients who achieved TI12, and key secondary endpoint, the proportion of patients who achieved transfusion independence for at least six consecutive months (TI6), was limited to the PES (n=27) as not all patients in the FAS had sufficient follow-up to be included in the analysis. For the non-time specific efficacy endpoints, the reporting of clinical effectiveness results will focus on the FAS (Table 14), considering that this analysis set includes the longest duration of follow-up (median: 16.7 months [range: 0.0 - 43.7 months]) for a larger sample size (n=48), and is more representative of the eligible patient population given the higher proportion of patients aged ≥12 and <18 years (see Table 13). The results of the secondary endpoints for the PES can be found in the CLIMB THAL-111 CSR (7, 8).

Table 14: Analysis of efficacy endpoints (CLIMB THAL-111 and CLIMB-131)

Efficacy endpoint	Analysis set(s)	Relevant trial(s)
Primary endpoint		
TI12	PES	CLIMB THAL-111
Key secondary endpoint		
TI6	PES	CLIMB THAL-111
Additional secondary endpoint		
Duration of period free from transfusion	FAS	CLIMB THAL-111, CLIMB-131
Monthly reduction in the volume, units and episodes of RBC transfusions	FAS	CLIMB THAL-111, CLIMB-131
Total Hb and HbF concentration	FAS	CLIMB THAL-111, CLIMB-131
F-cells over time	FAS	CLIMB THAL-111, CLIMB-131
Proportion of alleles with intended genetic modification	FAS	CLIMB THAL-111, CLIMB-131
Parameters of iron overload	FAS	CLIMB THAL-111, CLIMB-131
Use of iron chelation therapy	FAS, PES	CLIMB THAL-111, CLIMB-131
PROs	FAS	CLIMB THAL-111

Key: FAS: Full Analysis Set; Hb: haemoglobin; HbF: fetal haemoglobin; PES: Primary Efficacy Set; PRO: patient-reported outcome; RBC: red blood cell; TI6: transfusion independence for at least six consecutive months; TI12: transfusion independence for at least 12 consecutive months.
Source: CLIMB THAL-111 CSR (7).

B.2.3.8. Baseline characteristics

Table 15 presents key baseline characteristics for the CLIMB THAL-111 FAS and PES. For the 48 patients in the FAS, the mean (range) age of patients was 21.4 years (range 12 to 35 years), with 16 patients ≥12 and <18 years of age. The mean age in CLIMB THAL-111 aligns closely with the mean age of UK patients enrolled in the BoI study (24.8 years [range: 1 to 88 years]) (2, 3). The majority of patients were Asian (39.6%) or White (37.5%) (7, 8). The proportion of Asian patients enrolled onto CLIMB THAL-111 is lower than the proportion enrolled onto the UK BoI study (53.6%) (2, 3).

Baseline mean (standard deviation [SD]) annualised units of TDT-related RBC transfusions per year for the prior two years before screening in CLIMB THAL-111 was 35.3 (11.5) units (7, 8), a value similar to that reported by Shah et al., (2021) in a UK TDT population (39), and the baseline mean (SD) annualised volume of TDT-related RBC transfusions was 195.3 (63.4) mL/kg per year (7, 8).

In addition, the majority of patients (58.3%) in the FAS had β^0/β^0-like genotypes (Table 15) (7, 8),which reflects the broader eligibility criteria of exa-cel compared to previously appraised therapies (51). Clinical experts consulted by Vertex highlighted that the inclusion of patients with β^0/β^0-like genotypes was highly important, given that these patients are typically worst affected by TDT (52). The genotypes observed in CLIMB THAL-111 were considered to reflect the spectrum of genotypes of TDT seen in UK clinical practice (52).

Table 15: Baseline characteristics in CLIMB THAL-111 (FAS and PES)

Baseline Characteristics	FAS (n=48)	PES (n=27)
Sex, n (%)		
Male	23 (47.9)	14 (51.9)
Female	25 (52.1)	13 (48.1)
Childbearing potential, n (%)		
Yes	25 (100.0)	25 (100.0)
Age at screening (years), n (%)		
n	48	27
Mean (SD)	21.4 (6.6)	21.8 (5.9)
Median	20.0	20.0
Min, Max	12, 35	12, 32
Age category at screening (years), n (%)		
≥12 and <18 years	16 (33.3)	5 (18.5)
≥18 and ≤35 years	32 (66.7)	22 (81.5)
Race, n (%)		
White	18 (37.5)	11 (40.7)
Black or African American	0	0
Asian	19 (39.6)	13 (48.1)
Not collected per local regulation	6 (12.5)	0
Other	2 (4.2)	0
Multiracial	3 (6.3)	3 (11.1)
Genotype, n (%)		
β^0/β^0-like	28 (58.3)	15 (55.6)
β^0/β^0	16 (33.3)	6 (22.2)
β^0/IVS-I-110	9 (18.8)	6 (22.2)
IVS-I-110/IVS-I-110	3 (6.3)	3 (11.1)
Non-β^0/β^0-like	20 (41.7)	12 (44.4)
β^+/β^+	4 (8.3)	3 (11.1)

β^{+}/β^{0}	11 (22.9)	5 (18.5)
β^{E}/β^{0}	5 (10.4)	4 (14.8)
Annualised volume of RBC transfusion (mL/kg)		
n	48	27
Mean (SD)	195.3 (63.4)	196.3 (59.7)
Median	193.8	190.7
Min, Max	48.3, 330.9	115.2, 330.9
Annualised units of RBC transfusion		
n	48	27
Mean (SD)	35.3 (11.5)	36.7 (12.2)
Median	34.8	34.0
Min, Max	11.0, 71.0	20.5, 71.0
Annualised number of RBC transfusion episodes[a]		
n	48	27
Mean (SD)	16.4 (5.4)	17.2 (5.7)
Median	16.5	16.5
Min, Max	5.0, 34.5	10.5, 34.5
Total Hb concentration (g/dL)		
n	47	27
Mean (SD)	10.5 (2.0)	10.2 (2.0)
Median	10.1	10.0
Min, Max	6.9, 14.2	6.9, 14.1
HbF concentration (g/dL)		
n	47	27
Mean (SD)	0.6 (0.9)	0.5 (0.6)
Median	0.3	0.3
Min, Max	0.0, 5.8	0.0, 2.2
HbF concentration (%)		
n	48	27
Mean (SD)	6.5 (11.4)	5.6 (6.6)
Median	3.4	3.4
Min, Max	0.0, 74.0	0.0, 21.3
F-cell level (%)		
n	48	27
Mean (SD)	14.3 (15.3)	15.1 (13.9)
Median	8.7	8.6
Min, Max	2.3, 83.9	3.0, 50.1
Serum ferritin level (pmol/L)[b]		
n	48	27
Mean (SD)	3740.7 (2817.0)	3705.2 (3019.1)
Median	3157.0	3184.0
Min, Max	584.2, 10837.3	674.1, 10740.7
Cardiac T2* (msec)[c]		
n	48	27
Mean (SD)	34.5 (9.4)	36.4 (8.4)
Median	34.8	35.3
Min, Max	12.4, 61.1	20.4, 61.1
Liver iron concentration (mg/g)[d]		
n	48	27

Mean (SD)	4.7 (3.2)	5.3 (3.3)
Median	3.8	4.0
Min, Max	1.2, 14.0	1.8, 12.5
Weight (kg)		
n	48	27
Mean (SD)	54.4 (14.1)	54.3 (12.1)
Median	52.0	52.0
Min, Max	30.0, 96.0	34.0, 78.0

Key: FAS: Full Analysis Set; F-cells: circulating erythrocytes expressing γ-globin (HbF); Hb: haemoglobin; HbF: foetal haemoglobin; ICF: informed consent form; LIC: liver iron concentration; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassaemia.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. Baseline volume of RBC transfusions, units of RBC transfusions, and number of RBC transfusion episodes were based on the 2 years before signing of the ICF or the latest rescreening for patients who rescreened. RBC transfusions were excluded from the baseline calculation if they were not for TDT disease management. Annualised volume = total volume/number of years. Annualised units = total units/number of years. Annualised number of episodes = total number of episodes/number of years. One year = 365.25 days. Hb measurements in this table are from central laboratories. Percentages were calculated relative to the number of patients in the FAS or the PES, unless otherwise specified. Percentages for childbearing potential were calculated relative to the number of females in the FAS or the PES.
[a]An RBC transfusion episode was defined as all transfusions within 5 days, starting from the first transfusion in the episode.
[b]Serum ferritin level is the measurement of tissue iron content. Normal serum ferritin is ≤2,247 pmol/L according to UKTS 2016 guidelines (25).
[c]Cardiac T2* is the measurement of cardiac iron content. Normal cardiac T2* score is >20ms according to UKTS 2016 guidelines (25).
[d]Liver iron concentration was derived from Liver R2. Normal LIC score is <7mg/day according to UKTS 2016 guidelines (25).
Sources: Table 10-12, Table 10-11 CLIMB THAL-111 CSR; EHA 2023 slides (7, 8, 86).

Of the eight patients who rolled over to CLIMB-131 from CLIMB THAL-111, six were female and two were male. Five patients had non-β^0/β^0-like genotypes (two β^+/β^+, two β^+/β^0, and one β^E/β^0), and three patients had β^0/β^0-like genotypes (two IVS-I-110/β^0 and one β^0/β^0). Patient ages ranged from 19 to 29 years. The baseline annualised units of TDT-related RBC transfusions ranged from 23.5 to 61.0 units per year, with a baseline annualised volume of 125.65 to 307.27 mL/kg per year, for the prior two years before screening in CLIMB THAL-111 (7, 8).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1. Analysis population

At the interim analysis, efficacy analyses were performed using the FAS, where applicable, and the PES (7).

The analysis of safety was performed on the SAS, a subset of the Enrolled Set that included all patients who started the mobilisation regimen (7).

B.2.4.2. Sample size

With a total of 45 patients dosed, three interim analyses could be performed following a group sequential procedure in the study to allow for early evaluation of efficacy. This sample size provided at least 95% power to rule out a response rate of 50% when the true response rate is 80% for both the primary and key secondary efficacy endpoint with 1-sided alpha of 2.5% (7).

B.2.4.3. Statistical analysis

A summary of statistical analyses for CLIMB THAL-111 is available below in Table 16.

Table 16: Summary of key statistical analyses used in CLIMB THAL-111

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT03655678 (CLIMB THAL-111)	The null hypothesis for the primary and key secondary efficacy endpoints assumed a 50% response rate.	The proportion of responders will be provided with a one-sided p value (against a null hypothesis of 50% response rate). Two-sided 95% CIs were calculated using the Clopper-	A sample size of 45 patients was to provide at least 95% power to rule out a response rate of 50% when the true response rate is 80% for both the primary and key secondary efficacy endpoint with	Incomplete/missing data were not imputed, unless otherwise specified. For patients who were lost to follow-up or died, safety and efficacy analyses were based on their available data before death or loss to follow-up. Month was defined as 30 days.

		Pearson method.	1-sided alpha of 2.5%.	

Key: CI: confidence interval.
Source: CLIMB THAL-111 CSR (7).

B.2.4.3.1. Primary efficacy analysis

As described previously, the primary efficacy endpoint is the proportion of the patients achieving TI12 defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion. The evaluation of TI12 starts 60 days after the last RBC transfusion for post-transplant support or TDT disease management. At interim analyses, the analysis of the primary efficacy endpoint was based on the PES. The proportion of patients achieving TI12 will be provided, with one-sided p-value (against a null hypothesis of 50% response rate) and two-sided 95% exact Clopper-Pearson confidence interval (CI). If the prespecified efficacy boundary is crossed at any interim analysis overwhelming efficacy is considered established for exa-cel (7).

B.2.4.3.2. Key secondary analysis

As described previously the key secondary efficacy endpoint is the proportion of patients achieving TI6, defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 6 consecutive months any time after exa-cel infusion. The evaluation of TI6 starts 60 days after the last RBC transfusion for post-transplant support or TDT disease management. As for the primary efficacy endpoint, interim analyses of the key secondary efficacy endpoint was based on the PES (7).

B.2.4.3.3. Other secondary efficacy analysis

At the interim analysis, the analysis of secondary endpoints was based on the FAS where applicable. Secondary endpoints were summarised using descriptive statistics (7).

B.2.4.3.4. Safety analysis

The overall safety profile of exa-cel was assessed in terms of the following safety and tolerability endpoints:

- AEs, serious adverse events (SAEs), laboratory values, and vital signs from signing of the informed consent form through to the Month 24 visit
- Mortality, including all-case mortality and transplant-related mortality
- Engraftment

Safety analyses were based on the SAS, unless otherwise specified. Only descriptive analysis of safety was performed; no statistical testing was performed (7).

B.2.4.4. Participant flow

Details of participant flow in the CLIMB THAL-111 clinical study are provided in Appendix D1.2.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from CLIMB THAL-111, a Phase 1/2/3 single-arm, open-label, multi-site, single-dose study. The quality assessment of CLIMB THAL-111 was conducted using the Downs and Black checklist, full details of which are provided in Appendix D1.3.

B.2.6 Clinical effectiveness results of the relevant studies

Summary of clinical effectiveness results

- The efficacy and safety of exa-cel in the treatment of patients between 12 and 35 years of age with TDT has been demonstrated in the single-arm, open-label, multi-site, single-dose CLIMB THAL-111 study and the long-term follow-up study, CLIMB-131.
- Patients with TDT were defined as having a history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the 2 years before signing the informed consent form.
- As of the IA2 data cut on 06 September 2022, 24 of 27 patients (88.9%) in the PES achieved the primary endpoint of TI12.
- In the FAS, 42 of 44 patients (95.5%) achieved TI at IA2, and were transfusion free for a range of 2.9 to 40.7 months starting 60 days after the last RBC transfusion, including one patient who did not achieve TI12 in the PES.
- The two patients in the FAS who were still receiving RBC transfusion after exa-cel infusion at the time of IA2 experienced a 76.9% and 95.5% reduction from baseline in annualised RBC transfusion volume.
- Total Hb concentration increased from 10.2 g/dL at baseline to 12.6 g/dL at Month 9, and remained >12g/dL from Month 9 onwards, with a trend for progressively increasing Hb concentration out to Month 42.
- After exa-cel infusion, high levels of *BCL11A* edited alleles in CD34+ bone cells as well as in peripheral blood cells were maintained, indicating the durable engraftment of edited long-term HSCs and reflecting the permanent nature of the intended edit.
- The currently available data indicate that in patients with TDT, exa-cel results in robust, consistent, and durable benefits, offering the potential to deliver a disease-free state for patients with TDT while maintaining a favourable benefit to risk profile.

Exa-cel cohorts and analysis sets are summarised in Section B.2.3.7, and presented for clarity in Figure 12.

B.2.6.1. Primary and key secondary efficacy endpoints

Following infusion with exa-cel, 88.9% of patients (24 of 27 patients, 95% CI: 70.8%, 97.6%) in the PES achieved TI6 ($p<0.0001$), with the same proportion of patients going on to achieve TI12 (24 of 27 patients, 95% CI: 70.8%, 97.6%) ($p<0.01416$) (7, 8).

Information on the three patients in the PES who had not achieved TI12 at the time of IA2 data cut-off is presented below (7).

- [redacted] received less frequent RBC transfusions over time through 14.5 months after exa-cel infusion (70.3% annualised reduction from baseline in RBC transfusion volume). The patient did not receive any further RBC transfusion starting 14.5 months after exa-cel infusion through the most recent IA2 data-cut for a duration of approximately 4.9 months (includes RBC transfusion washout period and 2.9 months of transfusion free follow-up, with a total follow-up of 19.4 months after exa-cel infusion).

- [redacted] Following exa-cel infusion, this patient has received transfusions approximately 1 to 2 months since Month 8, with monthly transfusion volume decreasing over time (79.6% reduction from baseline). The last RBC transfusion was on Study Day 556 [redacted]

- [redacted] received less frequent RBC transfusion over time up to 12.2 months after exa-cel infusion (95.5% reduction in annualised RBC volume). After exa-cel infusion and post-transplant support treatment for 6.3 months, the patient did not receive any further RBC transfusions for a duration of approximately 5.9 months (includes RBC transfusion washout period) and 3.9 months of transfusion free follow-up. [redacted]

B.2.6.2. Secondary efficacy endpoints

B.2.6.2.1. Duration of period free from transfusion

At the time of the IA2 data cut-off, 42 of 44 patients in the FAS who had completed the RBC transfusion washout period were transfusion free, with duration free from transfusion ranging from 2.9 to 40.7 months (8, 86). The remaining 2 patients were still receiving RBC transfusions after exa-cel infusion. These patients (Patient [redacted] and Patient [redacted] above) had achieved a 79.6% and 95.5% reduction from baseline in annualised RBC transfusion volume, respectively, as described in the discussion of the primary endpoint. In the context of the pre-infusion RBC transfusion frequency among the same patients at baseline (53.5 units per year and 71.0 units per year, respectively), this represents a substantial reduction in transfusion burden [Table 15]) (8, 86).

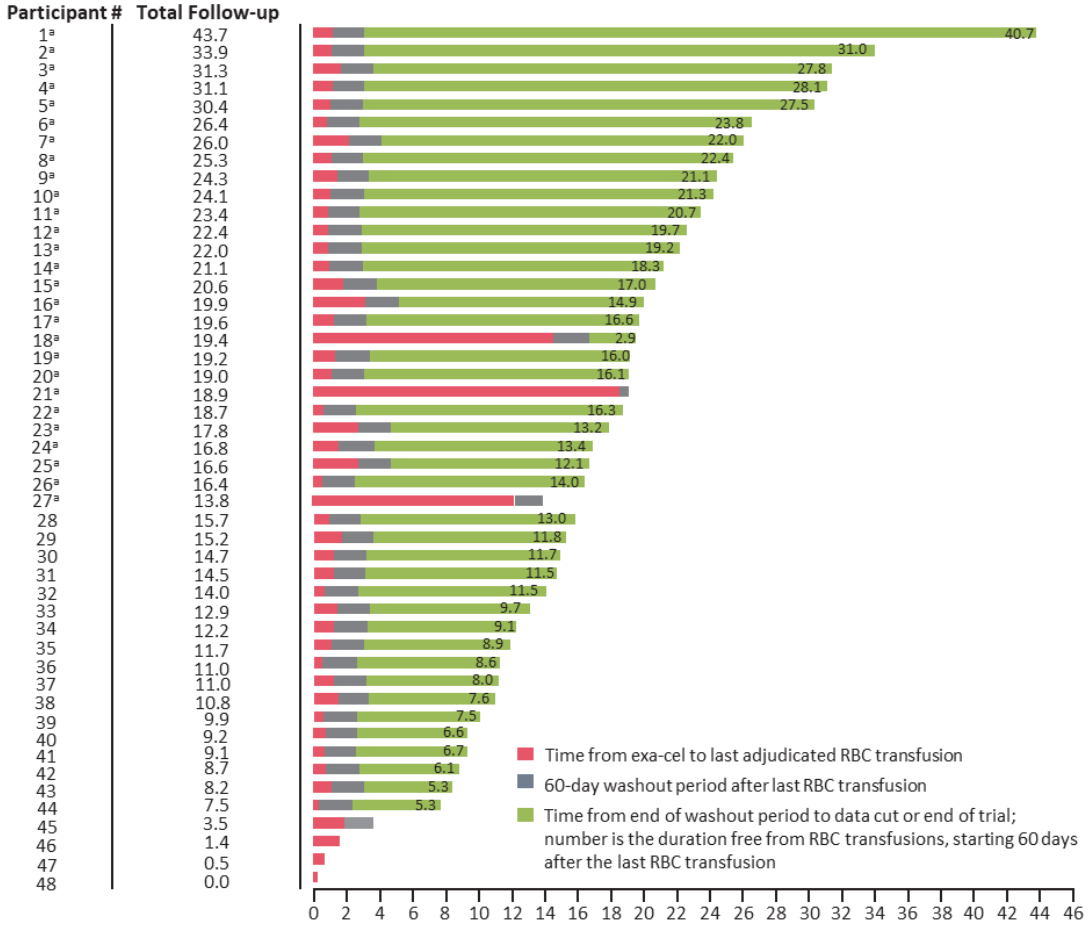
A further four patients had insufficient follow-up since exa-cel infusion. Of these, three patients stopped receiving RBC transfusions and were within the initial RBC transfusion washout period after exa-cel infusion. One patient was dosed with exa-cel on the day of the IA2 data cut-off (7).

As noted in Section B.1.3.2.1.a, regular RBC transfusions require a lifetime administration of ICT, which itself is associated with adverse events, including abdominal pain, nausea, and diarrhoea (6, 64). By achieving TI in 95.5% of patients in the FAS who had completed the RBC transfusion washout period, exa-cel helps patients eliminate the requirements for RBC transfusions and reduces complications associated with iron overload. Even for the minority that have not yet achieved TI with exa-cel, key opinion leaders with expertise in the treatment of β-thalassaemia considered a reduction in annualised transfusion volume of at least 60% to provide a clinically meaningful benefit to TDT patients and allow for improved iron management (88).

None of the eight patients who rolled over to CLIMB-131 have required any RBC transfusions. The total duration of time free from transfusion for these patients ranged from 22.0 to 40.7 months (8, 86).

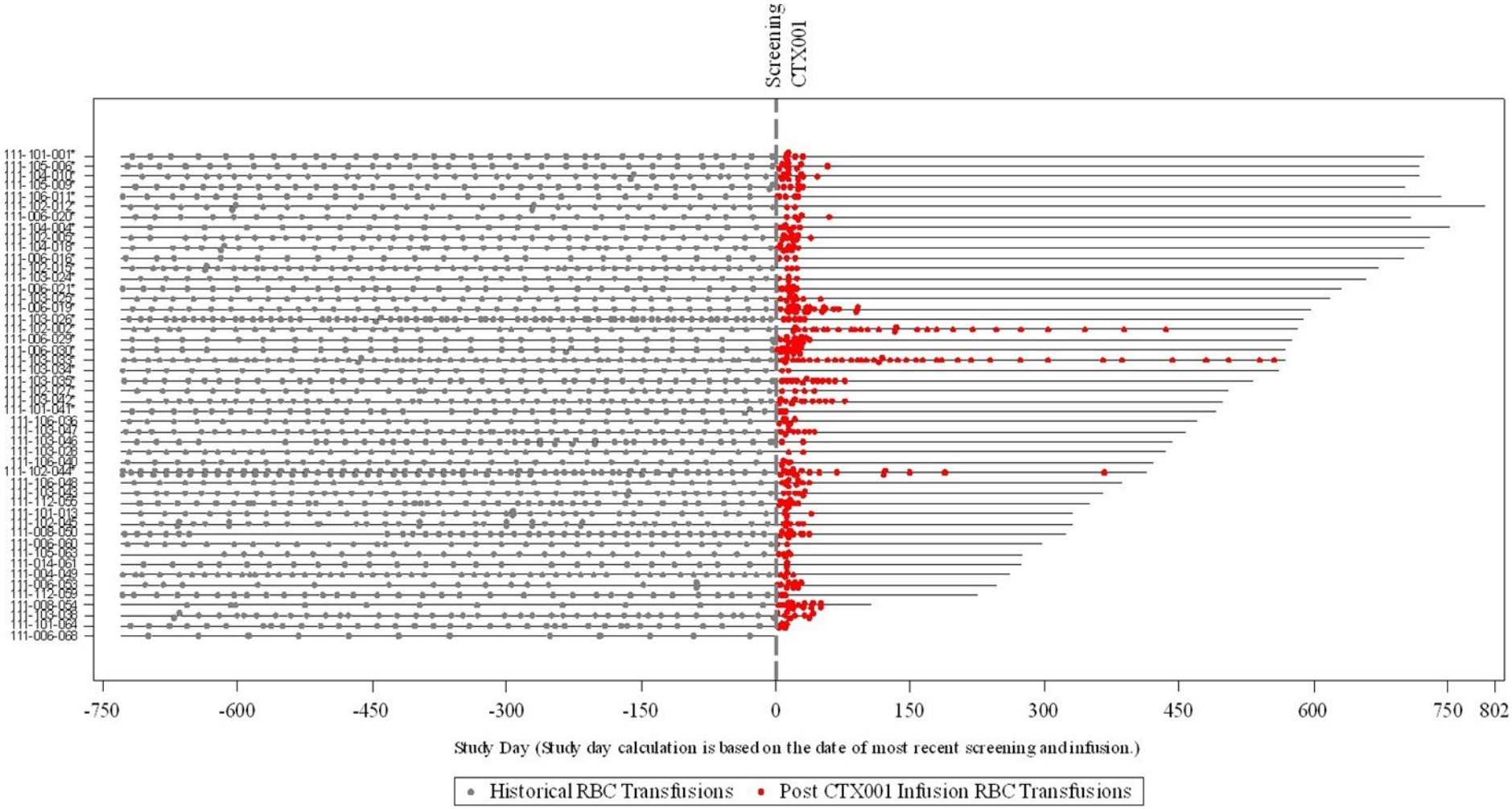
Duration of period free from transfusion by individual patient in CLIMB THAL-111 and CLIMB-131 is presented below in Figure 13. Frequency of transfusion data pre- and post- exa-cel are presented for the FAS are presented in Figure 14.

Figure 13: Duration of period free from transfusion (CLIMB THAL-111 and CLIMB-131, FAS)



Key: EAC: Endpoint Adjudication Committee; FAS: Full Analysis Set; PES: primary analysis set; RBC: red blood cells; TDT: transfusion-dependent β-thalassaemia; TI: transfusion independence.
Note: Each row in the figure represents an individual patient. Only RBC transfusions adjudicated by the EAC for post-transplant support or TDT disease management were included. The number on the right end is the duration of TI including the washout period of 60 days.
[a]Indicates patients in the PES.
Source: Figure 11-1, CLIMB-131 CSR; EHA 2023 slides (8, 86).

Figure 14: Historical and after exa-cel infusion RBC transfusions (CLIMB THAL-111, FAS)



Key: CTX001: exa-cel; FAS: Full Analysis Set; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassaemia.
Notes: Investigator reported TDT-related historical RBC transfusions and all post-infiusion RBC transfusions are included. This figure is not available for CLIMB-131.
*Indicates patients in the PES.
Source: Figure 11-4, CLIMB THAL-111 CSR (7).

B.2.6.2.2. Monthly reduction in the volume, units, and episodes of RBC transfusions

At Month 12, the mean (SD) monthly relative reduction from baseline in RBC transfusions was 98.0% (11.8%) by volume, 97.9% (2.5%) by units, and 97.9% (12.5%) by episodes (n=35), For patients with data at Month 24 (n=11), the mean monthly relative reduction from baseline in RBC transfusion volume, units, and episodes was 100.0% (86).

B.2.6.2.3. Total Hb and HbF concentration over time

In CLIMB THAL-111, increases in total Hb and HbF occurred within three months of exa-cel infusion and were maintained over the duration of follow-up (86).

Total Hb concentration increased substantially in TDT patients treated with exa-cel. Mean (SD) total Hb levels of 11.4 (2.3) g/dL were achieved by Month 3 after exa-cel infusion, with mean total Hb levels increasing to and maintained at >12 g/dL thereafter (Figure 15) (8, 86).Clinical advisors were encouraged by the data showing that steady-state Hb levels had increased (52).

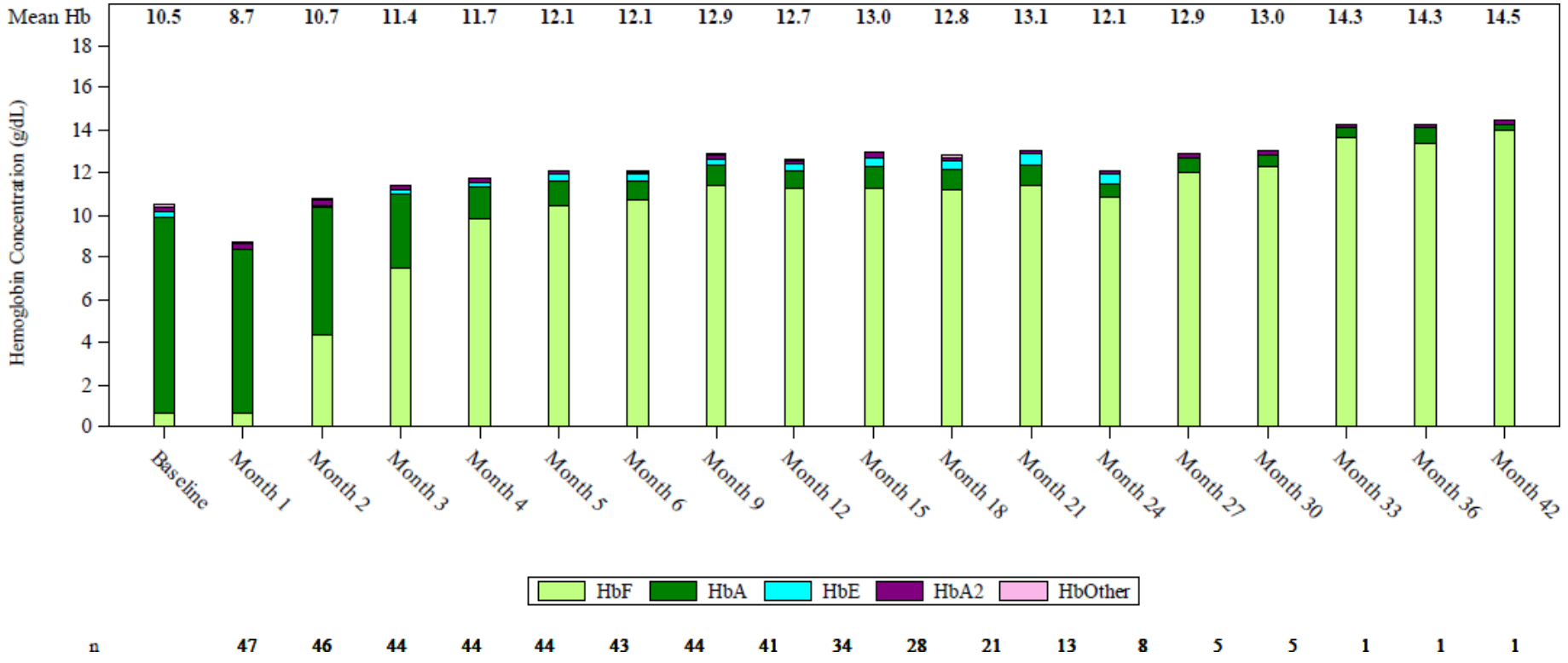
At Month 3 after infusion with exa-cel, mean (SD) HbF levels of 7.7 (3.0) g/dL were observed, which represented a substantial increase from baseline (mean: 0.63 [0.95] g/dL). Mean HbF levels were thereafter maintained at >10 g/dL over the duration of follow-up (Figure 16) (8, 86). The observed increase in HbF levels is consistent with the mechanism of action of exa-cel, which mimics the activity of HPFH, a naturally occurring genetic variation identified in some β-thalassaemia patients that causes continued expression of HbF into adulthood (10-12).

Patients with co-inheritance of β-thalassaemia and HPFH have raised HbF throughout their lives, and experience reduced or no β-thalassaemia-associated symptoms (10-12). The proportion of total Hb comprised by HbF was 66.0% at Month 3 after exa-cel infusion, substantially greater than the levels observed in patients with the HPFH phenotype, with the proportion increasing and maintained at >87% thereafter (Figure 15) (86). Published literature have demonstrated that increases in HbF have a protective effect ameliorating comorbidities of β-thalassaemia, including extramedullary haematopoiesis, pulmonary hypertension, venous thromboembolism,

heart failure, leg ulcers, abnormal liver function, diabetes, hyperthyroidism, hypogonadism, and osteoporosis (11).

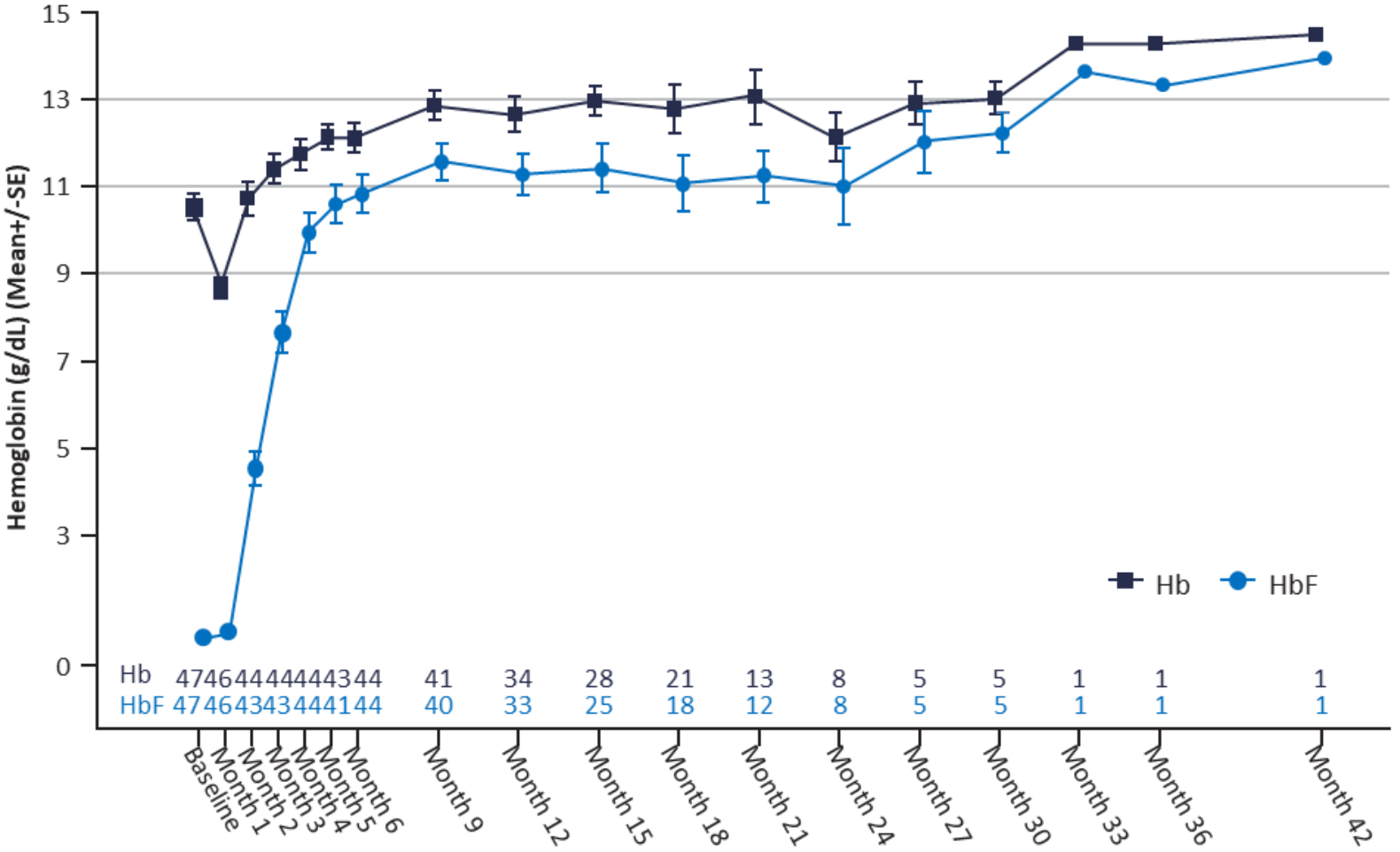
For the 8 patients who rolled over to CLIMB-131, the increases in mean total Hb and HbF levels observed in CLIMB THAL-111 from Month 6 were stable and were maintained after Month 24 in CLIMB-131, with mean total Hb levels >11.48 g/dL and mean HbF levels >9.92 g/dL for up to 42 months after exa-cel infusion (8, 86). Clinical experts confirmed that patients sustaining Hb concentration at 11.5 – 12.0 g/dL over a two-year period would be unlikely to develop the long-term sequelae of TDT (52).

Figure 15: Changes in Hb fractionation over time (CLIMB THAL-111 and CLIMB-131, FAS)



Key: Hb: haemoglobin, HbA: adult haemoglobin; HbE: haemoglobin E; HbA2: haemoglobin A2; HbF: fetal haemoglobin.
Notes: Mean Hb fractions are plotted at each visit. The numbers of patients with total Hb values available at the corresponding visits are shown at the bottom. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. Analysis visit was used in the figure.
Source: Figure 14.2.5.3a, CLIMB-131 CSR (86).

Figure 16: Summary of total Hb (g/dL) and HbF (g/dL) over time (CLIMB THAL-111 and CLIMB-131,FAS)

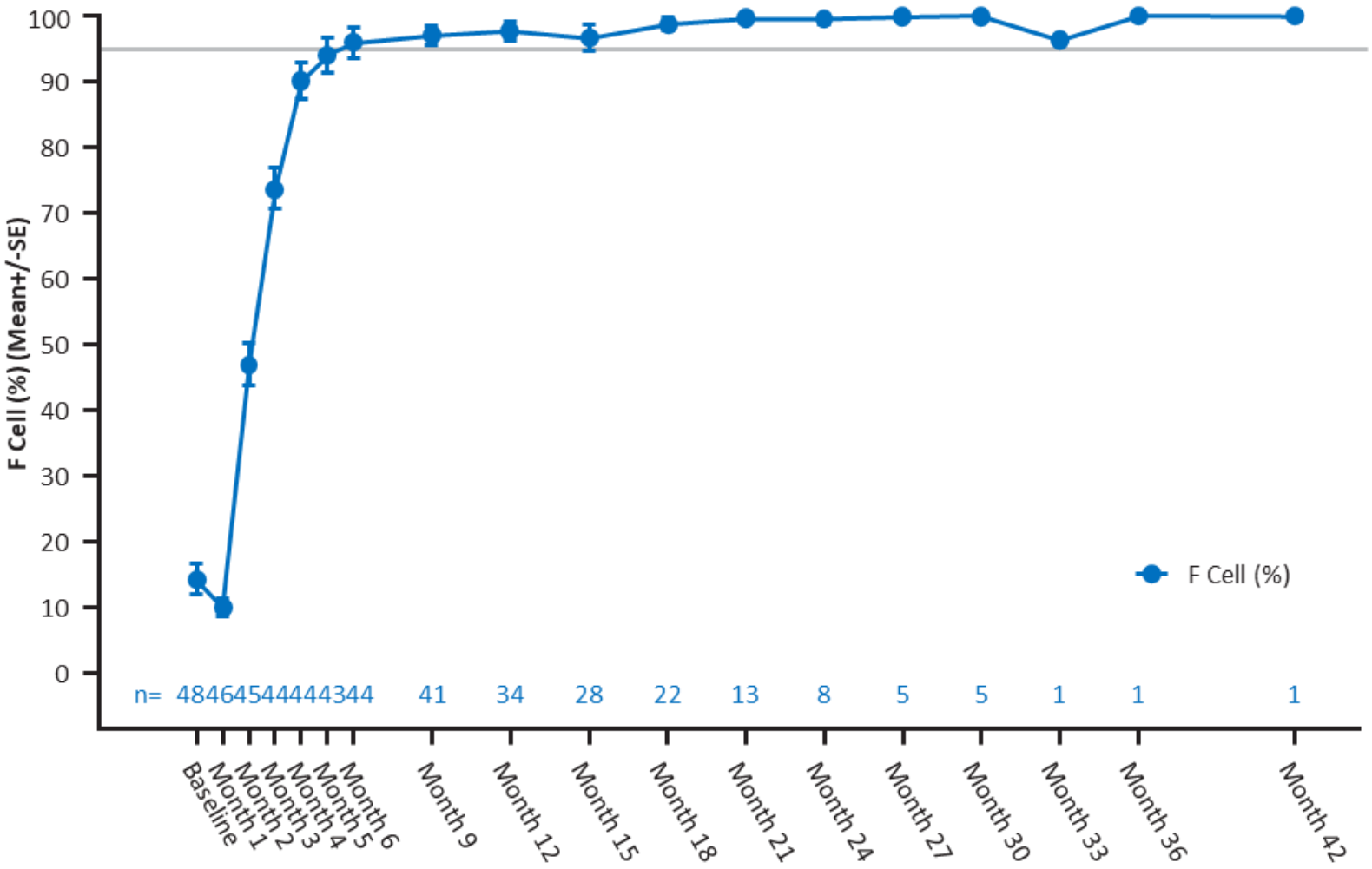


Key: FAS: Full Analysis Set; Hb: haemoglobin; HbF: fetal haemoglobin;SE: standard error.
Notes: Mean values are plotted in the line; mean + SE and mean – SE values are plotted as bars at each visit. The numbers of patients with total Hb and HbF values available at the corresponding visits are shown at the bottom. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. Analysis visit was used in the figure.
Source: Figure 11-4; CLIMB-131 CSR; EHA 2023 slides (8, 86).

B.2.6.2.4. F-cells over time

Consistent with observed HbF increases, the mean proportion of circulating RBCs expressing HbF (termed F-cells) was maintained at >95% from Month 6 through the duration of follow-up in CLIMB-131 (Figure 17) (8, 86). Elevated HbF can reduce the α-globin to β-globin chain imbalance by providing γ-globin chains that are able to bind to the unpaired α-globin (89). These raised levels of HbF are a characteristic of β-thalassaemia patients with the HPFH phenotype who, as already highlighted, experience reduced or no β-thalassaemia-associated symptoms (10-12).

Figure 17: HbF expression in circulating RBCs over time (CLIMB THAL-111 and CLIMB-131, FAS)



Key: FAS: Full Analysis Set; F-cells: erythrocytes expressing γ-globin (fetal haemoglobin).
Notes: Mean values are plotted in the line, mean + SE and mean - SE values are plotted as bars at each visit. The number of patients with F-cell values available at the corresponding visits are shown at the bottom. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. Analysis visit was used in the figure.
Source: Figure 11-10, CLIMB-131 CSR; EHA 2023 slides (8, 86).

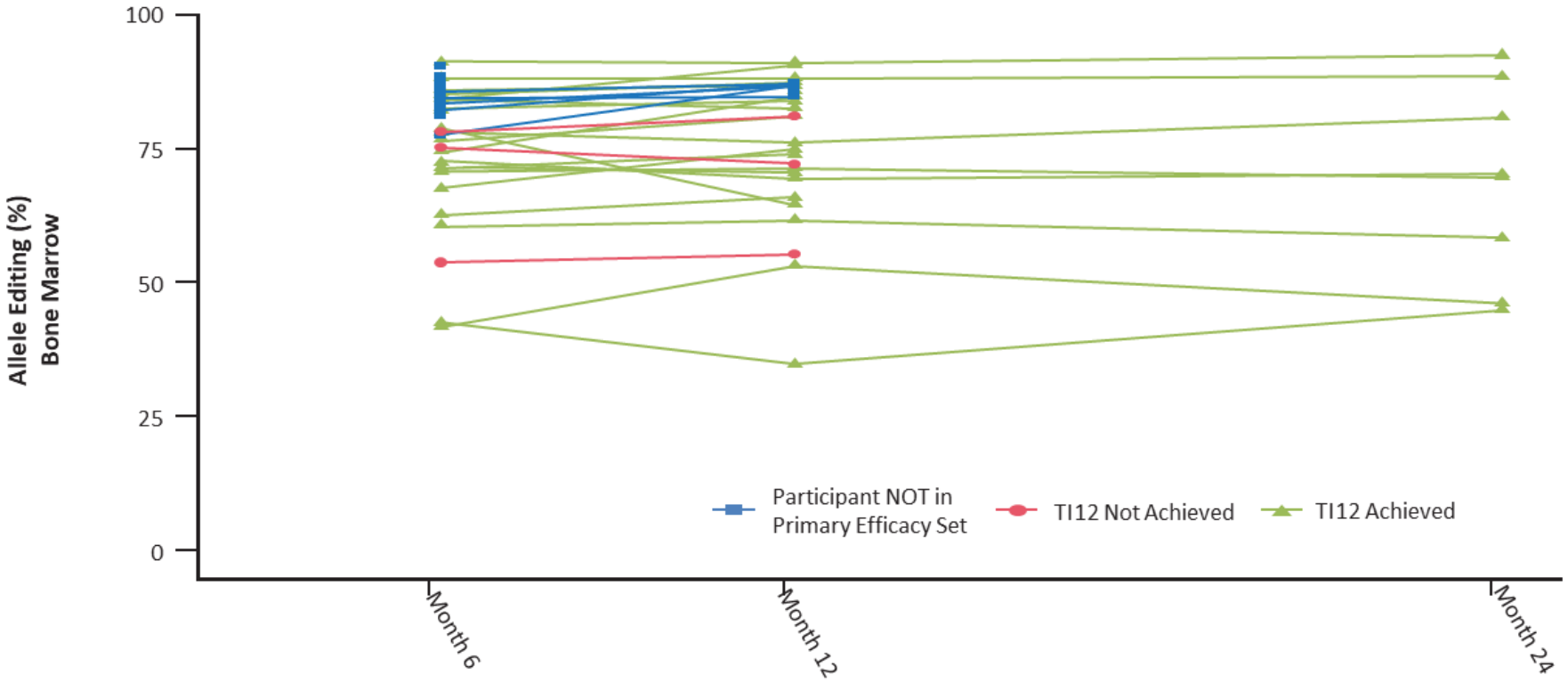
B.2.6.2.5. Proportion of alleles with intended genetic modification

A high, stable proportion of alleles with the intended genetic modification was observed in both the CD34+ cells of the bone marrow and peripheral blood, indicating durable engraftment of edited long-term HSCs and reflecting the permanent nature of the intended edit (52).

At Month 6 (first timepoint of evaluation), the mean (SD) proportion of alleles with intended genetic modification in the CD34+ cells of the bone marrow was 77.9% (11.7%), which was consistent with allelic editing of the drug product. The mean proportion of alleles with the intended genetic modification in the CD34+ cells of the bone marrow remained stable at Month 12 (≥68%) onwards (Figure 18). No patients who enrolled over to CLIMB-131 had bone marrow allelic editing data after Month 24 as of the most recent data cut-off (8, 86).

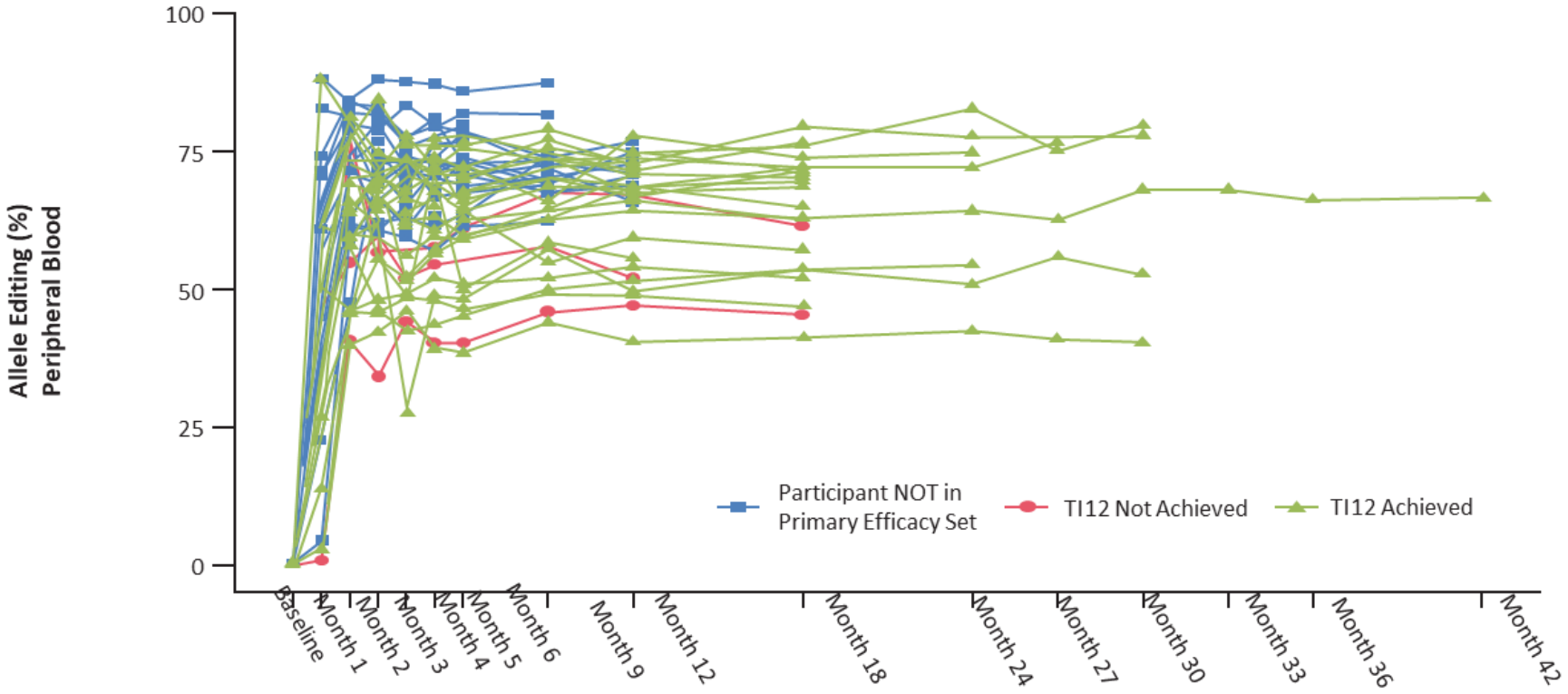
Similarly, allelic editing in the peripheral blood was detectable within one month after exa-cel infusion. The mean (SD) proportion of alleles with the intended genetic modification in peripheral blood was 58.6% (21.0%) at Month 1 and the mean remained ≥60% from Month 2 onwards (Figure 19) (8, 86).

Figure 18: Proportion of edited alleles in CD34+ bone marrow (CLIMB THAL-111 and CLIMB-131, FAS)



Key: FAS: Full Analysis Set.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. Analysis visit was used in the figure.
Source: Figure 11-8, CLIMB-131 CSR; EHA 2023 slides (8, 86).

Figure 19: Proportion of edited alleles in peripheral blood cells (CLIMB THAL-111 and CLIMB-131, FAS)



Key: FAS: Full Analysis Set.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. Analysis visit was used in the figure.
Source: Figure 11-7, CLIMB-131 CSR; EHA 2023 slides (8, 86).

Allelic editing in the peripheral blood is lower than allelic editing in the CD34+ cells of the bone marrow because the peripheral blood includes lymphocytes that are not derived from the edited CD34+ stem cells. With single agent busulfan conditioning, peripheral blood lymphocytes are not depleted. This results in a proportion of peripheral blood lymphocytes having been derived prior to therapy from stem cells that were not edited and led to the observed decreased allelic editing in the peripheral blood compared to the bone marrow CD34+ cells (90).

B.2.6.2.6. Parameters of iron overload

As described previously, exa-cel is expected to prevent further iron overload and progression of end-organ damage by eliminating the requirement for regular RBC transfusions. Once iron overload has been corrected, it will also eliminate the need for ICT.

In CLIMB THAL-111 and CLIMB-131, iron overload was evaluated by assessing liver iron content (LIC) and cardiac T2* by magnetic resonance imaging (MRI), and SF level (7, 86). Overall, biomarker data from CLIMB THAL-111 and CLIMB-131 indicates favourable changes in iron overload (7, 86). Results of changes in SF level, LIC, and cardiac T2* are explained in further detail below.

a. Serum ferritin level

The long-term control of SF has prognostic significance (71), with levels maintained in the region of 1,124-3,370 pmol/L over the longer term associated with a lower risk of cardiac disease and death (25). Maintenance of SF below 2,247 pmol/L may be associated with additional advantages in TDT, such as an improvement in cardiac function and prevention, or reversal, of endocrinopathies (71, 91, 92).

Among patients in CLIMB THAL-111 FAS, there was a transitory increase in mean SF values after exa-cel infusion, which subsequently decreased progressively over time. The mean (SD) SF levels at baseline were 3,740.7 (2,817.0) pmol/L. After exa-cel infusion, mean (SD) SF levels increased to 19,009.7 (35,079.7) pmol/L at Month 1 and subsequently decreased over the duration of follow-up. At Month 18 (n=22), mean (SD) values were below the mean baseline; 3,126.7 (2,460.6) pmol/L. Further

decreases in mean SF values were observed thereafter. At Month 24 (n=8), the mean (SD) SF values were 1,881.0 (1,530.8) pmol/L (86).

For patients who rolled over to CLIMB-131, SF levels generally continued to decrease after Month 24 (86).

b. LIC

Similar to SF levels, a transient increase in LIC was observed post exa-cel infusion. Mean (SD) LIC at baseline was 4.7 (3.2) mg/g in the FAS. After exa-cel infusion, LIC increased to a mean (SD) of 11.3 (8.0) mg/g at Month 12 (n=33). By Month 24 (n=8), LIC had decreased to a mean (SD) of 7.9 (5.6) mg/g (86). No patients who rolled over to CLIMB-131 had LIC data after Month 24 (86).

c. Cardiac T2*

All patients had normal cardiac iron content (myocardial T2* ≥20msec) at baseline and throughout the duration of follow-up. Mean (SD) baseline cardiac T2* was 34.5 (9.4) msec in the FAS. At Month 12 (n=34), the mean (SD) was 32.4 (8.0) msec. At Month 24 (n=9), the mean (SD) was 33.6 (7.7) msec (86). No patients who rolled over to CLIMB-131 had cardiac T2* data after Month 24 as of the data cut (86).

B.2.6.2.7. Use of iron chelation therapy

The proportion of patients in the FAS receiving ICT over time (every three months) is summarised below in Table 17. All 48 (100%) patients in the FAS were receiving ICT before exa-cel infusion. After exa-cel infusion, individual patient iron chelation was managed at the investigator's discretion. Use of iron chelation was recommended to be started as soon as possible >3 months (or >6 months for DFP) following exa-cel infusion if haematopoietic recovery was stable.

Overall, 18 patients received ICT at any time after exa-cel infusion: 35.3% of patients (12 of 34 patients) received ICT post-Month 12 to Month 15 and 42.9% of patients (6 of 14 patients) received ICT post-Month 21 to Month 24 (86).

Table 17: Proportion of patients receiving iron chelation therapy under each 3-month interval after exa-cel infusion (CLIMB THAL-111 and CLIMB-131, FAS)

Time Period	Total (n=48)

Prior to exa-cel infusion	
n	48
Proportion of patients receiving ICT, n (%)	48 (100.0)
Exa-cel infusion to Month 3	
n	48
Proportion of patients receiving ICT, n (%)	4 (8.3)
Month 3 to Month 6	
n	45
Proportion of patients receiving ICT, n (%)	12 (26.7)
Month 6 to Month 9	
n	44
Proportion of patients receiving ICT, n (%)	14 (31.8)
Month 9 to Month 12	
n	41
Proportion of patients receiving ICT, n (%)	13 (31.7)
Month 12 to Month 15	
n	34
Proportion of patients receiving ICT, n (%)	12 (35.3)
Month 15 to Month 18	
n	28
Proportion of patients receiving ICT, n (%)	9 (32.1)
Month 18 to Month 21	
n	22
Proportion of patients receiving ICT, n (%)	7 (31.8)
Month 21 to Month 24	
n	14
Proportion of patients receiving ICT, n (%)	6 (42.9)
Post-Month 24	
n	6
Proportion of patients receiving ICT, n (%)	3 (50.0)

Key: FAS: Full Analysis Set; ICT: iron chelation therapy.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation.
Source: Table 14.2.16.3a, CLIMB-131 CSR (86).

Data on ICT utilisation and/or phlebotomy is only available for the PES. At the time of the most recent data cut-off, six patients did not restart ICT or receive phlebotomy after exa-cel infusion and were off ICT and/or phlebotomy for a mean (SD) of 19.7 (3.4) months. A total of 21 patients restarted ICT and/or received phlebotomy after exa-cel infusion. Sixteen patients remained on ICT and/or phlebotomy and five patients subsequently stopped and were off ICT and/or phlebotomy for a mean (SD) 7.1 (4.9) months (7).

Of the 10 patients with >24 months of total follow-up in the PES (comprising eight patients who rolled over into CLIMB-131 and two patients who had not yet enrolled in CLIMB-131 but were past Day 720), six patients (60%) received ICT at any time after

Month 24. Two patients received phlebotomy any time after Month 24, including one patient who also received ICT during this interval (86).

B.2.6.2.8. Patient-reported outcomes

PRO scores indicated substantial improvement in general well-being, HRQoL, and overall health status, including improvements in fatigue scores, after exa-cel infusion. Consistent improvements were observed in the EQ-5D-5L and EuroQol-Visual Analogue Score (EQ-VAS) scores despite the high scores reported at baseline that were similar to the general UK population (Table 18) (7, 8). However, as discussed in Section B.1.3.2.2, EQ-5D-5L is not an effective tool for capturing the impact of TDT on HRQoL and may not be responsive to changes in this patient population.

Table 18: Change in PRO scores from baseline to Month 24 after exa-cel infusion (CLIMB THAL-111, PES)

PRO	Sample size, n	Baseline, mean	MCID	Change at M24, mean
EQ-5D-5L	22	0.87	0.08[a]	0.19
EQ-VAS	22	80.1	7.0 - 10.0[b]	21.0
FACT-BMT	22	110.7	2.0 - 3.0[c]	24.8
FACT-G	22	83.3	3.0 - 7.0[d]	17.0
BMTS	22	27.3	2.0 – 3.0[e]	7.8

Key: BMTS: bone marrow transplantation subscale; EQ-5D-5L: EuroQol Quality of Life Scale-5-dimensions-5 levels of severity; EQ-VAS: EuroQol-Visual Analogue Score; FACT-BMT: Functional Assessment of Cancer Therapy-Bone Marrow Transplant; FACT-G: Functional Assessment of Cancer-General; MCID: minimal clinically important difference; PES: Primary Efficacy Set.
Notes: The PES was used given this cohort of patients have been followed for at least 16 months after exa-cel infusion.
[a]Sourced from Henry *et al*., (2020) (93).
[b]Sourced from Pickard *et al*., (2007) (94).
[c]Sourced from McQuellon *et al*., (1997) (95).
[d]Sourced from King *et al*., (2010) (96).
[e]Sourced from McQuellon *et al*., (1997) (95).
Source: CLIMB THAL-111 CSR, EHA 2023 slides (7, 8).

Across all PRO instruments, the greatest change from baseline occurred in the last six months of follow-up. Improvements in HRQoL at later timepoints is in line with studies of patients who have undergone allo-SCT (97). This is not unexpected, given that patients require time to recover from the transplant procedure, and for their iron and Hb levels to return to normal. None of the patients who rolled over to CLIMB-131 had available EQ-5D-5L or: Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scores after Month 24 as of the IA2 data cut-off (86).

a. EQ-5D-5L

At baseline, mean (SD) EQ-5D-5L utility index scores in CLIMB THAL-111 were reported to be greater than the average UK population score (0.87 points) (Table 19) (7, 98). Despite the near normal baseline scores, positive changes in EQ-5D-5L utility scores were observed over time, indicating improvement in overall health status after exa-cel infusion. This trend of improvement is expected to continue out to M24 onwards (7).

Table 19: Summary of EQ-5D-5L scores (CLIMB THAL-111 and CLIMB-131, FAS and PES)

Visit	FAS		PES	
	EQ VAS	UK Health Utility Index Score	EQ VAS	UK Health Utility Index Score
Baseline				
n	32	32	22	22
Mean (SD)	82.8 (16.6)	0.90 (0.14)	80.1 (18.7)	0.87 (0.15)
Median	90.0	0.95	90.0	0.92
Min, Max	40,0, 100.0	0.49, 1.00	40.0,100.0	0.40, 1.00
Month 6				
n	29	29	22	22
Mean (SD)	86.0 (14.7)	0.87 (0.20)	85.3 (15.8)	0.87 (0.22)
Median	90.0	0.94	90.0	0.97
Min, Max	45.0, 100.0	0.29, 1.00	45.0, 100.0	0.29, 1.00
Month 12				
n	24	24	22	22
Mean (SD)	89.3 (12.1)	0.91 (0.14)	88.7 (12.5)	0.90 (0.14)
Median	95.0	1.00	95.0	1.00
Min, Max	60.0, 100.0	0.49, 1.00	60.0, 100.0	0.49, 1.00
Month 18				
n	19	19	19	19
Mean (SD)	87.8 (19.2)	0.91 (0.17)	87.8 (19.2)	0.91 (0.17)
Median	95.0	1.00	95.0	1.00
Min, Max	20.0, 100.0	0.28, 1.00	20.0, 100.0	0.28, 1.00
Month 21				
n	13	13	13	13
Mean (SD)	90.4 (13.6)	0.92 (0.11)	90.4 (13.6)	0.92 (0.11)
Median	95.0	95.0	95.0	0.92
Min, Max	50.0, 100.0	50.0, 100.0	50.0, 100.0	0.62, 1.00
Month 24				
n	8	8	8	8
Mean (SD)	93.5 (5.3)	0.96 (0.21)	93.5 (5.3)	0.96 (0.21)
Median	95.0	0.97	95.0	0.97
Min, Max	85.0. 100.0	0.86, 1.00	85.0. 100.0	0.86, 1.00

Key: EQ-5D-5L: EuroQol Quality of Life Scale-5-dimensions-5 levels of severity; FAS: Full Analysis Set; PES: Primary Efficacy Set; SD: standard deviation.

Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. No patients who rolled over to CLIMB-131 had any EQ-5D-5L data after Month 24. EQ-5D-5L responses were mapped to the 3L value set using the Hernández-Alava algorithm (99).
Source: Tables 14.2.9.1 and 14.2.9.3, CLIMB THAL-111 CSR; EHA 2023 slides (7, 8).

As discussed in Section B.1.3.2.2, empirical evidence suggests that EQ-5D-5L lacks content validity and the derived health utility index score may not fully represent the burden of disease in TDT. Support for this comes from vignette studies in which the general public valued TDT health state vignettes using the time trade-off (TTO) method (62, 63). The utility values from these valuations, even for the mildest TDT states valued (albeit not obtained via scoring on EQ-5D-5L) were far lower (0.63-0.75) than those observed at baseline in the FAS (0.90). Further issues may be the absence of a fatigue domain in the EQ-5D-5L, a symptom which is particularly relevant to TDT patients. A recent study demonstrated improved psychometric performance of the EQ-5D-5L in a chronic disease population when a fatigue domain was added (100).

b. FACT-BMT

FACT-BMT consists of FACT-G, which measures overall QoL (includes subscales for physical, social/family, emotional, and functional well-being) and treatment-specific concerns of bone marrow transplantation subscale (BMTS). For each total and subscale score, higher values indicate better quality of life (7).

Mean FACT-BMT total scores progressively improved from baseline to Month 24, with the mean (SD) change from baseline at Month 24 of 24.8 (25.4) points, indicating a robust improvement in general well-being and HRQoL after exa-cel infusion that was sustained through the duration of follow-up (Table 20).

Similarly, the FACT-G and BMTS scores progressively increased from baseline, with the mean (SD) change from baseline for FACT-G of 8.0 (16.6) points and BMTS of 4.4 (5.9) points at Month 18 (7, 8). Of note, the minimal clinically important difference is considered to be 3 to 7 points for FACT-G and 2 to 3 points for BMTS (Table 18). These minimal clinically important differences are not TDT-specific, however they are largely consistent across numerous conditions (96). FACT-G subscores indicated that improvements in the overall score at Month 18 were driven by the physical and emotional well-being subscales, with mean (SD) change from baseline of 4.1 (5.5) points and 2.4 (4.2) points, respectively (Table 20).

Table 20: Summary of FACT-BMT scores (CLIMB THAL-111 and CLIMB-131, FAS)

Visit	FACT-BMT total score	FACT-G total score	BMTS	FACT-G subscores			
				PWB score	EWB score	FWB score	SWB score
Baseline							
n	32	32	32	32	32	32	32
Mean (SD)	113.7 (19.2)	85.5 (15.2)	28.2 (4.7)	22.8 (5.2)	18.9 (3.6)	21.3 (5.2)	22.5 (4.6)
Median	116.5	86.5	28.9	25.0	20.0	20.5	23.7
Min, Max	68.0, 142.0	53.0, 107.0	15.0, 35.0	9.0, 28.0	11.0, 24.0	11.0, 28.0	10.5, 28.0
Month 6							
n	29	29	29	29	29	29	29
Mean (SD)	116.3 (21.9)	86.8 (16.7)	29.5 (5.8)	24.4 (5.6)	20.8 (3.8)	19.5 (5.6)	22.1 (4.9)
Median	122.0	90.0	29.0	26.8	21.0	20.0	23.0
Min, Max	44.0, 148.0	32.0, 108.0	12.0, 40.0	3.0, 28.0	6.0, 24.0	7.0, 28.0	10.0, 28.0
Month 12							
n	24	24	24	24	24	24	24
Mean (SD)	118.8 (19.1)	87.8 (14.7)	31.0 (5.1)	25.0 (4.8)	20.8 (2.8)	20.4 (6.1)	21.5 (6.4)
Median	122.0	90.0	31.5	27.0	21.0	21.0	21.6
Min, Max	73.0, 145.0	48.0, 108.0	18.0, 38.0	10.0, 28.0	12.0, 24.0	6.0, 28.0	4.0, 28.0
Month 18							
n	17	17	17	17	17	17	17
Mean (SD)	120.9 (15.8)	89.6 (12.5)	31.3 (4.1)	25.8 (3.5)	20.6 (2.8)	21.0 (5.5)	22.2 (4.4)
Median	127.0	92.0	32.0	27.0	20.0	21.0	22.0
Min, Max	93.0, 143.0	65.0, 106.0	24.0, 39.0	14.0, 28.0	14.0, 24.0	10.0, 28.0	15.0, 28.0
Month 24							
n	8	8	8	8	8	8	8
Mean (SD)	127.4 (15.0)	94.0 (11.4)	33.4 (4.2)	26.0 (2.0)	22.3 (2.3)	23.5 (4.9)	22.3 (5.8)
Median	132.5	97.5	34.5	26.5	23.5	26.0	23.0
Min, Max	102.0, 141.0	77.0, 106.0	25.0, 39.0	23.0, 28.0	18.0, 24.0	15.0, 28.0	14.0, 28.0

Key: BMTS: bone marrow transplantation subscale; EWB: emotional well-being; FACT-BMT: Functional Assessment of Cancer Therapy-Bone Marrow Transplant; FAS: Full Analysis Set; FWB: functional well-being; M: month; PWB: physical well-being; SWB: social/family well-being.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation.
Source: Table 14.2.10.3, CLIMB THAL-111 CSR (7, 8).

In addition, FACT-BMT fatigue-related scores progressively decreased over time. At Month 18, the mean (SD) change from baseline was -1.0 (1.4) for Question 1 'Lack of energy' and -0.4 (2.0) for Question 35 'Tiredness'. Overall, fatigue-related scores indicated improvements in energy and reduction in tiredness after exa-cel infusion that were sustained through follow-up (7) (Table 21).

Table 21: Summary of FACT-BMT fatigue related scores (CLIMB THAL-111 and CLIMB-131, FAS)

Visit	Question #1: Lack of energy	Question #35: Tiredness
Baseline		
n	32	32
Mean (SD)	1.6 (1.1)	2.0 (1.3)
Median	1.5	2.0
Min, Max	0.0, 4.0	0.0, 4.0
Month 6		
n	29	29
Mean (SD)	0.8 (1.1)	1.6 (1.3)
Median	0.0	1.0
Min, Max	0.0, 4.0	0.0, 4.0
Month 12		
n	24	24
Mean (SD)	0.5 (0.8)	1.2 (1.3)
Median	0.0	1.0
Min, Max	0.0, 3.0	0.0, 4.0
Month 18		
n	17	17
Mean (SD)	0.7 (0.8)	1.5 (1.3)
Median	1.0	1.0
Min, Max	0.0, 3.0	0.0, 4.0
Month 24		
n	8	8
Mean (SD)	0.8 (0.7)	0.9 (1.0)
Median	1.0	1.0
Min, Max	0.0, 2.0	0.0, 3.0

Key: FAS: Full Analysis Set; SD: standard deviation.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation.
Source: Table 14.2.10.6 and Table 14.2.10.12, CLIMB THAL-111 CSR (7).

B.2.6.2.9. Summary of exa-cel clinical effectiveness

The efficacy and safety of exa-cel for the treatment of patients with TDT aged 12-35 years has been demonstrated in the ongoing Phase 1/2/3 single arm CLIMB THAL-111 study. Transfusion dependence was defined as a history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the 2 years before signing the informed consent form (7).

Greater than half of the patients enrolled onto CLIMB THAL-111 have a β^0/β^0-like genotype (58.3%) (7, 8). This patient group was not included in the regulatory label for beti-cel (51), despite these patients typically being worst affected by the disease burden of TDT (52).

Treatment with exa-cel resulted in high clinical efficacy. As of the IA2 data cut-off, 24 of 27 patients (88.9%) in the PES achieved the primary endpoint of TI12. The remaining three patients who did not achieve TI12 have shown substantial clinical benefit, with one patients having stopped receiving RBC transfusions after 14.5 months and the other two experiencing a decrease in annualised RBC transfusions volume from baseline of 79.6% and 95.5% respectively In the FAS, 42 of 44 patients to complete the initial RBC transfusion washout period were transfusion free, with duration ranging from 2.9 to 40.7 months, starting after the 60 day RBC transfusion washout period (7, 8, 86).

For all patients in the FAS, clinically meaningful increases in mean total Hb, HbF, and F-cells were demonstrated early and were maintained over time from approximately Month 6 onwards, demonstrating the achievement of haematologic stability and consistent with TI. Mean Hb concentration increased from 10.2 g/dL at baseline to 12.5 g/dL at Month 12, and was consistently >12 g/dL from Month 9 onwards (7, 8, 86).

Furthermore, a high, stable proportion of alleles with the intended genetic modification was observed in both the CD34+ cells of the bone marrow and peripheral blood, indicating durable engraftment of edited long-term HSCs and reflecting the permanent nature of the intended edit (7, 8, 86).

The currently available data indicate that in patients with TDT, exa-cel results in robust, consistent, and durable benefits, offering a potential to deliver a disease-free state for patients with TDT while maintaining a favourable benefit to risk profile.

B.2.7 Subgroup analysis

Pre-planned subgroup analyses based on baseline disease covariates were prespecified and conducted for the primary and secondary endpoints. These subgroups were explored to better characterise patient populations for whom exa-cel may provide the most benefit. The FAS and PES were stratified by age, genotype, and sex to produce the following subgroups for analysis:

- TDT patients ≥12 and <18 years of age
- TDT patients ≥18 and ≤35 years of age
- Patients with β^0/β^0-like TDT genotype
- Patients with non-β^0/β^0-like TDT genotype
- Male TDT patients
- Female TDT patients

As predicted, the results of the subgroup analyses confirm a substantial treatment benefit of exa-cel in all patients with TDT, regardless of age, genotype, and sex. It must be noted that subgroup analyses should be interpreted with caution given the small sample sizes involved (7, 8).

The proportion of patients with TI12 with 2-sided 95% CIs was generated for subgroups of the PES. Full results are presented in Appendix E.

The proportion of patients achieving TI12 was generally consistent across the pre-planned subgroups. Whilst the proportion of patients achieving TI12 was highest in those with a non-β^0/β^0-like TDT genotype (12 of 12 patients, 100.0%), the proportion of patients with β^0/β^0-like TDT genotypes who achieved TI12 was 80.0% (12 of 15 patients) (Table 70, Appendix E) (7), supporting the effectiveness of exa-cel in the patient cohort that was excluded from the beti-cel regulatory label and typically worst affected by TDT (51, 52). Subgroup analysis of patients who achieved TI12 by age at screening and sex generated similar results (7) (Table 70, Appendix E), further highlighting the efficacy of exa-cel in its proposed positioning in UK clinical practice.

Furthermore, subgroup analyses in the FAS were performed on the following secondary efficacy endpoints: total Hb and HbF concentration over time, proportion of

alleles with intended genetic modification, and the proportion of F-cells over time. For each subgroup analysis, the results were generally consistent with the data presented in B.2.6. Descriptive statistics generated for each subgroup across each of the secondary efficacy endpoints is presented in Appendix E.

For patients who rolled over to CLIMB-131, subgroups generally had a sample size of n<5 and therefore were not compared; however, no clinically relevant effects different from those observed in CLIMB THAL-111 were apparent (86).

B.2.8 Meta-analysis

A meta-analysis is not required for exa-cel as a single study (CLIMB THAL-111) provides data on the efficacy and safety of this intervention.

B.2.9 Indirect and mixed treatment comparisons

Due to the single-arm nature of CLIMB THAL-111, an indirect treatment comparison (ITC) was conducted to generate estimates of comparative effectiveness versus SoC (comprising RBC transfusions and ICT) (101).

From the 98 studies identified from the SLR results, studies had to fulfil the following selection criteria to be considered for inclusion in the ITC (101):

- Patients with ages overlapping with CLIMB THAL-111 efficacy data
- Report on a transfusion-related outcome
- Administered an FDA-approved dose, and
- Include five or more treated patients

Four data sources across three studies were considered in the ITC feasibility assessment. The studies were BELIEVE (assessing luspatercept versus SoC) (102); the Northstar-2 trial (evaluating beti-cel in TDT patients with non-β^0/β^0 genotypes) and the Northstar-3 trial (evaluating beti-cel in TDT patients with β^0 or β+IVS-I-110 mutations on both *HBB* alleles) (103). The three identified studies are summarised in Table 22.

BELIEVE was a double-blind, randomised, placebo-controlled Phase 3 trial of luspatercept in patients 18 years of age or older who had confirmed ß-thalassaemia or haemoglobin E-ß-thalassaemia and were receiving regular transfusions (6 to 20 packed RBCs with no transfusion-free period of >35 days, within 24 weeks before randomisation). Patients were randomised in a 2:1 ratio to receive luspatercept or placebo every 21 days for at least 48 weeks. All patients received best supportive care (BSC), including RBC transfusions and ICT, according to local guidelines. The trial was conducted at 65 sites in 15 countries (Australia, Europe, Middle East, North Africa, North America and Southeast Asia) (102).

The primary endpoint was the percentage of patients who had an erythroid response, defined as a reduction in the transfusion burden of at least 33% from baseline during

weeks 13 through 24 plus a reduction of at least 2 red-cell units over the same 12-week interval (102).

Full details of the Northstar-2/Northstar-3 methodologies are described in the ITC report (101).

Table 22: Summary of the trials used to carry out the indirect treatment comparison

Trial	Intervention			
	Exa-cel	**Beti-cel**	**Luspatercept**	**Placebo**
CLIMB THAL-111	Yes			
BELIEVE			Yes	Yes
Northstar-2		Yes		
Northstar-3		Yes		

Key: beti-cel: betibeglogene autotemcel; exa-cel: exagamglogene autotemcel.
Source: Exa-cel TDT ITC Report (101).

Although we present the results of the ITC between exa-cel and SoC (the BSC arm in the luspatercept trial), these do not inform the economic model. Instead, baseline data from CLIMB THAL-111 was used to inform the relative efficacy and safety of exa-cel in patients with TDT. For further detail on the rationale for this, please see Section B.3.3.

B.2.9.1. Matching-adjusted indirect comparison (MAIC)

The ITCs employed unanchored MAIC methodology, due to the single-arm design of CLIMB THAL-111, and the lack of access to individual-patient data (IPD) for non-Vertex trials of SoC. In the context of this evidence submission, comparison with beti-cel was not considered relevant, as this therapy is not available in the UK for the treatment of TDT. For luspatercept, whilst this is also true, the BSC arm was considered potentially informative, and as such is presented here. Comparison versus luspatercept and beti-cel is included in the ITC report (101).

The MAIC was conducted in several steps. The first step was to conduct a feasibility assessment to determine the degree of overlap in study designs and populations and the extent that it is possible to generate unbiased comparisons. In the next step, IPD from CLIMB THAL-111 was re-weighted to make key baseline characteristics comparable with the comparators' aggregated data (101). The MAIC methodology

proposed by Signorovitch *et al*., (2010) was used to re-weight IPD from CLIMB THAL-111 to align with the matching variables' aggregate summary statistics as reported for each comparator of interest (104). Relevant baseline covariates, which were identified as the key effect modifiers and/or prognostic factors, were selected as matching variables for their potential influence on the ITC endpoints and confirmed by clinical expert consultation (101).

These steps above resulted in a CLIMB THAL-111 dataset with a weighted trial population that matched those of the comparator trials of interest for the included covariates. Using these weights, outcomes for exa-cel were predicted for the population in the comparator trial by re-weighting the observed outcomes from CLIMB THAL-111. Treatment comparisons were then conducted across the balanced populations. For all comparisons, if the effective sample size (ESS) was below five patients for the exa-cel cohort after re-weighting, no formal comparisons were made (101).

Due to the small sample size of patients who achieved either TI6 or TI12 in the CLIMB THAL-111 PES (n=24), no more than three variables were used for matching based on HTA expert input, starting with the variables ranked as the most important and moving onto lower-ranking variables if a match was not possible. The MAIC with BELIEVE matched on genotype, median of annualised RBC units at baseline and median age (101).

TI-related outcomes were assessed in the MAIC. In line with the reporting in the comparator trials, the specific definitions of these outcomes differed slightly between the MAICs. For comparisons versus BELIEVE, the percentage of patients who were TI for consecutive 12-week interval (TI3) was compared to the percentage of patients who were TI6 after exa-cel infusion in CLIMB THAL-111. (101). It should be noted that in CLIMB THAL-111, the evaluation for TI6 started 60 days after the last RBC transfusion for post-transplant support or TDT disease management, while in BELIEVE, the evaluation started on Day 1 after treatment (102).

B.2.9.2. Results of the MAIC

Using data from the four included studies (CLIMB THAL-111, BELIEVE, Northstar-2 and Northstar-3), the following sets of MAICs were conducted:

- Exa-cel versus SoC (as defined in BELIEVE trial)
- Exa-cel versus luspatercept (based on the BELIEVE trial)
- Exa-cel versus beti-cel (based on pooled Northstar-2 and Northstar-3 data)

In this submission, we only present the results on the MAIC versus SoC (as defined in BELIEVE trial) as this is the relevant comparator considered in this submission. The results of the MAICs versus luspatercept and beti-cel can be found in the accompanying ITC report (101).

B.2.9.2.1. Exa-cel versus SoC (as defined in BELIEVE trial)

The re-weighted proportion of patients who were TI6 with exa-cel was 86.5% (95% CI: 56.7%, 96.9%), compared with no patients in the SoC group who were TI for at least three months (TI3) as reported in the BELIEVE trial (Table 23) (102). No rate ratio was calculated as the proportion of patients who were TI3 in the SoC group was 0.0% (101).

Table 23: Proportion of patients who were TI3 in SoC arm of BELIEVE and TI6 with exa-cel

	SoC (n=112)	Exa-cel unweighted (before matching) (n=27)	Exa-cel re-weighted (after matching) (ESS=13)
n	0	24	-
Proportion (95% CI)	0.0% (-,-)	88.9% (70.8%, 97.6%)	86.5% (56.7%, 96.9%)
Rate ratio (95% CI)	-	-	NC[a]
***P* value**	-	-	NC[a]

Key: CI: confidence interval; ESS: effective sample size; NC: not calculated; SoC: standard of care; TI3: transfusion independence for at least three months; TI6: transfusion independence for at least six months.
Notes: [a]No statistical testing was conducted as the propotion in the SoC group was 0.0%.
Source: Table 3, Exa-cel TDT ITC Report (101).

B.2.9.3. Conclusions

The results of these MAIC analyses found that exa-cel had superior efficacy compared with the non-curative SoC (as defined in the BELIEVE trial of luspatercept). Based on the results of the ITC, the proportion of patients achieving transfusion-free for at least 6-months was 86.5–91.0% with exa-cel; no patients treated with SoC were transfusion free for at least 3 months in the BELIEVE trial.

B.2.9.4. Uncertainties in the indirect and mixed treatment comparisons

Due to the small exa-cel ESS, resulting from the relatively small sample size of the CLIMB THAL-111 PES (n=27), health technology assessment (HTA) experts recommended a maximum of three matching variables for each MAIC. One limitation relates to the comparison of a potentially curative treatment with SoC. This is demonstrated in the results for transfusion independence, where 0% of patients in the SoC arm of BELIEVE achieved TI3. Overall, the MAIC findings support the overwhelming efficacy of exa-cel compared to non-curative therapies in TDT (SoC and luspatercept), resulting in significantly higher proportions of patients being transfusion-free.

B.2.10 Adverse reactions

The safety and tolerability of exa-cel for the treatment of patients aged 12-35 years with TDT was evaluated in the SAS of CLIMB THAL-111.The SAS was defined as all enrolled patients who started mobilisation (Stage 1) (n=59) (see Figure 12). The discussion of AEs focuses on the period from exa-cel infusion to Month 24, with narrative added to the long-term study where applicable.

AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.

B.2.10.1. Exposure to exa-cel

In the FAS, the mean dose of exa-cel was 8.5 x 10^6 CD34+ cells/kg (range: 3.0-19.7 x 10^6 CD34+ cells/kg) (7, 8). The median follow-up duration after exa-cel infusion was 16.7 months (range: 0.0 to 43.7) months (Table 24) (8, 86).

Table 24: Summary of exa-cel exposure (CLIMB THAL-111 and CLIMB-131, FAS)

	Total (n=48)
Exa-cel dose (10^6 x CD34+ cells/kg)	
n	48
Mean (SD)	8.5 (4.4)
Median	7.5
Min, Max	3.0, 19.7
Follow-up duration after exa-cel infusion (months)	
n	48
Mean (SD)	17.2 (8.9)
Median	16.7
Min, Max	0.0, 43.7
Follow-up duration after exa-cel infusion by interval, n (%)	
≤3 months	3 (6.3)
>3 months to ≤6 months	1 (2.1)
>6 months to ≤12 months	10 (20.8)
>12 months to ≤24 months	24 (50.0)
>24 months to ≤36 months	9 (18.8)

>36 months to ≤60 months	1 (2.1)

Key: FAS: Full Analysis Set; SD: standard deviation.
Note: Follow-up duration after exa-cel infusion (months) = (data cutoff date or end of study date – exa-cel infusion date +1)/30.
Source: Table 12-1, CLIMB THAL-111 CSR and Table 12-1, CLIMB-131 CSR (7, 8, 86).

In the PES, the mean dose of exa-cel was 7.4 x 10^6 CD34+ cells/kg (range: 3.0-15.7 x 10^6 CD34+ cells/kg) (7, 8).

B.2.10.2. Summary of safety

The cumulative safety profile of exa-cel in CLIMB THAL-111 and CLIMB-131 was generally consistent with myeloablative busulfan conditioning, which has a well-established safety profile (7, 86). The therapies used for mobilisation and apheresis (plerixafor and G-CSF) also have well-characterised safety profiles.

All treated patients had at least one AE, and 13 of 48 patients (27.1%) had exa-cel related or possibly related AEs (i.e., related to exa-cel only or exa-cel and busulfan), with eight patients (16.7%) experiencing exa-cel related AEs that were Grade 3 or higher (7, 86). The most common Grade 3 or above AE after ex-cel infusion was febrile neutropenia (28 of 48 patients, 58.3%) (7, 8).

Among the patients who completed myeloablative busulfan conditioning and received exa-cel, 17 of 48 patients (35.4%) had at least one SAE, while only two of 48 patients (4.2%) had SAEs considered related or possibly related to exa-cel (7, 8, 86). There were no deaths recorded in both CLIMB THAL-111 and the long-term follow-up study, CLIMB-131 (7, 8, 86).

An overview of the AEs experienced by patients in CLIMB THAL-111 and CLIMB-131 in the SAS are presented in Table 25 (7, 8). Of note, starting after the Month 24 visit, only AEs related or possibly related to exa-cel, SAEs, new malignancies, and new or worsening haematologic disorders were collected (86).

Table 25: Overview of AEs before and after exa-cel infusion and overall (CLIMB THAL-111 and CLIMB-131, SAS)

Visit	Enrolment to <exa-cel (n=59)	Exa-cel to M24 (n=48)	>M24 (n=9)
Patients with exa-cel infusion, n	--	48	9

Patients with busulfan dosing, n	48	48	9
Patients with any AEs, n (%)	56 (94.9)	48 (100.0)	--
Patients with AEs related or possibly related to exa-cel, n (%)	--	13 (27.1)	0
Patients with AEs related or possibly related to busulfan, n (%)	32 (66.7)	45 (93.8)	--
Patients with Grade 3 or 4 AEs	18 (30.5)	41 (85.4)	--
Patients with SAEs	9 (15.3)	17 (35.4)	1 (11.1)
Patients with SAEs related or possibly related to exa-cel	--	2 (4.2)	0
Patients with SAEs related or possibly related to busulfan	0	9 (18.8)	--
Patients with AEs leading to study discontinuation	0	0	0
Patients with AEs leading to death	0	0	0

Key: AE: adverse event; exa-cel: exagamglogene autotemcel; M: month, SAE: serious adverse event; SAS: Safety Analysis Set.
Notes: AEs were coded using MedDRA Version 25.0. The SAS included 59 patients. Percentages were calculated as n/N1×100. When summarising number and percentage of patients for each study interval, a patient with multiple events within a category and study interval was counted only once in that category and study interval. The table is sorted in descending order of frequency of the exa-cel to M24 column by preferred term.
[a]Study intervals: enrolment to <exa-cel: enrolment to the day before exa-cel infusion; exa-cel to M24: Day of exa-cel infusion to M24 visit or end of study visit; >M24: after Month 24 for patients enrolled on CLIMB-131.
Source: Table 12-2 CLIMB THAL-111 CSR ,Table 12-3 CLIMB-131 CSR, EHA 2023 slides (7, 8, 86).

B.2.10.3. Common adverse events

AEs that occurred in ≥25% of patients who completed myeloablative busulfan conditioning and received exa-cel (n=48) are summarised below in Table 26. From exa-cel infusion onward, the most common AEs (occurring in ≥25% of patients) were febrile neutropenia, headache, stomatitis, thrombocytopenia, anaemia, nausea and mucosal inflammation. All common AEs were consistent with myeloablative busulfan conditioning and allo-SCT (7, 8).

Table 26: AEs occurring in ≥25% of patients after exa-cel infusion (CLIMB THAL-111, SAS)

MedDRA Preferred Term, n (%)	Exa-cel to M24 (n=48)
Patients with any AEs	**48 (100.0)**

Febrile neutropenia	28 (58.3)
Headache	26 (54.2)
Stomatitis	24 (50.0)
Thrombocytopaenia	23 (47.9)
Anaemia	21 (43.8)
Nausea	21 (43.8)
Mucosal inflammation	20 (41.7)
Hypokalaemia	18 (37.5)
Vomiting	18 (37.5)
Abdominal pain	17 (35.4)
Arthralgia	17 (35.4)
Platelet count decreased	16 (33.3)
Constipation	15 (31.3)
Epistaxis	15 (31.3)
Pruritus	14 (29.2)
COVID-19	13 (27.1)
Decreased appetite	13 (27.1)
Diarrhoea	13 (27.1)
Neutrophil count decreased	12 (27.1)
Pyrexia	12 (25.0)

Key: AE: adverse event; exa-cel: exagamglogene autotemcel; M: month; SAS: safety analysis set.
Notes: AEs were coded using MedDRA Version 25.0. The SAS included 59 patients. Percentages were calculated as n/N1×100. When summarising number and percentage of patients for each study interval, a patient with multiple events within a category and study interval was counted only once in that category and study interval. The table is sorted in descending order of frequency of the exa-cel to M24 column by preferred term.
Source: Table 12-3 CLIMB THAL-111 CSR, EHA 2023 slides (7, 8).

The most common AEs (occurring in more than one patient) considered related or possibly related to exa-cel only were headache (two patients, 4.2%) and anaemia, acute respiratory distress syndrome, chills, haemophagocytic lymphohistiocytosis, paraesthesia, sinus tachycardia, and tachycardia (one patient each, 2.1%) (7).

AEs of Grade 3 or above after exa-cel infusion are summarised below in Table 27 (7). In the long-term follow-up study CLIMB-131, no patients experienced AEs related to exa-cel (86).

Table 27: Grade 3 or above AEs occurring in >10% of patients after exa-cel infusion (CLIMB THAL-111, SAS)

MedDRA Preferred Term, n (%)	Exa-cel to M24

	(n=48)
Patients with any Grade 3 or above AEs	**41 (85.4)**
Febrile neutropenia	24 (50.0)
Stomatitis	19 (39.6)
Anaemia	18 (37.5)
Thrombocytopaenia	17 (35.4)
Platelet count decreased	15 (31.3)
Mucosal inflammation	14 (29.2)
Neutrophil count decreased	13 (27.1)
Decreased appetite	11 (22.9)
WBC count decreased	7 (14.6)
Epistaxis	5 (10.4)
Neutropenia	5 (10.4)
Veno occlusive liver disease	5 (10.4)

Key: AE: adverse event; exa-cel: Exagamglogene autotemcel; M: month; WBC: white blood cell; SAS: safety analysis set.
Notes: AEs were coded using MedDRA Version 25.0. The SAS included 59 patients. Percentages were calculated as n/N1×100. When summarising number and percentage of patients for each study interval, a patient with multiple events within a category and study interval was counted only once in that category and study interval. The table is sorted in descending order of frequency of the exa-cel to M24 column by preferred term.
Source: Table 12-4 CLIMB THAL-111 CSR, EHA 2023 slides (7, 8).

Two patients (4.2%) had SAEs considered related or possibly related to exa-cel (7, 8):

- One patient had SAEs of headache, haemophagocytic lymphohistiocytosis, and acute respiratory distress syndrome that were considered related or possibly related to exa-cel only, and one SAE of idiopathic pneumonia syndrome that was considered related to busulfan and possibly related to exa-cel (all SAEs occurred in the context of haemophagocytic lymphohistiocytosis).

- One patient had SAEs of delayed engraftment and thrombocytopenia that were considered related or possibly related to both busulfan and exa-cel (no serious infections or bleeding occurred; the patient achieved neutrophil and platelet engraftment without the use of back-up cells).

In the long-term follow-up study CLIMB-131, one patient had a Grade 3 SAE of influenza after the Month 24 visit. However this was assessed by the investigator as not related to exa-cel.

B.2.10.4. Engraftment

B.2.10.4.1. Neutrophil engraftment

All patients with sufficient follow-up who completed myeloablative busulfan conditioning and received exa-cel (n=46) achieved neutrophil engraftment. The median (range) time to neutrophil engraftment was 29.0 (12.0 to 56.0) days. Forty-five of 46 patients (97.8%; 95% CI: 88.5, 99.9) achieved neutrophil engraftment by Study Day 43. As outlined above, one patient achieved neutrophil engraftment after Study Day 43 (on Study Day 56) and had an SAE of delayed engraftment. The two remaining patients in the FAS who had not achieved neutrophil engraftment at the IA2 data cut-off were at Study Day 1 and 15 (7, 8).

There was no use of backup CD34+ stem cells in any patient enrolled onto CLIMB THAL-111 (7).

B.2.10.4.2. Platelet engraftment

Of the 46 patients who achieved neutrophil engraftment, 45 had achieved platelet engraftment at the timing of the most recent data cut-off. The remaining patient was at Study Day 43 at the time of the IA2 data cut-off, who achieved neutrophil engraftment on Study Day 39. The median (range) time to platelet engraftment was 44.0 (20.0 to 200.0) days (7, 8).

B.2.10.5. Safety overview

The safety profile observed in CLIMB THAL-111 was generally consistent with myeloablative busulfan conditioning and allo-SCT, which have well established safety profiles. The safety profile of exa-cel was also generally similar to that of beti-cel, with limited treatment-related adverse events reported across the clinical study programmes (103).

In comparison with other gene therapies, exa-cel is unique in that it offers a non-viral, one-time treatment that addresses the underlying cause of TDT, without the risks of insertional mutagenesis, transcriptional deregulation, or the potential loss of response associated with viral vector-based gene therapies.

Notably, EQ-5D-5L and FACT-BMT data presented in Section B.2.6.2.8 suggests no long-term impact of AEs on patient HRQoL, with results improving from Month 3 onwards, and above baseline from Month 9 onwards (7).

In addition, in the long-term follow-up study, no new safety signals have been observed over a follow-up time of 25.3 – 43.7 months, indicating favourable long-term safety in patients with TDT (8, 86).

With up to 43.7 months of follow-up, there have been no instances of transplant-related mortality, graft rejection or GvHD. The advantages of exa-cel over allo-SCT include much broader availability due to the lack of requirement for a suitable donor, as well as substantially reduced risks of graft failure (7, 8). Furthermore, as an autologous therapy, there would be no risk of GvHD. No instances of mortality were reported in CLIMB THAL-111.

B.2.11 Ongoing studies

CLIMB THAL-111 is ongoing and will provide additional evidence for the efficacy and safety of exa-cel in patients aged 12-35 years of age with TDT. The data cut-off from IA2 was taken on 06 September 2022. Further data cut-offs are expected to be made available during the evaluation process, with the next data cut-off planned for June 2023. This is expected to provide further evidence of the continued benefits of treatment with exa-cel over the longer term.

All patients who complete CLIMB THAL-111 (followed-up for approximately two years after exa-cel infusion) or discontinue from the study will be asked to participate in a multi-site, open-label, Phase 3 rollover study, CLIMB-131 (NCT04208529). This study is designed to evaluate the long-term efficacy and safety of exa-cel in patients who received exa-cel in a parent study (CLIMB THAL-111 or CLIMB SCD-121) for a total follow-up of 15 years after exa-cel infusion (105). On this basis, the final study completion date is estimated to be September 2039. Given CLIMB THAL-111 remains ongoing, only a small subset of TDT patients (n=8) have completed the study and enrolled into CLIMB-131 at IA2 (8, 86).

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Principal findings from the clinical evidence

The efficacy and safety of exa-cel in TDT patients aged 12-35 years was investigated in a Phase 1/2/3 single-arm, open-label, multi-site, single-dose study.

The CLIMB THAL-111 cohort represents a population with a high transfusion burden, with patients averaging 35.3 units of TDT-related RBC transfusions per, and more than half (58.3%) possessing a β^0/β^0-like genotype (7, 8). Feedback received from clinical experts practicing in the UK was that the inclusion of patients possessing a β^0/β^0-like genotype is very important, as these patients are arguably the worst affected by TDT, and were not included in the regulatory label of beti-cel (52, 106).

As of IA2, 42 of 44 patients (95.4%) to complete the initial RBC transfusion washout period have stopped RBC transfusions after exa-cel infusion and have been transfusion-free for 2.9 – 40.7 months, starting 60 days after the last RBC transfusion. The remaining two patients who did not stop RBC transfusions experienced a substantial reduction in transfused volume (by 79.6% and 95.5% respectively) (8, 86).

Clinical data from 44 patients with TDT infused with exa-cel and past the initial washout period show that a single dose of exa-cel leads to early increases in HbF and total Hb that are durable for up to three years (8, 86). HbF levels recorded after exa-cel infusion were similar to those observed in patients with β-thalassaemia who co-inherit HPFH (Figure 15), a group of patients who exhibit little or no symptoms, and are generally healthy (10-12). Clinical advisors were encouraged by the trial data because substantial HbF was produced which caused the steady-state Hb level to also increase significantly (52). Increases in HbF have a protective effect, ameliorating comorbidities of β-thalassaemia, including extramedullary haematopoiesis, pulmonary hypertension, venous thromboembolism, heart failure, leg ulcers, abnormal liver function, diabetes, hyperthyroidism, hypogonadism, and osteoporosis (11).

Furthermore, patients with more than one year of follow-up had stable proportions of *BCL11A* edited alleles in bone marrow and peripheral blood, indicating successful and durable editing of long-term HSCs. In CLIMB THAL-111, the durability of response has

been confirmed for up to 43.7 months (7, 8). Over 95% of circulating RBCs expressed HbF at Month 6, and this figure remained above 95% through follow-up (8, 86).This observation is indicative of the durable engraftment of edited long-term HSCs and reflect the anticipated permanent nature of the intended edit.

Clinical experts consulted as part of this submission explained that a durable effect demonstrated out to two years would be expected to be sustained over the long-term (52). Further support for this comes from studies exploring long-term survival of β-thalassaemia patients who received allo-SCT. In these studies, almost all relapses were restricted to the first two years post-treatment (5, 107-109), with thalassaemia-free survival reported at a similar rate to overall survival, indicating that most patients who survived remained thalassaemia-free. In addition, 80-90% of patients received busulfan as their conditioning regimen, the regimen used in CLIMB THAL-111.

The safety profile of exa-cel was generally consistent with that of myeloablative conditioning and allo-SCT; the long-term safety profile of exa-cel will further be substantiated in CLIMB-131, an ongoing follow-up study of patients enrolled in CLIMB THAL-111 (86).

Exa-cel offers a one-time treatment that does not rely on insertion of a functional gene and subsequent transgene overexpression. This mechanism of action eliminates the risk of insertional mutagenesis, transcriptional deregulation or loss of response, whilst allowing patients to achieve a disease-free state by addressing the underlying cause of the disease for patients with TDT.

B.2.12.2. Strengths and limitations of the evidence base

To date, almost all evaluable patients with TDT in the CLIMB THAL-111 study have achieved a disease-free state after a single dose of exa-cel and no longer require treatment with RBC transfusions. Despite the high mean annual RBC transfusion burden at baseline (35.3 units), as of IA2, 42 of 44 (95.4%) patients who were through the washout period in the CLIMB THAL-111 FAS stopped RBC transfusions post-exa-cel infusion and maintained TI for the duration of follow-up (range: 2.9 to 40.7 months post washout period) (8, 86). By eliminating the need for RBC transfusions and ICT, exa-cel is expected to reduce the incidence of new complications associated with

transfusion and iron overload in these patients, thereby decreasing the need for ongoing medical care and interventions.

The clinical effectiveness data on total Hb levels compares favorably with previously appraised treatments for TDT in the UK. At Month 3, the proportion of total Hb comprised by HbF was consistent with that in individuals who co-inherit β-thalassaemia and HPFH. These patients suffer from mild or no symptoms of β-thalassaemia. The level of HbF increased at Month 6 and was maintained throughout the duration of follow-up (>87%) (7, 8). The substantial increase in HbF caused steady-state Hb level to rise significantly and remain at >12 g/dL from Month 9 onwards (8, 86). Importantly, clinical advisors felt that the additional increase in Hb concentration achieved with exa-cel would be associated with clinical benefit over the long-term (52). In addition, the ITC demonstrated the superior efficacy of exa-cel compared with non-curative SoC (as defined in the BELIEVE trial of luspatercept), with 86.5% of patients in CLIMB THAL-111 achieving TI6, compared to 0.0% of patients in the BELIEVE SoC arm (101).

Furthermore, allelic editing data in CD34+ cells of the bone marrow and peripheral blood were indicative of the durable engraftment of edited long-term HSPCs, reflecting the permanent nature of the intended edit (7, 8). Following successful engraftment, the effects of exa-cel are expected to be lifelong because there is no known mechanism for the edited CD34+ cells to revert to unedited cells. There is currently no consensus in the field regarding the minimum duration of follow-up to demonstrate durability of response, although consensus from clinical experts consulted as part of this submission was that two years of follow-up would be sufficient to have confidence in long-term durability of effect (52). In CLIMB THAL-111 and CLIMB-131, durability of response has been demonstrated for up to 43.7 months (8, 86). The long-term follow-up study, CLIMB-131, will follow patients for 15 years after exa-cel infusion and is expected to provide additional evidence in support of these observations.

It should be acknowledged that the CLIMB THAL-111 study is a single-arm, open-label, trial. The treatment procedure for exa-cel means it would be impossible to blind against existing SoC. Further, it would neither be feasible nor ethical to perform apheresis, myeloablation, and transplantation in a placebo group.

Patients enrolled onto CLIMB THAL-111 reported near normal health index scores of EQ-5D at baseline, despite the significant morbidity associated with the condition. Empirical evidence suggests that EQ-5D-5L descriptive system lacks content validity and the derived health utility index scores may not fully represent the burden of disease in TDT (4). Clinical experts also reported that the impact of TDT on HRQoL is often under-reported as patients typically exhibit high resiliency and adaptation to their condition (52). Therefore, as demonstrated in previous studies, EQ-5D may not fully capture the impact of TDT and may not be responsive to change in this population (4, 51). Despite the normal baseline scores, positive changes in EQ-5D-5L were observed over time, indicating improvement in overall health status after exa-cel infusion (7). Although an initial drop-off in mean EQ-5D-5L is observed from baseline to Month 3, HRQoL shows progressive improvement through follow-up (7).

B.2.12.3. Applicability of clinical evidence to practice

B.2.12.3.1. Patient characteristics

The population enrolled in CLIMB THAL-111 is considered highly generalisable to those expected to receive exa-cel in UK clinical practice. For the 48 patients in the FAS, the mean age at baseline was 21.4 years (range 12 to 35 years) (7, 8). This was slightly lower than the mean age of UK patients enrolled in the BoI study (24.8 years [range: [redacted] years]) (2, 3). Although the draft label does not include the trial upper age limit of 35, based on the age range of historical stem-cell transplant cohorts (see Santarone *et al*., (2022) and studies cited within (5)), we expect the age range in clinical practice to remain largely similar to that of CLIMB THAL-111. This is supported by clinical expert feedback noting that younger patients were likely to be prioritised for treatment initially (52).

The majority of patients were Asian ([redacted]) or White ([redacted]) (7). Baseline mean annualised units of TDT-related RBC transfusions per year for the prior two years before screening in CLIMB THAL-111 was 35.3 units (7, 8), a value similar to that reported by Shah *et al*., (2021) in a UK TDT population (39).

In addition, the majority of patients (58.3%) in the FAS had β^0/β^0-like genotypes (Table 15) (7, 8), which reflects the broader eligibility criteria of exa-cel compared to

previously appraised therapies (51). The genotypes observed in CLIMB THAL-111 were considered to reflect the spectrum of genotypes of TDT seen in UK clinical practice (52).

Furthermore, the eligibility criteria for CLIMB THAL-111 are primarily driven by the individual patients' fitness to safety undergo myeloablative conditioning with busulfan. Fitness to receive busulfan will also form a key part of eligibility to receive exa-cel in clinical practice. As such, we expect that patients eligible to receive exa-cel in UK clinical practice will be similar to those treated in CLIMB THAL-111 (52).

CLIMB THAL-111 included two study sites from the UK, namely Imperial College Healthcare NHS Trust and University College London Hospitals NHS Foundation Trust. Only patients enrolled from Imperial College Healthcare NHS Trust were evaluable in the FAS ([redacted] of 48 patients, [redacted]) (7).

Although the majority of patients in the FAS were recruited from study sites in Canada, Germany, Italy, and the US, local guidelines in each of the study locations are closely aligned with those issued by the TIF (6, 25, 110-114). Of note, a small proportion of patients in the SAS ([redacted] of [redacted] patients, [redacted]) had prior treatment with luspatercept, which is not available in the UK (7). Despite this, the management and treatment of patients with TDT in CLIMB THAL-111 is expected to be similar to UK guidelines.

B.2.12.3.2. Analysis sets

In consideration of the most appropriate analysis set for decision making, the FAS in CLIMB THAL-111 (n=48) is presented and the data is used in the subsequent cost-effectiveness analysis. This analysis set includes all patients dosed with exa-cel in CLIMB THAL-111, irrespective of follow-up, and as such provides the largest sample size (7).

B.2.12.3.3. Service provision

Exa-cel must be administered in an authorised treatment centre by a physician(s) with experience in allo-SCT and in the treatment of patients with β-haemoglobinopathies.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted to retrieve cost-effectiveness studies of gene therapy in patients with TDT. The SLR methods are detailed in Appendix G. The relevant identified studies are summarised in Table 28. No cost-effectiveness studies were identified for exa-cel. Several cost-effectiveness studies were identified for beti-cel, but only one was from a UK perspective relevant to decision-making in England and the pertinent values were redacted (51).

Table 28: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Beaudoin F. et al. (103)	2022	3-state Markov Model, (dead, TI, TD), lifetime time horizon, yearly discount rate of 3%, US health system perspective	Patients with TDT aged 2-50 years (mean entry age 22.2 years)	Beti-cel: 18.70 SoC: 13.76	Beti-cel: $2,730,000 (2021 USD) SoC: $2,260,000 (2021 USD)	$95,900
Kansal et al. (115)	2021	Microsimulation model, lifetime time horizon, yearly discount rate of 3%, US commercial payer perspective	Patients with TDT aged 2-50 years (mean entry age of 22.5 years)	Beti-cel: 19.96 SoC: 13.13	Beti-cel: $2,277,093 (2020 USD) SoC: $2,038,384 (2020 USD)	$34,833
NICE ID968 report, company base-case (51)	2021	DICE, lifetime time horizon, discount rate of 1.5%, NHS and PSS perspective	Patients with TDT aged 12 and above	Beti-cel: 30.34 SoC: 17.20	Beti-cel: Redacted SoC: Redacted	Redacted
NICE ID968 report, ERG re-analysis (NICE) (51)	2021	DICE, lifetime time horizon, discount rate of 3.5%, NHS and PSS perspective	Patients with TDT aged 12 and above	Beti-cel: 18.53 SoC: 15.48	Beti-cel: Redacted SoC: Redacted	Redacted
FINOSE report (116)	2020	Microsimulation model, lifetime time horizon, yearly discount rate of 3%, Swedish healthcare payer perspective	Patients with TDT aged 12-34 years (mean entry age not reported)	Beti-cel: 21.59 SoC: 13.42	Beti-cel: 18,517,977 kr (SEK; currency year not reported) SoC: 7,167,765 kr (SEK; currency year not reported)	1,388,918 kr
Undreiner et al. (117)	2020	DICE, yearly discount rate of 2.5%, HAS guideline perspective	Patients with TDT aged 12 and above	Beti-cel: 20.80	Beti-cel: €1,521,307 (EUR; currency year not reported)	€48,998

		(all payers without indirect cost)		SoC: 14.39	SoC: €1,207,166 (EUR; currency year not reported)	
CADTH report (118)	2021	Decision tree followed by semi-Markov model, lifetime time horizon, yearly discount rate of 1.5%, perspective of the Canadian healthcare system	Patients with TDT aged 30 years and above	Luspatercept: 7.77 SoC: 6.40	Luspatercept:: $2,159,135 (CAD, currency year not reported) SoC: $1,849,494 (CAD, currency year not reported)	$225,894

Abbreviations: CAD, Canadian Dollar; CADTH, Canadian Agency for Drugs and Technologies in Health; CEA, cost-effectiveness analysis; DICE, discretely integrated condition event; EUR, Euro; FINOSE, Nordic collaboration; HAS, French National Authority for Health; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; QALYs, quality-adjusted life years; SEK, Swedish Krona; SoC, standard of care; UK, United Kingdom; US, United States; TD, transfusion dependence; TI, transfusion independence; USD, the United States Dollar

B.3.2 Economic analysis

The SLR of cost-effectiveness studies identified that none of the studies addresses the decision problem presented in section B.1.1. A *de novo* cost-effectiveness model was therefore developed to appraise the cost-effectiveness of exa-cel for the treatment of TDT in patients 12 years of age and older for whom a HLA-matched related HSC donor is not available.

B.3.2.1. *Patient population*

The patient population included in the economic evaluation is defined as patients with TDT, who are 12 years of age and older and are eligible for an autologous SCT and without an HLA-matched donor. The model population is derived from the FAS population of the pivotal clinical trial, CLIMB THAL-111, in which transfusion dependence (TD) was defined as having a history of at least 100 mL/kg/year or 10 units/year of packed red blood cell transfusions in the 2 years preceding trial enrolment (7).

Patient baseline characteristics used in the model are summarised in Table 29. Mean age at baseline is 21.4 years and 52.1% are female. Mean baseline body weight is 54.4 kg. Patient weight was required in the model for estimating costs for treatments requiring weight-based dosing. To estimate mean patient weight across cycles as a patient ages, mean body weight was calculated as a weight ratio (0.76) of the mean baseline weight of CLIMB THAL-111 trial patients (54.4kg) over the matched age at baseline mean body weight of the standard UK national reference (71.4kg) (119). This approach was supported by clinical expert opinion.

The distributions of iron levels for SF, myocardial T2*, and LIC are used to determine risk of developing complications over the model time horizon. At baseline, all patients are assumed to have non-normal iron levels (i.e., low, medium, and high) for SF, myocardial T2*, and liver iron concentration, informed by a chart review study of nine UK NHS centres by Shah *et al*., 2021 (n = 165) (39). Shah was used in preference to the CLIMB THAL-111 baseline values because the study excluded patients with high T2* and LIC at baseline, whereas patients could have potentially developed high T2*

and LIC over the course of their lifetime had they remained on SoC. As no longitudinal data were available from which to derive transition matrices for TDT patients' iron levels over the course of their lifetime (see section B.3.3.1) it is assumed that SoC patients remain in their baseline iron health states. We therefore consider the chart review to be a more representative source of patient iron distribution than the clinical study, since it captures prevalence in a population unrestricted by exclusion criteria applied at a timepoint within an evolving disease history.

The model captures the risk of developing cardiac and liver complications, osteoporosis, diabetes, and hypogonadism. Cardiac and severe liver complications were exclusion criteria in the CLIMB THAL-111 trial and therefore these are excluded from the model at baseline. Furthermore, the model is only able to calculate a cumulative incidence of complications, whereas there is potential for osteoporosis to be reversed. The single patient with diabetes was considered to be representative of the general UK population rather than representing a TDT-specific morbidity and was therefore excluded. Only complications considered irreversible were therefore included at baseline, comprising infertility (10.1% for males and 12.5% for females based on the population prevalence rates in the UK general population across all age groups, stratified by gender (120), hypogonadism and splenectomy (both sourced from the CLIMB THAL-111 FAS population).

At baseline, all TDT patients are assumed to receive an average of 16.4 transfusions of 2.2 units based on CLIMB THAL-111 FAS data (calculated from the annualised transfusion episodes and annualised RBC units). Six different regimens of ICT were considered in the model. ICT use at baseline was not available from the CLIMB THAL-111 at the time of submission. To align ICT use with UK clinical practice, the baseline distribution of ICT treatments was estimated based on data from a UK chart review study.

Table 29: Baseline clinical inputs

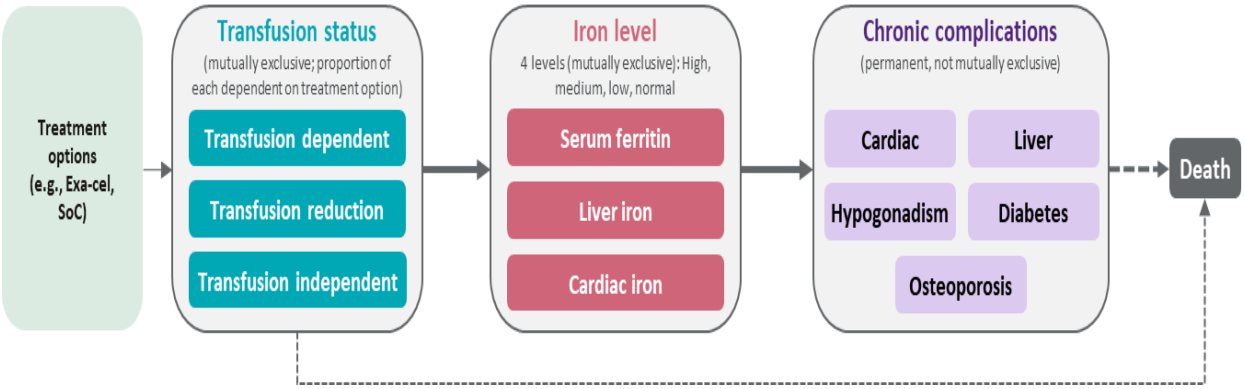
Variable	Value	Reference
Patient demographics		
Age (years)	21.4	CLIMB THAL-111 FAS (7)
Female (%)	52.1	CLIMB THAL-111 FAS (7)

Weight (kg)	54.4	Calculation, CLIMB THAL-111 FAS (7)
Proportion of patients with baseline iron levels		
Serum ferritin (%)		
Low (above normal to ≤1,000 ng/ml)	23.0	Shah et al., 2021 (39)
Moderate (1,000-2,500 ng/ml)	38.8	Shah et al., 2021 (39)
High (>2,500 ng/ml)	38.2	Shah et al., 2021 (39)
Myocardial T2* (%)		
Low (>20ms to below normal)	88.2	Shah et al., 2021 (39)
Moderate (10-20 ms)	11.8	Shah et al., 2021 (39)
High (<10 ms)	0.0	Shah et al., 2021 (39)
Liver iron concentration (%)		
Low (above normal to <7 mg/g)	60.5	Shah et al., 2021 (39)
Moderate (7-15 mg/g)	23.5	Shah et al., 2021 (39)
High (≥15 mg/g)	16.0	Shah et al., 2021 (39)
Proportion of patients with complications (%)		
Cardiac	0	CLIMB THAL-111 Trial (exclusion criteria) (7)
Liver	0	CLIMB THAL-111 Trial (exclusion criteria) (7)
Osteoporosis	0	Assumption
Diabetes	0	Assumption
Hypogonadism	2.1	CLIMB THAL-111 Trial (Table 14.1.5) (7)
Splenectomy	31.3	CLIMB THAL-111 Trial (Table 14.1.5) (7)
Infertility (by gender)		
Male	10.1%	Datta 2016 (120)[Table 1] (120)
Female	12.5%	Datta 2016 (120)[Table 1] (120)
Red blood cell transfusions		
Annual RBC transfusion frequency	16.4	CLIMB THAL-111 Trial (FAS, Table 14.1.4.1) (7)
Units of blood per RBC transfusion	2.2	CLIMB THAL-111 Trial (FAS, Table 14.1.4.1) (7)
Iron chelation therapy regimen distribution (%)		
DFX	58.0	Shah et al., 2021 (39)
DFP	6.8	Shah et al., 2021 (39)
DFP	14.2	Shah et al., 2021 (39)
DFP + DFO	11.1	Shah et al., 2021 (39)

DFP + DFX	4.9	Shah et al., 2021 (39)
DFX + DFO	4.9	Shah et al., 2021 (39)

B.3.2.2. *Model structure*

Figure 20: Model structure



A Markov model was developed in Microsoft Excel. The Markov structure is presented in Figure 20. Transfusion status is the defining characteristic of TDT. This is because transfusion status drives patient iron levels (e.g., SF, myocardial T2*, and LIC) which have an impact on complication risks, mortality, and quality of life, as well as healthcare resource use and costs. Therefore, a Markov model, using transfusion status (i.e., transfusion independent [TI], transfusion reduced [TR], and transfusion dependent [TD]) and death as health states was developed to simulate the natural history and clinical pathways of TDT for the modelled patient population. Patients with different transfusion status are assumed to have different iron levels and hence receive different amounts of RBC transfusions. This is discussed in detail in section B.3.3. Transfusion reduction was included as a relevant health state in the economic model to capture the treatment benefit for patients who do not achieve transfusion independence but experience a significant reduction in RBC transfusion frequency. Data for TR patients were derived from the CLIMB THAL-111 trial PES. See section B.3.3 .2 or further details.

The SLR of cost-effectiveness models presented in section B.3.1 demonstrated that there is precedence for using a Markov model structure in the evaluation of therapeutic options for TDT. Moreover, the company submission to NICE for betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia used a discretely integrated condition event (DICE) simulation framework model, driven by a series of conditions (e.g., development of iron overload) and events (e.g., blood transfusion) (121). This model was criticised by the NICE Evidence Review Group (ERG) as an overly complex structure, which did not make use of the patient-level approach given the limited clinical data that exists to inform the complex disease process. Hence, the ERG stated that there is limited additional benefit of a patient-level simulation approach when data are scarce. Lastly, a Markov model structure was deemed appropriate by advisors from NICE Scientific Advice when consulted by Vertex (121).

Given the aforementioned considerations, a Markov model structure was therefore selected for this analysis. A summary of the features of the de novo model for exa-cel is provided in Table 30.

Table 30: Features of the base-case economic analysis

	Previous evaluations	Current evaluation	
Factor	**STA ID968 (Discontinued)**	**Chosen values**	**Justification**
Time horizon	Lifetime	Lifetime	As per the NICE reference case. Sufficient to capture meaningful differences in technologies
Cycle length	N/A (continuous-time model)	1 month (with half-cycle correction)	Sufficient to capture meaningful changes in patient disease history and treatment effects
Discount rate	1.5%	1.5%	Exa-cel meets the criteria for a non-reference case discount rate of 1.5% as laid out in the NICE methods guide: The technology is for people who would otherwise die or have a very severely impaired life. • In the UK BoI study conducted by Vertex, the crude mortality rate in the TDT cohort was more than 5 times that of the matched general population (1.38 v. 0.26 per person-year) (2, 3), in line with findings from a previous UK study (1). The mean age at death was 55 years old. Moreover, as described in section B.1.3.2, patients with TDT not only have poor daily HRQoL compared with the general population but are also at risk of developing severe complications over the course of their lifetime. Cardiac and liver complications, as well as diabetes, bring with them not only substantial morbidity but also mortality. In a retrospective cohort analysis of UK TDT patients, 76% had at least one co-morbidity, 54% suffered from two of more, and 37% suffered from three or more (1). • In summary, TDT patients on SoC have a limited life span and a high risk of co-morbidities affecting many organs in their body. They also have to manage the huge impact of regular transfusion and iron chelation, including fatigue, and pain, as shown in our HRQoL study (4).

			It is likely to restore them to full or near-full health: • Patient treated with exa-cel will experience improved survival, reduced risk of co-morbidities (both thalassaemia/anaemia-related and iron overload related) and they will no longer need transfusion or iron chelation, which are hugely burdensome treatments. They will have improved HRQoL and reduced fatigue, pain, plus more time released, more likely to return to work. The benefits are likely to be sustained over a very long period: • The expected benefits of exa-cel as a one-time gene editing therapy include ameliorating a life-long disease indefinitely (see section B.2.12.1). There is no biological plausibility to lose treatment effect, and experts are aligned that if there is sustained effect at 2 years there is no reason to believe the effect would wane (given past experience with SCT in this indication (5)).
Treatment waning effect?	No	No	See section B.2.12.1. Relapse to TD is not expected to be observed during or beyond the trial period as late relapses ≥2 years following SCT are extremely rare and frequently driven by GvHD (5).
Source of utilities	Vignette study	Vignette study	A vignette study was used as the EQ-5D does not adequately capture the impact of TDT on HRQoL (see section B.1.3.2 for discussion): • TDT is an inherited condition, the symptoms of which are experienced from early childhood. Patients are likely to adapt to their condition, leading to high baseline EQ-5D and introduction of a ceiling for increase in HRQoL following treatment with exa-cel; • A significant contributor to poor quality of life in TDT is fatigue, which is not captured in the EQ-5D.
Source of costs	As per the reference case, except for costs which could not be obtained for the UK.	As per the reference case, except for HRU which could not be obtained for the UK.	See section B.3.5
Health	No	Yes	Principle 9 of NICE's charter aims to reduce health inequalities. Thus,

inequalities			NICE considers inequality or unfairness in the distribution of health to be an important factor in decision-making (9). People of Asian and Southeast Asian descent living with TDT experience lower life expectancy and health related quality of life compared to other ethnicities due to development of secondary morbidities later in life. The medications and regular transfusions that constitute TDT disease management are burdensome and time-consuming, making it difficult for patients to socialise and to maintain regular employment. Consequently, patients experience social isolation and significant negative financial constraints, and a lack of access to funding support can often limit patients' ability to travel to treatment centres, which further contributes to worsening of their condition. As part of this submission, Vertex has conducted a distributional cost-effectiveness analysis (DCEA) as a framework for incorporating health inequality concerns into the economic evaluation of exa-cel. Outputs from the DCEA are used to estimate how exa-cel could potentially reduce population-level health inequality. A key aspect of DCEA is to explicitly incorporate a decision-maker's aversion to inequality, based on a Social Welfare Function, into the calculation of the ICER. Using this function, QALYs and Opportunity Costs can be weighted based on an indirect equity weighting. Thus, a DCEA, similar to the principle of a severity modifier, can be used to modify the ICER based on quantitative estimates of how much exa-cel potentially reduces health inequalities. For detailed discussion on DCEA methods, please see section B.3.9.

Key: HRU, healthcare resource use

As shown in Figure 21, the model included several tunnel phases to track time-to-iron-normalisation, post- exa-cel treatment. Specifically, the model includes a treatment phase, an iron normalisation/change phase, and an “ongoing phase” for the remainder of the model horizon. Patients enter the model at the time of exa-cel infusion, and any pre-infusion costs and disutilities are applied as a lump sum at model entry. During the treatment phase and the response phase for exa-cel, patients are assumed to remain in the TD health state with iron levels unchanged from baseline. Thus, patients are assumed to receive the same RBC transfusions and ICTs during the treatment/response phase as received at baseline. Exa-cel patients are assumed to undergo premobilisation, mobilisation, and apheresis, myeloablative conditioning and infusion, and engraftment during the model’s treatment phase. The frequency of RBC transfusions for the remainder of the model (iron normalisation/change phase and ongoing phase) is based on the transfusion status achieved at the end of the treatment or response phase.

Patients who remain in the TD health state are assumed to remain at the baseline frequency of RBC transfusions; patients who achieve TR are assumed to experience a reduction in the frequency of RBC transfusions, and patients who achieve TI experience no further transfusions. Since SoC patients remain TD, model phases are not relevant to SoC as these patients do not experience any reduction in transfusions or changes to baseline iron levels. Hence, the number of transfusions and the dose/frequency of ICT is assumed to remain the same as baseline for patients that remain in the TD health state, post-treatment phase.

During the iron normalisation/change phase, patients’ iron levels change based on their transfusion status. Three measures of iron levels are included in the model: SF, myocardial T2* (the cardiac iron concentrate), and LIC. Iron levels are considered normal or non-normal, with non-normal further categorised as low, moderate, or high, based on pre-specified thresholds. All TDT patients had non-normal iron levels at baseline.

The model assumes patients who remain in the TD health state remain at the iron levels set at baseline, whereas patients who achieve TI achieve normal iron levels. Patients who achieve TR have reduction in iron levels and thus move to a lower iron

category (i.e., one level lower) than baseline, but do not achieve iron normalisation. During the iron normalisation phase, all (both exa-cel and SoC) patients are also assumed to receive the same level of ICT as baseline (i.e., full dose ICT) because ICT is required until iron normalisation is achieved (based on expert opinion). The model assumes that the change in patients' iron levels occurs at a constant rate over the duration of the iron normalisation/change phase.

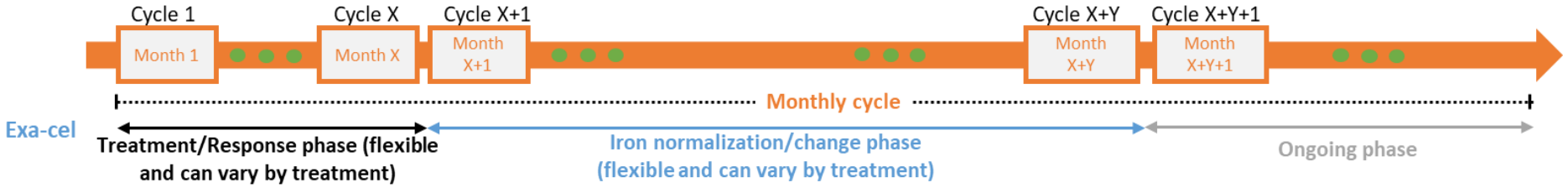
During the ongoing phase, patient transfusion status and iron levels remain the same from the end of the iron normalisation/change phase until the end of the model horizon (base case assumes no treatment waning).

As noted above, patients in the TD health state receive the same frequency of RBC transfusions, frequency/dosage of ICT, and maintain the same iron levels as baseline. Patients who achieve TR experience a reduction in the frequency of RBC transfusions but continue to receive full dose ICT. Patients who achieved TI are assumed to receive no further RBC transfusions or ICT.

Patients are at risk of death every model cycle. Mortality risk is estimated based on transfusion status, the prevalence of complications, and occurrence of other transplantation-related events, including autologous graft failure. Further details are provided in section B.3.3.4.

Figure 21: Model phases

A: exa-cel



Transfusion status	• TD	• TD, TR, or TI, based on treatment response and treatment waning effect	
Iron level	• Baseline level	• Based on transfusion status; change constantly over time or at the end of this phase	• Based on transfusion status
Phase specific procedures	•Mobilization, apheresis, and conditioning •Transfusion received by all patients •ICT received by all patients	• No transfusions for patients in TI, reduced transfusion received by patients in TR, and regular transfusion received by patients in TD •ICT received by all patients	•Regular transfusion received by patients in TD; reduced transfusion received by patients in TR; no transfusions for TI patients •Full dose ICT received by patients in TD and TR and not received by patients in TI
Phase specific events	•Treatment withdraw, engraftment failure, complications, and infertility	•Complications and infertility	
Factors that impact mortality	•Transfusion status, transplantation, complications, infertility, and age	•Transfusion status, transplantation, complications, infertility, and age	

B: SoC

Transfusion status	• TD	•SOC: TD	
Iron level	• Baseline level	• Based on transfusion status; change constantly over time or at the end of this phase	• Based on transfusion status
Phase specific procedures	•Transfusion received by all patients •ICT received by all patients	•Regular transfusion received by patients in TD and reduced transfusion received by patients in TR •ICT received by all patients	•Regular transfusion received by patients in TD and reduced transfusion received by patients in TR •Full dose ICT received by patients in TD and TR and not received by patients in TI
Phase specific events	•Complications		
Factors that impact mortality	•Transfusion status, complications, and age		

B.3.2.3. Intervention technology and comparators

The intervention considered in the cost-effectiveness model is exa-cel. The comparator is SoC, assumed to comprise lifelong RBC transfusions and ICT.

B.3.3 Clinical parameters and variables

CLIMB THAL-111 is a single-arm trial and thus could not provide comparator data for SoC. As evidenced in the SLR and ITC of clinical efficacy (see section B.2.9), no TD patients on SoC can spontaneously revert to TI or TR without an active intervention. Furthermore, no outcomes on iron levels could be obtained from the trials identified in the SLR. Patients on SoC are therefore assumed to retain their baseline transfusion status, frequency and volume and iron distribution over the course of the model time horizon. This is of course a conservative assumption for the paediatric patients, whose transfusion and chelation requirements are likely to increase as they grow and reach adulthood.

B.3.3.1. Transfusion status and iron normalisation

As shown in Figure 21, the model is divided into several phases. For exa-cel, the treatment phase includes pre-mobilisation, mobilisation and apheresis, myeloablative conditioning and infusion, and engraftment. Treatment efficacy is only assumed in the post-treatment phase. A summary of efficacy-related input parameters is provided in Table 31.

The treatment phase is assumed to last for 12 months, based on the CLIMB THAL-111 protocol (87). This is in line with the phase-length accepted by the ERG in the beti-cel NICE submission (67), and it was also considered appropriate by clinical experts.

Treatment withdrawal is defined as patients who were never dosed with exa-cel, and so these patients were not analysed in the FAS or PES trial data. This input is therefore informed by 2 of the 50 patients (4.0%) from CLIMB THAL-111 who were never dosed with exa-cel (9 other patients included in the FAS were awaiting dosing with exa-cel at the time of the data cut, see Figure 33). The pre-treatment costs of these patients are accounted for via a cost uplift.

Patients with engraftment failure from exa-cel are assumed not to receive any clinical benefits and their transfusion status and their iron levels are assumed to return to SoC levels (i.e., baseline levels). However, no patients experience engraftment failure from exa-cel in the base case model. This is because the initial engraftment success rate was based on CLIMB THAL-111 FAS data where 48 out of 48 patients experienced engraftment success (17, 67, 121). Patients treated with exa-cel who are alive at the end of the treatment phase can remain in the TD health state or transition to the TR or TI health states.

During the iron normalisation/change phase, 92.6% of exa-cel patients transition to the TI health state post-treatment, informed by 25 of the 27 infused patients with TDT who were transfusion-independent in CLIMB THAL-111 at the time of the data cut. (Subject [redacted] achieved TI despite reaching it later in their treatment journey [14.5 months]). Exa-cel patients who transition to TI or TR from TD do so in the first cycle following the treatment phase, which is a conservative assumption given that the majority of patients transitioned far earlier than this (see the exa-cel draft SmPC).

This leaves a 7.4% probability of exa-cel patients transitioning to the TR health state, as all remaining patients in the PES saw a reduction in their transfusion frequency. Patients who transition to TR experience an 87.6% reduction in transfusions from baseline, informed by 2 of the 27 patients (CLIMB THAL-111 PES data) who had not yet stopped transfusions at the time of the PES analysis but had experienced significant reductions in RBC transfusion frequency. Specifically, these patients had 79.6% and 95.5% reductions in transfusion volume compared to their pre-study rates (see section B.2.6.1). The mean reduction in transfusion volume (87.6%) was then used as the transfusion reduction weighting in the TR health state in the first cycle following the treatment phase. In the SoC arm, all patients are assumed to remain in the TD health state, as patients cannot spontaneously revert to TI without active therapy, as evidenced by the results of the ITC (see section B.2.9).

The iron-normalisation/change phase was assumed to be 4 years, based on clinical expert opinion. Over the course of the iron normalisation period, patients who were TI at the start of the normalisation period transition to normal ferritin, T2* and LIC values in a linear manner until the end of the normalisation period, at which point 100% of TI

patients have normal iron levels. Over the same period, TI patients who have not achieved normal iron levels are apportioned across the non-normal iron health states as per their distribution at baseline. Patients who were TR at the start of the normalisation period transition to the next lowest ferritin, T2* and LIC values (i.e., high to medium, medium to low) in a linear manner until the end of the normalisation period. Patients who remain TD (only relevant to SoC) remain at their baseline iron health state distribution. This is a limitation of the model as baseline iron distribution represents a cross-sectional prevalence and no longitudinal data are available from which to derive transition matrices for TDT patients' iron levels over the course of their lifetime. For example, no patients in the CLIMB THAL-111 study had T2*<10ms or LIC>15 mg/g at baseline due to the trial exclusion criteria, but these patients could have potentially developed low T2* and high LIC had they remained on SoC.

As discussed previously, transfusion status and iron levels remain the same from the end of the iron normalisation/change phase until the end of the model time horizon. Thus, all patients with engraftment success from exa-cel who achieved TI were assumed to have normalised iron levels. These patients are assumed to remain in the TI health state for the remainder of the model time horizon. Since TI patients are assumed to have normal iron levels, these patients also do not receive ICT, whereas TR and TD continue to receive ICT at their baseline levels. Note that this is likely to bias against exa-cel with respect to TR patients, who require less ICT given the substantial reduction in transfusion volume. Additional details on transfusion status, iron levels, and patient use of RBC transfusions and ICT during the treatment/response and iron normalisation/change phase have been described in the section above.

Treatment waning for exa-cel is not considered in the analysis. A detailed discussion on exa-cel's mechanism of action and the anticipated permanence of gene editing is presented in section B.2.12.1 of this submission. Although relapse has been observed following SCT, it occurs almost exclusively within two years of transplant and late relapses tend to be associated with GvHD (5). Thus, patients who have not relapsed within two years of being infused with exa-cel are highly unlikely to relapse in the future. The expected benefits of one-time gene editing therapies such as exa-cel

include ameliorating a life-long disease indefinitely and thus it is expected that the clinical and economic benefits will materialise over a patient's lifetime.

Table 31: Treatment procedure and response inputs

Variable	Value	Reference
Exa-cel		
Treatment phase (months)	12.0	CLIMB THAL-111 Trial
Iron normalisation/change phase (months)		
Serum ferritin	48.0	Clinical opinion.
Myocardial T2*	48.0	Clinical opinion.
Liver iron concentration	48.0	Clinical opinion.
Treatment procedure (%)		
Treatment withdrawal rate	4.0	CLIMB THAL-111 Trial (Table 14.1.1, FAS)
Initial engraftment success rate	100	CLIMB THAL-111 Trial (Table 14.1.1, FAS)
Response (after treatment phase %)		
Proportion with TI	92.6	Proportion of PES patients who were transfusion-independent at the time of the data cut.
Proportion with TR	7.4	CLIMB THAL-111 Trial (PES, Subjects [redacted], & [redacted])
% of transfusion reduction at TR	87.6	CLIMB THAL-111 Trial (PES, Subjects [redacted], & [redacted])
Proportion with TD	0.0	CLIMB THAL-111 Trial
Standard of Care		
Patients on SoC remain at baseline levels. See Table 29.		

B.3.3.2. Complication inputs

As discussed within the model structure section, the complications of TDT included in the model are cardiac complications, liver complications, osteoporosis, diabetes, and hypogonadism. Literature-based rates and risk equations were used to estimate the rate of developing complications of TDT based on iron levels and transfusion status (see Table 32). Literature-based rates and risk equations were selected according to the generalisability of the study population to the model population as well as the appropriateness of the results to the model health states (i.e., iron level stratification). The most appropriate values based on the model decision context, i.e., UK and/or European sources, were then selected as base-case inputs. The results of the literature search have been provided in a separate Excel file (122).

The risk of the cardiac complications in patients with TDT is based on myocardial T2* iron levels, estimated from a prospective multicentre study of 481 TDT patients with 36 cardiac events over a mean follow-up time of 57.91 months (123). The proportion of patients within each myocardial T2* level who experienced cardiac complications were 17 out of the 322 subjects with low myocardial T2* levels, 9 out of the 103 with moderate myocardial T2*, and 10 out of the 56 with high myocardial T2*. These proportions have been converted to an annual risk of experiencing cardiac complications for each myocardial T2* strata. The model thus assumes that patients with low myocardial T2* have an 1.12% annual risk, patients with moderate myocardial T2* have an 1.88% annual risk, and patients with high myocardial T2* have an 3.99% annual risk of developing cardiac complications, respectively.

The risk of liver complications, which, in the model, is dependent on LIC level, was 8.5% per year in patients with high LIC level, based on fibrosis progression in a sample of 211 patients who underwent bone marrow transplantation and were thalassaemia-free (median follow-up of 64 months) (124). The risk of liver complications among those with low and moderate LIC levels was assumed to be the same as the risk in patients with normal LIC levels. This was due to the lack of evidence to support an elevated risk of liver complications in patients with low or moderate iron levels. The risk of liver complications for TDT patients with normalised iron was assumed to be

same as the risk among the general (non-TDT) population, based on the results from matched control cohort of Vertex's TDT UK BoI study (2, 3).

The risk of osteoporosis was estimated based on age- and gender-specific rates of osteoporotic fractures among the general (non-TDT) UK population multiplied by rate ratios dependent on transfusion status (see Table 32). The incidence rate ratio was assumed to be [redacted] for patients in the TD health state, based on the incidence rates of osteoporosis observed among TDT patients compared with matched controls in Vertex's TDT UK BoI Study (2, 3). Patients with TI were assumed to have no increased risk and therefore have the same rate of osteoporosis as the general (non-TDT) population (see Table 32). Patients with TR were assumed to have a rate ratio of [redacted], calculated as the mean of the rate ratios for TI and TD.

Among patients with non-normal iron levels, the risks of developing diabetes or hypogonadism were calculated as a function of age, SF level, and myocardial T2* level. This was based on a published retrospective analysis of 92 patients with beta thalassaemia major from a tertiary adult thalassaemia unit in the UK. The study collected longitudinal data on routine measurements of iron load and conducted multivariate analyses using logistic regression which analysed risk factors for diabetes and hypogonadism in adult patients with thalassaemia major (37); see Table 32 for further details. The annual risk for diabetes or hypogonadism among patients with normal iron levels was [redacted] %, derived from Vertex's TDT UK BoI Study (2, 3).

Given the recent shift in treatment patterns away from splenectomising patients, the model base-case assumes the ongoing risk of splenectomy to be 0% for all patients, regardless of transfusion status (i.e., TI, TR, TD). The exclusion of splenectomy as an ongoing TDT complication in the economic model base-case was considered a reasonable assumption based on expert opinion.

The risk of complications among patients who reach a disease-free state from TDT (i.e., patients who achieve TI and subsequent iron normalisation) is assumed to be the same as the risk of complications in the general (non-TDT) population. This was also considered reasonable based on expert opinion. The risk of complications from the general (non-TDT) population was derived from the matched control cohort of Vertex's UK TDT BoI study (2, 3).

Table 32: Risk of complications

Variable	Value	Reference
Cardiac: annual risk based on myocardial T2* level (%)		
Myocardial T2* Normal	[redacted]	Matched control cohort, UK BOI study (2, 3)
Myocardial T2* Low	1.12	Pepe et al., 2018 (123)
Myocardial T2* Moderate	1.88	Pepe et al., 2018 (123)
Myocardial T2* High	3.99	Pepe et al., 2018 (123)
Liver: annual risk based on LIC level (%)		
LIC Normal	[redacted]	Matched control cohort, UK BoI study (2, 3)
LIC Low	[redacted]	Matched control cohort, UK BoI study (2, 3)
LIC Moderate	[redacted]	Matched control cohort, UK BoI study (2, 3)
LIC High	8.5	Angelucci et al., 2002 (124)
Osteoporosis: monthly incidence rate in general (non-TDT) population (by gender and age group)		
Male		
< 30	0.0000225	Hippisley-Cox et al., 2009 (125)
30-34	0.0000450	
35-39	0.0000475	
40-44	0.0000475	
45-49	0.0000508	
50-54	0.0000600	
55-59	0.0000725	
60-64	0.0000883	
65-69	0.0001242	
70-74	0.0002117	
75+	0.0003625	
Female		
< 30	0.0000208	Hippisley-Cox et al., 2009 (125)
30-34	0.0000417	
35-39	0.0000517	
40-44	0.0000733	
45-49	0.0001100	
50-54	0.0001642	
55-59	0.0002250	
60-64	0.0003325	

65-69	767	
70-74	708	
75+	092	
Increased risk of osteoporosis by transfusion status: rate ratio		
TI	1.00	Assumed same as general (non-TDT) population
TR	[redacted]	Assumed average of TI and TD
TD	[redacted]	UK BoI study (2, 3)
Diabetes		
Annual risk for normal iron level		
When both serum ferritin and myocardial T2* are normal	[redacted]	Matched control cohort, UK BoI study (2, 3)
Risk equation (log-odds of 8-year risk) for non-normal iron levels		
Intercept	-8.019	Ang et al., 2014 (37)
Serum ferritin (moderate or high)	2.695	Ang et al., 2014 (37)
Myocardial T2* (moderate or high)	2.960	Ang et al., 2014 (37)
Age	0.095	Ang et al., 2014 (37)
Hypogonadism		
Annual risk for normal iron level		
When both serum ferritin and myocardial T2* are normal	[redacted]	Matched control cohort, UK BoI study (2, 3)
Risk equation (log-odds of 8-year risk) for non-normal iron levels		
Intercept	-4.422	Ang et al., 2014 (37)
Serum ferritin (high)	1.065	Ang et al., 2014 (37)
Myocardial T2* (moderate or high)	1.361	Ang et al., 2014 (37)
Age	0.095	Ang et al., 2014 (37)
Splenectomy: annual risk based on transfusion status		
TI	0.0%	Assumption
TR	0.0%	Assumption
TD	0.0%	Assumption

Abbreviations: LIC, liver iron concentration; NICE, National Institute for Health and Care Excellence; TD, transfusion dependent; TI, transfusion independent; TR, transfusion reduced

B.3.3.3. Other condition inputs

Among patients treated with SoC, the risk of infertility was assumed to be 10.1% in males and 12.5% in females (120), which reflects infertility in the general (non-TDT) UK population already described in Section B.3.3.1 (120).

Among patients treated with exa-cel, the risk of infertility was assumed to increase following myeloablative conditioning by 24% (prevalence ratio: 1.24) in males and by 57% (prevalence ratio: 1.57) in females, based on the assumptions applied in the NICE assessment for beti-cel in TDT (67). The range of fertile age was assumed to be from 16 to 51 years old in both males and females; the upper bound was based on the mean age of menopause in females in the UK (126). These inputs are summarised in Table 33.

Table 33: Other conditions

Variable	Value	Reference
Infertility rate (by sex)		
SoC (annual %)		
Male	10.1	Datta et al., 2016 (120)
Female	12.5	Datta et al., 2016 (120)
Exa-cel (prevalence ratio)		
Male	1.24	NICE ID968 (67)
Female	1.57	NICE ID968 (67)
Age at Fertility and Infertility		
Age at fertility	16	Datta et al., 2016 (120)
Age at infertility	51	British Menopause Society, 2022 (126)

B.3.3.4. Mortality inputs

Patients are at risk of death throughout the modelled lifetime horizon. Risk of death is dependent on the patients' transfusion status, occurrence of complications, and other transplant-related events. A summary of mortality inputs can be found in Table 34. As for complication inputs, mortality input values were based on a targeted literature review. The results of the literature search are provided in a separate spreadsheet (122). The most applicable input mortality values were selected according to the generalisability of the study population to the model population and decision context.

Transplant-related mortality can be applied as an instant risk at the end of the treatment phase. However, patients treated with exa-cel were assumed to have no risk of transplant-related mortality based on the CLIMB THAL-111 FAS data. The model also includes death following engraftment failure (25.0%) based on clinical expert opinion. Again, this risk is not applicable to the model base case because the exa-cel engraftment success rate was 100%. The risks of transplant-related mortality events were applied at the end of the treatment phase (at 12 months).

Transfusion status-dependent mortality is captured via two routes; (1) a standardised mortality ratio (SMR) multiplicatively applied to general UK population mortality rates and (2) a mortality related to the cardiac complications and diabetes. This approach is necessary as the model does not capture all potential causes of excess mortality in TDT such as infection. This is discussed in detail below.

The all-cause mortality rates for the UK general population were obtained from the England and Wales life tables (127). Although modern ICT has substantially decreased mortality in TDT (128), more contemporary studies suggest that TDT patients remain at increased risk of early death compared with-matched controls (1-3). Despite improvements in pathogen-free blood, iron monitoring techniques, and advances in ICT, TDT patients have been observed to have mortality rates more than 5 times that of the matched UK general population (1-3).

In comparison, if only SMRs related to specific complications are included, the model predicts an SMR of 2.37. This SMR was estimated from the model by dividing the

mortality rates on SoC by that of the general population at the end of the 79-year time horizon, i.e.,

$$\frac{-llll(ccccccccllcccccccccc\ \ ssccssccccccccllssssss)}{-llll\blacksquare ccccccccllcccccccccc\ \ sscssscccccccllGGGGGG\ PPSSPP\blacksquare}$$

Based on the above rationale, an additional SMR of 3.45 is incorporated for patients in the TD health state to ensure robust estimation of TDT-related all-cause mortality. Following application of the SMR of 3.45 for TD patients, the model predicts an SMR of 5.0 over the modelled time horizon, which is in line with the values estimated in contemporary UK studies (1-3). We consider the application of an SMR of 3.45 for TD patients (before application of complication-specific SMRs) as thus reasonable since it reflects current real-world evidence on the disease-related mortality of TD patients in the UK.

With respect to the disease-related mortality of TI and TR patients, patients who achieve TI are assumed to have an SMR of 1.25 to reflect the potential mortality impact of myeloablative conditioning. In the absence of a specific SMR for patients in the TR health state, the mean of the SMRs for patients with TD (3.45) and TI (1.25) is assumed (i.e., 2.35). An SMR of 1.25 for TI patients and using the mean TI and TD SMRs for TR patients was considered a reasonable assumption by the ERG in the NICE assessment for beti-cel in TDT (67).

Excess mortality associated with complications is included for cardiac complications and diabetes. A 13% annual mortality risk for cardiac complications is estimated based on a study of 52 patients with β-thalassaemia and heart failure, which was also used in the NICE assessment of beti-cel in TDT (67). An SMR of 1.5 for diabetes complication is applied, based on 2004-2019 UK National Diabetes Audit data (129). Excess mortalities associated with complications are conditional on being alive after SMR-adjusted background mortality is considered.

Table 34: Mortality inputs

Variable	Value	Reference
Transplantation-related mortality		
Instant risk (probability) of death due to procedure (%)		
Exa-cel	0.0	CLIMB THAL-111 (FAS)
Instant risk (probability) of death (%)		
Exa-cel engraftment failure	25.0	Assumption
Transfusion status-dependent mortality		
SMR		
TI	1.25	Assumption; NICE ID968 (67)
TR	2.35	Assumption (mid-point of TI and TD SMR)
TD	3.45	Manual calibration to achieve an SMR of 5 overall.
Complication-dependent mortality		
Annual risk (%)		
Cardiac	13.0	Kremastinos et al.,2001 (138) NICE ID968 (67)
Osteoporosis	0.0	Assumption
SMR		
Liver complications	1.00	Assumption
Diabetes	1.50	National Diabetes Audit (129).
Hypogonadism	1.00	Assumption

Additional mortality risks due to osteoporosis, liver complications, and hypogonadism are not included in the model as these are assumed to be captured in the risk of mortality applied to the TD health state (SMR of 3.45). Moreover, there is limited evidence to support additional mortality risks associated with these complications and thus this also avoids potential double-counting of these mortality risks. Lastly, infertility is not associated with additional mortality, consistent with assumptions used in previous cost-effectiveness models in TDT (67, 103).

Lastly, in the base-case analysis, mortality risks were combined multiplicatively. Hence, the joint mortality risks related to transplantation and complications are

assumed to be independent of each other. The impact of combining mortality using additive and maximising interactions are explored in scenario analyses.

B.3.3.5. Adverse event inputs

Grade 3+ treatment-related AEs are considered in the model. All adverse event inputs are summarised in Table 35.

For patients receiving exa-cel, in the base case all AEs assume to occur at the hospital during the transplant procedure, and thus are captured in transplantation or transplantation-related hospitalisation disutility and costs. This is in line with the NICE assessment of beti-cel in TDT (67). However, an additional scenario is conducted in which the costs of additional AEs are captured, based on a post-hoc analysis of CLIMB THAL-111 in which [redacted] of patients spent an average of [redacted] days in hospital after having been discharged for the initial procedure. This is only included as a scenario as it is unclear whether these represented routine day visits already captured in other model resource use as opposed to hospitalisations for AEs and/or whether the readmissions occurred within 100 days of treatment start (which is included in the autologous-SCT reference cost and transplant-related disutility). No disutility is applied to the scenario, for reasons explained in section B.3.4.4.

For SoC, recurring AE rates are applied in each model cycle. The rate of any grade 3+ AEs for SoC are derived from the Phase 3 clinical trial of luspatercept (median follow-up: 64 weeks). The observed probability of the overall grade 3+ AE rate for SoC from the trial has been converted to constant monthly event rates before being used as model inputs (130).

Table 35: Adverse events inputs

Treatment	Monthly rates of any grade 3+ AEs	Reference
SoC	1.14%	Cappellini et al., 2020 (102, 130)
Exa-cel (scenario only)	[redacted]	Post-hoc analysis of CLIMB THAL-111 FAS.

Abbreviations: SoC, standard of care

B.3.4 Measurement and valuation of health effects

In line with the NICE reference case, health effects in the model are measured in quality-adjusted life years (QALYs). QALYs are calculated based on life years and various utility/disutility inputs, including health state utilities (TD, TR, TI), age- and gender-related utility adjustment, and decrements in utility for transplantation, complications, infertility, and type of ICT.

B.3.4.1. Health-related quality-of-life data from clinical trials

EQ-5D-5L was used to measure patients' health-related quality of life in the CLIMB THAL-111 trial. In line with the NICE methods guide, 5L utility values were mapped to the 3L UK value set using the Hernandez-Alava algorithm (99). The utility values have previously been presented and discussed in section B.2.6.2.8. Notably, the FAS baseline values were high when compared with the age- and gender-matched general population, which we believe may be the result of adaptation and may lead to ceiling effects when capturing improvement following treatment with exa-cel. A further limitation is that the EQ-5D-5L was not collected in patients aged under 18 (representing 33% of the FAS). The EQ-5D-Y collected in these patients has to date not been converted to utilities using any of the published value sets (131). noting that there is currently no value set available for the UK. As a result, we do not use the EQ-5D values in the model base case. Further justification for this decision is provided in more detail in section B.3.4.5.

B.3.4.2. Mapping

No mapping to utility data was carried out, given that EQ-5D questionnaires had been completed.

B.3.4.3. Health-related quality-of-life studies

An SLR was conducted to identify utility data for use in the economic model (see Appendix H). Findings from the identified clinical trials and observational studies in TDT show high baseline EQ-5D health utility index scores that are similar to those reported in the general (non-TDT) population (see Table 82). As discussed in section

B.2.6.2.8, this suggests that the EQ-5D descriptive system (DS) and its derived health utility index scores does not adequately capture the impact of TDT. Reasons for this are revisited in section B.3.4.5 below.

When EQ-5D DS evidence is not available or does not appropriately capture health-related quality of life in a particular patient population, NICE requires evidence of the lack of content validity, construct validity and responsiveness to allow for the use of an alternative method to elicit utilities. NICE notes that an alternative method involving the “direct valuation of vignettes by members of the general public or patients” may be used in technology appraisal and highly specialised technology evaluations (9). While generic instruments such as the EQ-5D are not designed to be sensitive to treatment process variables, vignette-based methods are proposed as useful for this purpose as health states can be designed to focus on treatment process attributes. Accordingly, existing utility value sets associated with treatment approaches for TDT have been estimated using vignette-based methodology with general population respondents in England (62, 63).

Although other utility value sets representing TDT health states have been published, these value sets have been proposed to have limitations. For instance, several studies have focused on utilities associated with various types of iron chelation therapy, for example differentiating between oral and subcutaneous chelation, but have failed to quantify the burden of ongoing blood transfusions and iron chelation therapy and associated fluctuation in symptoms (132-136). One study derived utilities based on perceptions of nurses, which is a less preferred method of utility estimation of NICE, compared to using perceptions of patients or general population respondents (134).

Of the vignette studies identified, one study by Matza et al. specifically valued health states relevant to treatment with curative therapies (63) and is thus considered the most relevant to the exa-cel treatment setting. In this study 207 respondents from the general population in England valued eight health state vignettes (developed with clinician, patient, and parent input) in time trade-of interviews ((63)). This study (49.8% female; mean age = 43.2 years) estimated mean (SD) utilities for the pre-transplant health states of 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 addition

therapy. Post-transplant utilities were 0.93 (0.15) for transfusion independent and 0.75 (0.25) for 60% transfusion reduced patients ((63)). The 0.93 value for transfusion independent patients corresponds with the UK general population utility of an 18-24 year-old, in line with a study demonstrating that SCT-treated TDT patients report HRQoL close to that of the general population (137).

B.3.4.4. Adverse reactions

For exa-cel, the base case model assumes that disutilities associated with AEs are captured in transplantation-related disutility, discussed in section B.3.3.5. Disutilities related to transplantation, complications, infertility, and ICT use are applied to the proportion of the cohort experiencing these events. Transplantation-related disutilities are also sourced from the previously mentioned vignette study in the UK (63). Disutility due to engraftment failure (-0.40) is estimated based on the utility difference between patients without graft failure (0.95) and patients experiencing graft failure (0.55), derived from a decision analysis model used to compare HSCT with other treatment strategies in SCD (138).

As discussed in section B.3.3.5, a scenario analysis explores the impact of possible AEs following discharge for the initial procedure. We do not apply a disutility for this scenario given that the transplantation disutility is assumed to last one year, and it is unlikely that exa-related AEs would occur after this time.

The difference between the reported utility values for TD with subcutaneous and oral ICT from Matza et al. (63) (0.10) was applied as an ICT-related disutility in the model. This source has also been used to inform disease state utility inputs in several other economic evaluations of TDT (67, 103, 116).

For SoC, disutilities associated with AEs related to ICT treatment are considered because ICT is often poorly tolerated. Again, the types of AEs have been detailed in section B.3.3.5. The ICT-related AEs disutility data derive from clinical trials data found in published literature (see Table 36).

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

To recap from section B.2.6.2.8, utility measured on the EQ-5D-5L instrument in CLIMB THAL-111 (and subsequently mapped to 3L) had high utility at baseline (0.90 in the FAS) when compared with the age- and gender- matched UK population (0.93) (98). We further explained that, due to having an inherited condition with chronic symptoms since early childhood, TDT patients may have adapted to their condition (61). We discussed how TDT health state vignettes valued by the general public using the TTO method delivered lower utility values than observed in the CLIMB THAL-111 study (62, 63).

Vertex conducted a mixed-methods study into the appropriateness of EQ-5D-5L in adults with transfusion-dependent with beta-thalassaemia. Key findings suggest the EQ-5D-5L does not accurately capture symptoms (notable fatigue) or functional impact of TDT (4). There were notable examples where the qualitative descriptions were worse than patient reports on the EQ-5D-5L. The EQ-5D-5L DS lacks the capacity to capture fluctuating symptoms over time (i.e., given the recall period of “today”). In TDT, EQ-5D-5L DS responses are highly dependent on where patients are in their RBC transfusion cycle – likely a reflection of fluctuating haemoglobin levels.

Despite these limitations, in the subset of eight patients in the PES with EQ-5D-5L scores up to 24 months, an increase in utility of 0.19 from baseline was observed in patients with 24 months of follow-up (Table 19) (7). While this represents a small proportion of the PES population, more substantial improvement in HRQoL at later timepoints is in line with studies of HRQoL in transplanted patients, which demonstrate that time since transplant is a key determinant of HRQoL (97). This is not unexpected, given that patients need time to recover from the transplant procedure, and for iron and Hb levels to return to normal. The observed increase in HRQoL does demonstrate that, despite having baseline EQ-5D-5L levels similar to that of the general population (98), patients felt an improvement in their HRQoL following treatment with exa-cel (as was also observed following treatment with beti-cel) (51). This again supports the theory that patients may have adapted to their condition and only become aware of how poor their HRQoL was once they begin to feel an improvement.

While a large improvement was observed in the eight patients with 24 months of follow-up, their baseline utility value of 0.77 was lower than the PES average of 0.87. This magnitude of gain is simply not possible in the remaining patients due to ceiling effects.

Given these concerns with the EQ-5D values, we apply the utility values from the vignette study by Matza *et al*., (2020), summarised in the paragraph below, in the base case economic analysis.

Based on the Matza et al. vignette study, the economic model base-case applies health state utility values as follows: a value of 0.93 for patients with TI, 0.75 for patients with TR, 0.73 for patients with TD receiving oral ICT, and 0.63 for patients with TD receiving subcutaneous ICT (due to a utility decrement of -0.10 for subcutaneous ICT) (63).

An age- and gender-related utility adjustment based on Ara and Brazier is also applied to health state utilities over the model time horizon (139) to reflect decreases in HRQoL seen in the UK general population. The utility adjustment was estimated by a regression model with age and gender as variables, with the equation:

$$0.95086 + 0.02121 * \%\,ccccllcc - 0.00026 * ccaacc - 0.00003 * ccaacc2.$$

However, within the context of exa-cel's treatment value, it is important to consider the conservativeness of this assumption. For patients treated with exa-cel who may reach a disease-free state, QALY gains are achieved further on in the model time horizon, at which time survival for patients receiving SoC is substantially lower. This also means that adjustments for the age- and gender-related utility decrements impact exa-cel more than the comparator over the modelled lifetime time horizon.

Disutilities for TDT-related complications were sourced from the literature and are summarised along with all health state utility and disutility inputs in Table 36. For diabetes, a weighted average value of -0.0599 is applied. Disutilities for patients with 2, 3, and 4 or more comorbidities (140) were weighted by the age- matched proportions of patients with 2, 3, or 4 or more comorbidities from a prospective UK study of TDT patients (1). The weighted average approach results in the same value as estimated in Jalkanen et al. 2019 (140) for diabetes patients with at least 3

comorbidities (-0.06). Since the model cannot track individual patient comorbidities and that the weighted average estimate and Jalkanen et al 2019 (140) value for 3 comorbidities closely align, we consider this a reasonable approach which adequately calculates the average disutility of patients throughout their lifetime while also avoiding any potential undercounting of the lifetime disutility of diabetic TDT patients with one or more comorbidities (see Appendix J.1.1 for further discussion).

Like mortality risks, the interaction of complication-related disutilities is considered using a multiplicative approach in the base-case, and additive and maximising approaches in scenario analyses. Caregiver disutilities are also considered in a scenario analysis.

When the caregiver scenario is applied, it is assumed that caregivers of TDT patients ≤26 years of age experience a utility decrement based on the patient's transfusion status. The utility decrement for caregivers of TD patients was assumed to be 0.03, derived from an observational study that evaluated the patient- and carer-reported outcomes in UK patients with TDT, and used in the base-case of a previous economic assessment of TDT (39, 67). Caregivers of patients who achieved TR were assumed to have a disutility of 0.015, derived as the midpoint of the disutility for caregivers of TD patients (0.03) and TI patients (0.00). Additionally, when the caregiver scenario is applied, the caregiver is assumed to experience a 0.05 decrease in utility following the death of the TDT patient until the end of the model horizon.(141) This assumption is consistent with that used by the Institute for Clinical and Economic Review in the assessment of chronic medications in the treatment of SCD (141).

Table 36: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Justification
TI	0.93 (0.010)	0.95-0.91	See sections B.3.4.3 and B.3.4.5
TR	0.75 (0.017)	0.78-0.73	As above
TD	0.73 (0.17)	0.75-0.69	As above
Comorbidity			
Cardiac	-0.11	-0.086 to -0.145	See section B.3.4.5

Liver	-0.11	-0.094 to -0.128	As above
Diabetes	-0.06	-0.053 to -0.112	As above
Osteoporosis	-0.08	-0.053 to -0.112	As above
Hypogonadism	-0.03	-0.154 to -0.049	As above
Splenectomy	0.00	N/A	As above
Infertility	-0.06	-0.053 to -0.063	As above
Transplantation-related disutilities			
Treatment with exa-cel in transplant year	-0.11	-0.071 to -0.157	See section B.3.4.5
Engraftment failure in transplant year	-0.40	-0.249 to -0.561	As above
ICT-related disutilities			
Receiving oral ICT	0.0	N/A	Calculation, see section B.3.4.5
Receiving subcutaneous ICT	-0.10	-0.064 to -0.142	As above
TI + oral ICT	0.93	N/A	As above
TI + subcutaneous ICT	0.83	N/A	As above
TR + oral ICT	0.75	N/A	As above
TR + subcutaneous ICT	0.65	N/A	As above
TD + oral ICT	0.73	N/A	As above
TD + subcutaneous ICT	0.63	N/A	As above
Treatment with exa-cel	0.62	-0.571 to -0.667	See section B.3.4.5
Patient caregiver up to age (years)	26	N/A	Beti-cel ICER report (103)
TI	0.00	N/A	Assumption
TR	-0.015	N/A	Assumption (midpoint of TI and TD caregiver disutility)
TD	-0.030	N/A	Shah et al., 2021 (39); Beti-cel ICER report (103)

Utility decrement for patient death (included until end of model time horizon)	-0.05	N/A	Bradt et al., 2020 (141)

B.3.5 Cost and healthcare resource use identification, measurement, and valuation

The cost-effectiveness analysis is conducted from the UK NHS and Personal Social Services (PSS) perspective. Therefore, only direct costs are considered in the base-case analysis. A scenario analysis was conducted for the societal perspective, including both direct healthcare costs and indirect costs. Where applicable, costs are inflated to 2022 UK pound sterling using the UK Health Consumer Price Index (142).

B.3.5.1. Intervention and comparators' costs and resource use

For exa-cel, the drug acquisition costs are applied to all patients assigned to the therapy at the beginning of the model. Exa-cel patients are assumed to undergo phlebotomy once every other week during normalisation/change phase based on clinical expert feedback. Treatment acquisition and administration costs are summarised in Table 37.

In addition to the treatment acquisition costs for exa-cel, other costs related to transplant are considered in the model. These include pre-transplant costs, hospitalisation, administration, and post- transplant monitoring costs. Pre-transplant costs include both mobilisation/apheresis costs and all other transplant preparation costs (e.g., MRI, physician visits, sperm/egg storage). Note that patients who withdrew from treatment incur a pre-transplant cost but do not incur transplantation and treatment-related costs. Pre-transplant physician visits are based on the requirements set forth in the CLIMB THAL-111 trial and clinical expert feedback.

There are no NHS reference costs nor an existing NHS tariff to provide delivery costs for transplantation with CRISPR-edited cells. However, the procedure uses similar resource to that required for chimeric antigen receptor-T cell therapy (CAR-T) (which

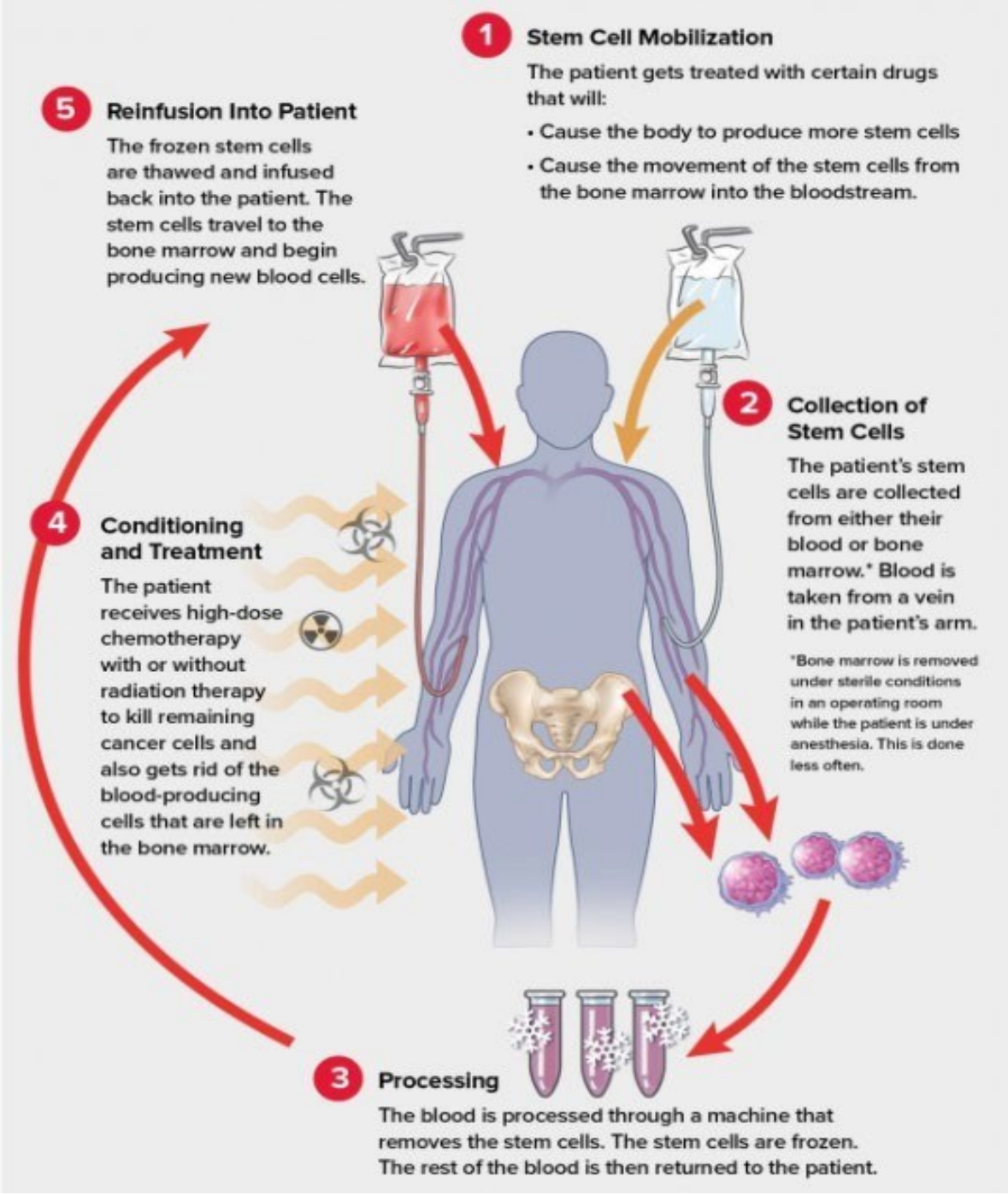
also does not have any published reference costs) or autologous SCT (which does have published reference costs), as can be seen by comparing Figure 22 below with Figure 3 in section B1. This was confirmed via consultation with UK clinical experts. There are therefore published NHS reference costs for autologous SCT available to provide reasonable estimates of the cost of exa-cel delivery. These costs are likely to be an overestimate given the recovery time and consequent length of stay in hospital (largely to manage cytopenias) more closely resembles that following CAR-T and that both procedures involve the gene-editing of the recipient's own cells. Healthcare resource use required for CAR-T administration has been shown to be substantially less than that required for both allogeneic SCT and autologous SCT in real-world settings (143, 144), including the length of stay required for the procedure.

As per existing autologous-SCT stem-cell mobilisation processes within the NHS, exa-cel patients undergo stem cell mobilisation with a combination of G-CSF, which clinical experts confirmed was captured within the NHS reference cost for peripheral blood stem cell harvest (145). We conservatively assume 100% inpatient stay for the mobilisation and harvest procedure. Patients in the CLIMB THAL-111 trial additionally received plerixafor, which is a high-cost drug not included within the Healthcare Resource Group (HRG) and is therefore costed separately.

Patients then undergo myeloablative conditioning with intravenous busulfan administration, which is a standard regimen used for myeloablation in the NHS, before exa-cel infusion. Patients also require hospitalisation for the exa-cel infusion procedure. According to clinician input, myeloablation, hospital stay and associated transplantation management costs are captured up to day 100 post-SCT within the published NHS reference costs for autologous SCT, assuming 100% inpatient stay (145). In a post-hoc analysis the mean length of stay (LoS) of patients from start of myeloablation to discharge post-transplantation in the CLIMB THAL-111 trial was [redacted] days (noting that this analysis did not differentiate between day visits and true inpatient admissions and that patients are likely to be kept in hospital longer in a clinical trial setting). We therefore consider the transplantation and after-care costs to be adequately covered by the autologous-SCT inpatient NHS reference cost. Nevertheless, alternative assumptions are explored in a scenario analysis, whereby

the acquisition and intravenous delivery costs of busulfan are costed separately (4 days of regular day/night attendance).

Figure 22: Autologous stem cell transplantation process



Source: Leukemia & Lymphoma Society (146)

The cost of regular RBC transfusions is estimated based on the NHS reference costs of packed RBC transfusions per unit and administration per RBC transfusion procedure (staff time and disposables) (67). Patients with TDT receive 2.2 units per RBC transfusion procedure. This quotient is calculated from the mean annualised unit of RBC transfusions divided by the mean annual transfusions per patient - both derived from CLIMB THAL-111 (FAS, Table 14.1.4.1).

Costs related to ICT are considered based on the type and route of administration of the ICTs. DFX and DFP do not incur an administration cost as these are orally administered. Although DFO is subcutaneously administered, this is self-administered using balloon infusers in the UK (52), hence no administration cost for DFO is applied. In the absence of data, patients were assumed to be 100% adherent to ICT in the base case. Patients received a full dose of ICT in the treatment/response phase and iron normalisation/change phase, regardless of their transfusion status, and in the ongoing phase among patients with TD and TR. For SoC, drug acquisition costs are comprised of RBC transfusion- and ICT-related treatment and administration costs and healthcare resource use (HRU).

Fertility preservation costs are also included in pre-transplant costs to account for the proportion of exa-cel patients who undergo egg retrieval or sperm freezing prior to myeloablative conditioning (147, 148). We conservatively assume that 100% of exa-cel patients undergo fertility preservation. Pre-transplant infertility costs are differentiated from post-transplant infertility costs (discussed in section B.3.5.4) to provide a comprehensive approach to costing exa-cel treatment.

Lastly, the model base case assumes no drug wastage. Though the model ICER is insensitive to changes in these costs, drug wastage is applied as an optional scenario analysis in the model .

Table 37: Treatment and transplant related costs

Variable	Value	Reference
Exa-cel		
Drug acquisition cost	[redacted]	N/A
Pre-transplant costs (exa-cel)		

Total screening and fertility preservation costs	£3,483	Calculation (sum of screening and fertility unit costs)
Screening and fertility unit costs		
Cardiac/liver MRI	£206	Weighted average of CLIMB THAL-111 age distribution and NHS reference costs for MRI RD02B and RD02A. (145)
Screening clinician visits	£317	Weighted average of CLIMB THAL-111 age distribution and NHS reference costs of adult and paediatric clinical haematology consultant-led face to face follow-on appointments. (145)
Fertility preservation	£2,008	Weighted average of CLIMB THAL-111 gender distribution and NHS reference costs of Oocyte Recovery, Gynaecology Service, OPROC, Currency code: MC12Z, Service Code: 502 and Collection of Sperm, Urology Service, OPROC, Currency code: MC21Z, Service Code: 101 (145)
Screening and fertility HRU		
Cardiac/liver MRI	1	Clinician opinion
Screening clinician visits	4	Clinician opinion
Fertility preservation	1	Clinician opinion
Total mobilisation cost	£[redacted]	Calculation
Mobilisation unit costs		
Plerixafor cost per unit	£4,880	BNF(Sanofi)
Plerixafor unit strength (mg)	24	BNF & CLIMB THAL-111 Protocol
Hospitalisation for harvesting procedure	£5,375	Peripheral Blood Stem Cell Harvest, Elective Inpatients, Currency code: SA34Z (145)
Mobilisation HRU		
Mobilisation cycles	1.2	CLIMB THAL-111 (FAS, Table 14.1.7)
Plerixafor daily dose (mg/kg)	0.24	CLIMB THAL-111 Protocol
Plerixafor length (days)	3	CLIMB THAL-111 Protocol
Total myeloablation cost (base case)	£0	Assumed included in NHS reference cost for autologous SCT costs SA26A and SA26B

Total myeloablation cost (scenario)	£3,852	Calculation
Myeloablation unit costs (scenario only)		
Busulfan cost per unit	£169.18	Drugs and pharmaceutical electronic market information tool (eMIT)
Busulfan unit strength (mg)	60	NHS drug tariff, June 2023 (149)
Cost of busulfan administration	£314	Regular Day/Night delivery of simple chemo [SB12Z] over 4-day cycle (145)
Number of additional transfusions	2	Clinical inputs by Vertex (assumption from Clinical Development)
Myeloablation HRU (scenario only)		
Busulfan daily dose (mg/kg)	3.75	CLIMB THAL-111 (FAS, Table 11-1)
Myeloablation length (days)	4	CLIMB THAL-111 (FAS, Table 11-1, total exposure divided by exposure/day)
Number of busulfan administrations	4	CLIMB THAL-111 (FAS, Table 11-1, total exposure divided by exposure/day)
Additional costs for transplant (exa-cel)		
Hospitalisation costs for procedure	£26,602	Peripheral Blood Stem Cell Transplant, Autologous, Elective Inpatient SA26A and SA26B HRG codes, weighted by CLIMB THAL-111 age distribution (145)
Number of years to apply post-transplant monitoring costs	15	Clinical inputs by Vertex (assumption from Clinical Development)
Monthly post-transplant monitoring cost (exa-cel)		
Year 1	£99.8	NICE ID968 (67)
Year 2	£99.8	NICE ID968 (67)
Year 3	£82.0	NICE ID968 (67)
Year 4	£82.0	Assumption – same as year 3
Year 5+	£82.0	Assumption – same as year 3
Phlebotomy during normalisation and change phase for exa-cel		
Cost per procedure	£4.70	NHS reference costs, DAPS08 (145)
Frequency per week	0.5	Clinical inputs from Vertex
Red blood cell transfusions		
Monthly RBC transfusion costs	£822.58	Calculation

Cost per RBC transfusion unit	£238.00	NHS Blood and Transplant price list (2022–23) (150)
Cost per procedure	£89.61	Calculation, lump cost of staff time and disposable costs, NICE TA743 (151)
Iron chelation therapy		
DFO		
Cost per unit	£4.66	NHS drug tariff, June 2023 (149)
mg per unit	500	NHS drug tariff, June 2023 (149)
Daily dose (mg/kg)	40	UKTS
Dose per week	5	UKTS
Administration cost per time	£0.00	UKTS: self-administered using balloon infusers
DFX		
Cost per unit	£4.20	NHS drug tariff, June 2023 (149)
mg per unit	90	NHS drug tariff, June 2023 (149)
Daily dose (mg/kg)	21	Expert opinion [UKTS guidelines cite out-dated 25mg/kg)
Dose per week	7	UKTS
Administration cost per time	£0.00	UKTS: Oral Administration
DFP		
Cost per unit	£1.30	NHS drug tariff, June 2023 (149)
mg per unit	500	NHS drug tariff, June 2023 (149)
Daily dose (mg/kg)	88	SmPC for Ferriprox (152)
Dose per week	7	SmPC for Ferriprox (152)
Administration cost per time	£0.00	UKTS: Oral Administration

Abbreviations: NICE, National Institute for Health and Care Excellence; HRU, healthcare resource utilisation; DFO, desferrioxamine, DFP, deferiprone; DFX, deferasirox; ICT, iron chelation therapy; PSSRU, personal social services research unit; RBC, red blood cell

B.3.5.2. Routine monitoring costs and resource use

Routine monitoring costs - as stipulated by UKTS guidelines - were omitted to avoid double-counting. The model assumes that these costs are captured in the lump-sum disease management costs, discussed in the next section, which track patient HCRU and costs by transfusion status, i.e., by model health state.

B.3.5.3. Disease management costs

Given the nature of TDT, which is associated with complications such as iron overload and organ damage if patients are not closely monitored, the model accounts for ongoing disease management costs. For patients alive in the model, the monthly cost of emergency room, inpatient, and outpatient visits were based on the weighted average of 2022/2023 NHS reference costs for SA11Z (Elective, non-elective long and short stays, and regular day/night admissions) (145). The costs of these services are divided by 12 to derive a monthly apportion for every cycle. The costs were also weighted by the proportion of patients receiving these services within each health state (TD, TI, or TR). The proportions of the patients within each health state receiving these services are based on Shah et al. 2021 (39) (identified in the healthcare resource use (HRU) SLR) and clinical expert opinions. The frequency of HRU associated with disease management was adjusted for the TI and TD health states to reflect the impact of transfusion avoidance and reduction on disease management costs. Costs associated with acute sepsis and thrombosis are assumed to be captured in the disease management costs. The HRU and associated costs are summarised in Table 38.

Table 38: Disease management costs

Variable	Value	Reference
Unit costs		
Cost per inpatient visit	£1,241.04	NHS 2021/2022 (145)
Cost per day case visit	£839.34	NHS 2021/2022 (145)
Cost per outpatient visit	£209.00	NHS 2021/2022 (145)
Cost per ER visit	£276.00	NHS 2021/2022 (145)
Monthly disease management costs (monthly)		
TI		

Total costs	£34.83	Calculation
Number of inpatient visits	0.0	Expert opinion
Number of day case visits	0.0	Expert opinion
Number of outpatient visits	0.167	Expert opinion
Number of ER visits	0.0	Expert opinion
TR		
Total costs	£103.33	Calculation
Number of inpatient visits	0.004	Assumption[a]
Number of day case visits	0.021	Assumption[a]
Number of outpatient visits	0.375	Assumption[a]
Number of ER visits	0.008	Assumption[a]
TD		
Total costs	£171.83	Calculation
Number of inpatient visits	0.0083	Shah et al., 2021 (39)
Number of day case visits	0.0417	Shah et al., 2021 (39)
Number of outpatient visits	0.5833	Shah et al., 2021 (39)
Number of ER visits	0.0167	Shah et al., 2021 (39)

Abbreviations: ER, emergency room; HRU, healthcare resource use, SE, standard error; NHS, National Health Service; TD, transfusion dependence; TI, transfusion independence; TR, transfusion reduction. Note: [a]Midpoint of TI and TD

B.3.5.4. Complication and other condition costs

All unit costs of TDT-related complications are applied to the proportion of patients experiencing these complications. The monthly costs of complications related to TDT were estimated based on published literature from the UK.

The cost of cardiac complications, diabetes and hypogonadism are based on a cost-utility analysis of DFX in TDT patients with iron overload (153). The costs of these complications are divided by 12 to derive a monthly apportion for every cycle. The unit cost of liver complications are based on a weighted average of 2021/2022 NHS reference costs (specifically cost categories GC01C, GC01D, GC01E, and GC01F) (145). Complication costs in the first year for cardiac and osteoporosis complications are differentiated from subsequent years since the treatment pathways that patients experience between the first and subsequent years of treatment for these

complications are dissimilar (140, 159). The cost of osteoporosis is based on an economic burden study of osteoporosis in the UK (154).

The cost of post-transplant infertility consisted of a one-time cost for the proportion of female patients who undergo in vitro fertilisation (IVF) as well as monthly recurring costs, varied by gender, to account for the ongoing post-transplant costs of storing a patient's preserved oocyte or sperm. We conservatively assume that 100% of female patients who underwent preservation go on to receive IVF. These costs are sourced from the treatment charges listed by the NHS Birmingham Women's Fertility Centre (147). All complications and other conditions costs are presented in Table 39 below.

Table 39: Complication and other condition costs

Variable	Value	Reference
Complications		
Cardiac (year 1, monthly)	£625.23	Karnon et al., 2012 (153)
Cardiac (year 2+, monthly)	£322.01	Karnon et al., 2012 (153)
Liver (year 1, monthly)	£259.03	2022/2023 National reference costs [weighted average of GC01C, GC01D, GC01E, GC01F] (145)
Liver (year 2+, monthly)	£259.03	2022/2023 National reference costs [weighted average of GC01C, GC01D, GC01E, GC01F] (145)
Osteoporosis (year 1, monthly)	£690.50	Ivergard et al., 2013 (154)
Osteoporosis (year 2+, monthly)	£38.10	Ivergard et al., 2013 (154)
Diabetes (year 1, monthly)	£485.60	Karnon et al., 2012 (153)
Diabetes (year 2+, monthly)	£485.60	Karnon et al., 2012 (153)

Hypogonadism (year 1, monthly)	£52.59	Karnon et al., 2012 (153)
Hypogonadism (year 2+, monthly)	£52.59	Karnon et al., 2012 (153)
Other conditions		
Infertility (one-time IVF cost)		
Female (IVF)	£2,631.55	NHS fertility centre (147)
Infertility (monthly cost of sperm/oocyte storage)		
Male	£19.79	NHS fertility centre (147)
Female	£19.79	NHS fertility centre (147)

Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Care Excellence

B.3.5.5. Health-state unit costs and resource use

Complication and other condition costs are conditional on patient transfusion status and the proportion of patients experiencing complications and other conditions. See the section on Disease management costs for further details.

B.3.5.6. Adverse reaction unit costs and resource use

AE costs for exa-cel from pre-transplantation to discharge post-engraftment are assumed to be captured in the pre-transplantation or transplantation-related hospitalisation costs, as inpatient admission HRG codes were used in section B.3.5.1. In a post-hoc analysis, [redacted] of patients spent an average of [redacted] days in hospital after having been discharged for the initial procedure. However, it is unclear whether these represented day visits as opposed to hospitalisation and/or whether the readmissions occurred within 100 days of treatment start (which is included in the autologous-SCT reference cost). We therefore include a scenario whereby [redacted] of patients incur the cost of an admission for thalassaemia (trim point 5 days), plus the cost of [redacted] additional days in hospital (thalassaemia admission cost x [redacted]).

In contrast, AE costs for SoC are estimated based on monthly rates of recurring AEs summarised in Table 35 and the unit cost found in Table 40 below. The cost of a grade 3+ AE is assumed to be equal to the cost of a single physician visit based on NHS national reference costs (145).

Table 40: Adverse reaction unit costs and HRU

Treatment	Unit cost	Reference
SoC	£209	2021/2022 NHS reference costs [WF01A Non-admitted face-to-face attendance] (145)
Exa-cel (scenario only)	£1,852	Weighted average of Thalassaemia (adult) and Thalassaemia CC score 1+ (paediatric) inpatient admission [redacted] (145)

B.3.5.7. Miscellaneous unit costs and resource use

B.3.5.7.1. Terminal care costs

The base-case analysis includes a one-time cost of terminal care (£12, 397), in accordance with the average costs for end-of-life care reported by Personal Social Services Research Unit (PSSRU).

B.3.5.7.2. Societal costs

In the societal perspective scenario analysis, costs associated with patient productivity and caregiver burden (Table 41).

Due to the severity of the condition and the significant time associated with managing disease, TDT patients are less likely to be employed than the general (non-TDT) population, and those who are employed are known to miss work (absenteeism) and

experience decreased productivity when at work (presenteeism). A survey of UK patients indicated significant challenges with employment including (155):

- Time off for transfusions and appointments;
- Fatigue felt before transfusions and treatment;
- Lack of awareness amongst employers and colleagues;
- Lack of flexible working hours;
- Uncertainty whether or not to disclosure to employers;
- Pain as a result of thalassaemia;
- Mobility issues

The model estimates the proportion of the cohort that is employed based on the Li et al., 2022 study, which reported that 10.1% of patients with TDT were receiving/awaiting disability payments or on leave due to TDT (59, 60). The model assumed that patients who were cured from TDT would have the same level of employment as the general (non-TDT) population (156).

Rates of absenteeism and presenteeism for patients in the TD health state were also informed by Li et al. 2022, which reported that patients with TDT had substantial productivity loss (absenteeism and presenteeism) associated with the disease (59, 60). Patients in the TI health state were assumed to have 0% absenteeism/presenteeism. Absenteeism/presenteeism for patients in the TR health state was estimated as the midpoint of the inputs assumed for TD and TI (i.e., half of TD). Additionally, TDT patients who were unemployed due to the disease (calculated as the difference between rate of employment in the general population and the rate for patients with TDT) were assumed to have 100% absenteeism.

Caregiver burden was estimated based on the patient's transfusion status while age ≤26 years (103). Assuming caregiver employment equal to that of the general population, the productivity losses (absenteeism/presenteeism) for the caregiver were assumed to be equal to those assumed for the patient. This is consistent with the assumptions made by the Institute for Clinical and Economic Review in the assessment of beti-cel for TDT (103).

Table 41: Indirect costs

Variable	Value	Reference
General population inputs		
Patients below retirement age who are employed (%)	75.5%	ONS employment rate(156)
Average number of working hours per week	33.2	ONS Annual Survey of Hours and Earnings(157)
Mean employment start age (years)	18	Assumption
Mean retirement age (years)	68	State Pension Age(158)
Percent wage loss due to absenteeism	100%	Assumption
Percent wage loss due to presenteeism	50%	Assumption
National average wages		
Wage per hour	£18	ONS Annual Survey of Hours and Earnings(157)
Patient productivity inputs		
TDT patient who are employed (%)		
TI	75.5%	Assume same as general population
TR	70.5%	Assume average of TI and TD
TD	65.4%	Li et al., 2022 (59, 60)
Cost per month of unemployment due to TDT	£2,591	Assumed equal to 100% absenteeism
TI		
Absenteeism	0.0%	Assumption
Presenteeism	0.0%	Assumption
TR		
Absenteeism	9.8%	Assume half of TD
Presenteeism	17.2%	Assume half of TD
TD		
Absenteeism	19.5%	Li et al., 2022 (59, 60)
Presenteeism	34.4%	Li et al., 2022 (59, 60)
Caregiver burden inputs		

Patient caregiver up to patient age of	26	ICER beti-cel final evidence report (103)
TI		
Absenteeism	0.0%	Assume same as patient
Presenteeism	0.0%	Assume same as patient
TR		
Absenteeism	9.8%	Assume same as patient
Presenteeism	17.2%	Assume same as patient
TD		
Absenteeism	19.5%	Assume same as patient
Presenteeism	34.4%	Assume same as patient
Patient out-of-pocket costs		
Out-of-pocket costs as percentage of health state costs (%)	0.0	Assumption
Other indirect costs (monthly)		
TI	£0	Assumption
TR	£0	Assumption
TD	£0	Assumption

Abbreviations: ONS, Office for National Statistics TD, transfusion dependent, TI, transfusion independent; TR, transfusion reduced

[a] Calculated as the difference between general population employment (75.5%) and proportion of patients with TDT receiving/awaiting disability payments or on leave from work due to TDT (10.1%).

B.3.6 Severity

Exa-cel meets the criteria for a 1.7 severity modifier at the base case 1.5% discount rate and a 1.2 modifier at a 3.5% discount rate. The QALY shortfall was calculated using the economic model discounted QALY projection for SoC using the baseline characteristics of the CLIMB THAL-111 FAS population, which is considered to be generalisable to the UK population that will be offered exa-cel (see section B.2.12.3.1). Utility value in the shortfall calculation was underpinned by the vignette health utility value for TDT (section B.3.4.5), with additional disutilities for use of subcutaneous ICT and the complications of iron overload. Mortality was underpinned by an SMR applied to the age- and gender- matched UK population with additional mortality impacts from comorbidities (section B.3.3.4).

The QALY shortfall was calculated relative to the age- and gender- matched UK population using the online QALY shortfall calculator tool, using the reference case MVH value set and HSE 2014 survival model (159).

Table 42: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	52.1% female	B.3.2.1
Starting age	21.4	B.3.2.1

Table 43: Summary list of QALY shortfall from previous evaluations

Not applicable; beti-cel was appraised prior to the introduction of the severity modifier.

Table 44: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
Transfusion-independent	0.93 (0.010)	0
Transfusion-reduced	075 (0.017)	0
Transfusion-dependent	0.73 (0.017)	28.98

Note: Health state values are presented before application of disutilties

Table 45: Summary of QALY shortfall analysis

Discount rate	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall, absolute (proportional)
1.5%	34.51	13.31	21.20 (61.42%)
3.5%	22.51	10.48	12.03 (53.5%)

B.3.7 Uncertainty

Key areas of uncertainty and any issues with their collection are detailed in Table 46 in the following section. These include:

- Durability of transfusion independence
- Sustained Hb and HbF levels
- Sustained engraftment
- Safety of exa-cel

B.3.8 Managed access proposal

Vertex proposes that a managed access agreement within the Innovative Medicines Fund would be appropriate for exa-cel given the highly innovative nature of the therapy, its potential to address unmet need and significant clinical benefits (see sections B.1.2, B.2.12.1 and B.3.6).

The uncertainties described in Table 46 could be addressed through a period of managed access. At present, the main source of clinical evidence is the index CLIMB THAL-111 study in TDT patients; it is anticipated that supportive long-term data will primary come from the corresponding long-term extension study for consenting patients treated with exa-cel (CLIMB-131) and a post-authorisation safety study (PASS), with an European Society for Blood and Marrow Transplantation (EBMT) extension component that may capture additional UK patients and further augment the totality of data in the future.

Table 46: List of uncertainties and the data that could be collected to resolve them

Clinical uncertainty	Outcome data	Data source
Durability of transfusion independence	• Time period transfusion-free following exa-cel infusion • RBC transfusion events in non-transfusion-independent patients: number of transfusions, reductions in disease-related RBC transfusion events, clinical indication for transfusion (capturing only disease-related procedures), number of units transfused	CLIMB THAL-111, EBMT Registry, CLIMB-131
Sustained Hb and HbF levels	Haemoglobin concentration, grams per decilitre (g/dL) Haemoglobin fractionation measured to assess the relative proportion of Hb variants produced, including percent HbF Change from baseline in proportion of circulating F-cells (HbF distribution)	CLIMB THAL-111, EBMT Registry, CLIMB-131
Sustained engraftment	Proportion of alleles with intended genetic modification present in peripheral blood and in the CD34+ cells of the bone marrow over time	CLIMB THAL-111, CLIMB-131
Safety of exa-cel	SAEs related to exa-cel, mortality and survival data (with primary and contributory cause of death)	CLIMB-131, EBMT Registry

B.3.8.1. Proposed Data Source to gather evidence for Managed Access Agreement

The EBMT was established in 1970s and is an established data source on allo-SCT or cellular infusion therapy procedures. The EBMT registry currently receives data from approximately 80% European transplant centres and is the principal source of transplant data to conduct retrospective clinical studies, epidemiological trends, and feasibility studies to design prospective clinical studies, in the field of oncology. In more recent years, the EBMT registry has been qualified by the European Medical Agency (EMA) as a suitable platform for collection of data for post-authorisation studies (160).

The EBMT registry is the proposed data source in UK, France, Germany, and Italy for Vertex's regulatory mandated PASS in which exa-cel treated patients will be followed for a maximum period of 15 years. Vertex considers that the EBMT registry would be a relevant data source to gather evidence on effectiveness and safety of exa-cel in the real-world setting, given its primary data collection capabilities and availability of secondary data to support long-term follow-up studies.

Vertex plans to leverage its existing collaboration with EBMT for the proposed PASS and has assessed the feasibility of extending the PASS data collection mechanism to also gather evidence on exa-cel treated patients in the UK for a managed access agreement. Based on frequent communications with EBMT, Vertex surmises that it is feasible to extend data collection to exa-cel treated patients in real-world settings in the UK.

B.3.8.2. Data Collection

Long-term data on the UK patients treated with exa-cel following MHRA approval will be collected by EBMT to conduct a mandated study. Data will be collected on TDT patients ≥ 12 years of age and treated with exa-cel at any of the authorised treatment centres in the UK. Vertex acknowledges that the number of exa-cel treated patients included in the mandated study will depend on commercial uptake, and availability of patients' informed consent to share their data for research purposes. All patients will be entered into the study for the first 3 years post-approval and will be followed for 15 years. Long-term data on consenting exa-cel treated patients will also be collected

from CLIMB-131, a rollover follow-up extension of the pivotal trials in TDT and SCD patients.

Data on key outcomes, as well as important patient demographic and clinical characteristics, will be collected up to a maximum of five years or a period specified in the managed access agreement. EBMT will facilitate retrospective data collection for Vertex using standard existing registry forms such as Med-A and Med-B, and prospective data collection using a study-specific reporting form (Med-C) developed for Vertex PASS in collaboration with EBMT investigators.

Vertex anticipates that, based on expert opinion, a timeline of 3 years' data collection following recommendation into the IMF would be sufficient to address uncertainties around sustainability of clinical efficacy. Clinical experts, when consulted, have indicated that if a patient is transfusion independent after 2 years of exa-cel treatment, with sustained HbF levels and engraftment plus improved iron status, that they are likely to maintain transfusion independence and, in turn, less likely to encounter further disease complications and subsequent organ damage. Table 47 presents estimated numbers of patients that are predicted to have undergone therapy with exa-cel and engrafted over the initial five years.

Table 47: Forecast of Patients Commencing Engraftment

	Year 1	Year 2	Year 3	Year 4	Year 5
TDT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B.3.8.3. Additional considerations that may impact feasibility of data collection

Informed consent – Lack of patient consent to give access to their data after treatment with exa-cel.

Follow up – Patients will be routinely followed up by the transplant centres (as part of the transplant clinic for year 1 and the long-term effects monitoring clinics thereafter). These clinics are resourced for data collection for EBMT and this will be part of their routine care. Patients will also be followed up by their haemoglobinopathy team with

respect to long term thalassaemic complications. Haemoglobinopathy patients represent a non-malignant population, and therefore may perceive less of a clinical imperative to adhere to follow-up visits when compared with patients with a malignant disease. It will be essential that patients are well informed about the needs for long term follow up to ensure they attend for the long term effects monitoring clinics at the transplant centre.

Socioeconomic status – Patients in England with TDT are disproportionately represented in ethnic minority groups and lower socioeconomic communities; thus, potential increased fluidity in population movement may also challenge adherence to follow-up.

In order to mitigate these considerations, Vertex will produce supportive educational materials for patients that fully detail the treatment process and explain the importance of compliance with data collection in the post-treatment period.

Table 48: Overview of data source 1

Study	**A Long-term Follow-up Study of Subjects With β-thalassaemia or Sickle Cell Disease Treated with Autologous CRISPR-Cas9 Modified Hematopoietic Stem Cells (CLIMB-131)**
Study design	• Multi-site, open-label, rollover study
Population	• **Patients 12-35 years of age who received exa-cel in a parent study (CLIMB THAL-111)**
Intervention(s)	• Exa-cel
Comparator(s)	• N/A
Outcomes	• **Total haemoglobin** • **Total fetal haemoglobin (HbF) and % concentration** • **Proportion of alleles with intended genetic modification present in peripheral blood and bone marrow CD34+ cells** • Change from baseline in proportion of circulating F-cells (HbF distribution)
Indicate if study used in the NICE economic model	• Yes, via parent study CLIMB THAL-111 (as described in section **B.2**)
Trial start date	• September 2018
Data cut submitted to NICE	• Not applicable
Anticipated data cut after a period of managed access	• **TBC**

Table 49: Overview of data source 2

Registry	European Society for Blood and Marrow Transplantation (EBMT)
Type of registry	Optional dataset for regulatory purposes and retrospective clinical trials
Population	All patients with beta-thalassaemia treated with exa-cel in participating centres reporting data to EBMT
Relevant data items collected	**RBC transfusion events pre- and post-transplant (to be defined as the receipt of RBC transfusions for the purpose of primary disease management, i.e. anaemia):** • **Number of RBC transfusions** • **Number of units transfused** • Time from HSCT to most recent transfusion **Haemoglobin measures pre- and post-transplant:**

Registry	European Society for Blood and Marrow Transplantation (EBMT)
	• **Haemoglobin concentration (g/dL) pre- and post-transplant** • **Haemoglobin fractionation pre- and post-transplant, including percent HbF** • SAEs and mortality
Data analysis	Vertex sponsored data that is collected and managed by EBMT will be analysed by registry statisticians per a statistical analysis plan developed by Vertex in collaboration with EBMT investigators. Data will be collected at pre-specified timepoints over the study duration: baseline, Day 100, Month 6, Year 1 and annually (Years 2-5). Results from all analyses will be shared by EBMT with Vertex as reports. Data on safety and effectiveness outcomes among exa-cel treated patients will be evaluated separately for TDT patients. Subgroup and sensitivity analyses will be performed on *a priori* identified characteristics, as appropriate. Ad hoc analyses may be conducted as per requirement.
Governance	Data collected by EBMT on exa-cel treated patients will be stored and maintained by the registry following internal protocols and processes. Currently, EBMT uses a web-based relational database management system called ProMISe as the platform to collect, store, conduct quality checks, and report on data collected by the standard registry forms. Prospective data collected using the study-specific reporting form will be stored in the EBMT system in a separate validated database. EBMT will be responsible for processing and storing the data according to the EU General Data Protection Regulation (GDPR) laws. Vertex will not have access to identifiable patient records but will be given access to data cuts by EBMT at pre-specified timepoints (annual progress reports after completion of the first 5 years of the study; interim analysis reports after enrolment completion [Year 3], minimum 5 years' follow up for all enrolled patients [Year 8], minimum 10 years' follow up for all patients [Year 13]). These data cuts will be stripped off any identifiable patient information and will be stored on a secure server. Additional details on governance and Vertex-wide use of data will be provided once a legal contract is signed.
Indicate if registry previously used within a NICE managed access	No

B.3.9 Distributional cost-effectiveness analysis

DCEAs are Cost-Effectiveness Analyses that provide information, at the population level, about both equity and efficiency in the distribution of health care costs and effects. At a basic level, DCEA involves exploring the implications of giving special priority or 'equity weight' to improving the health of intervention recipients compared with the health of non-recipients. The key aspect of DCEA that distinguishes it from other weighting methods, such as NICE's severity modifier, or other ways of addressing equity concerns, is that it provides information about distributional consequences; that is, differences in the benefits and burdens of alternative decisions across different sub-populations according to their deprivation status. Thus, in general, DCEA provides analyses on the equity impact of an intervention and reweights cost-effectiveness results based on a decision-makers aversion to inequality (161).

The outputs of the DCEA are used to reweight the incremental costs and incremental QALYs of the base case incremental cost-effectiveness ratio (ICER). In the model base case, weight values for each IMD group are 6.67 for IMD 1 (most deprived), 3.13 for IMD 2, 2.17 for IMD 3, 1.33 for IMD 4, and 1 for IMD 5 (least deprived). These weights are applied to the proportion of incremental costs and QALYs received within each quintile IMD group. The aggregate of these weighted incremental costs and QALYs, i.e., the summed amount of incremental costs and QALYs distributed across all groups, is then used to calculate the equity-weighted ICER. Details of the DCEA methods can be found in Appendix I.

B.3.10 Summary of base-case analysis inputs and assumptions

B.3.10.1. Summary of base-case analysis inputs

Table 50: Summary of variables applied in the economic model

	Base case	Upper CI 97.5%	Lower CI 2.5%	Included in PSA?	Distribution	Reference to section in submission
Cohort Inputs:						
Demographics						
Age (years)	21.40	23.27	19.53	Y	Normal (truncated - restricted to upper age of 50)	B.3.2.1
Weight ratio of TDT/general public	0.76	N/A	N/A	N	N/A	B.3.2.1
Females (%)	52	66.53	37.49	Y	Beta	B.3.2.1
Proportion <18 years old (%)	33.3	47.12	20.86	Y	Beta	B.3.2.1
Baseline iron level (%)						
Serum ferritin						
Low (above normal - ≤1,000 ng/ml) (%)	23.0	23.53	22.53	Y	Dirichlet	B.3.2.1
Moderate (1,000-2,500 ng/ml) (%)	38.8	39.37	38.21	Y	Dirichlet	B.3.2.1
High (>2,500 ng/ml) (%)	38.2	38.76	37.61	Y	Dirichlet	B.3.2.1
Myocardial T2 (%)						
Low (>20ms - below normal) (%)	88.2	88.73	87.66	Y	Dirichlet	B.3.2.1
Moderate (10-20 ms) (%)	11.8	12.34	11.27	Y	Dirichlet	B.3.2.1
High (<10 ms) (%)	0	0	0	N	Dirichlet	B.3.2.1
Liver iron concentration (%)						
Low (above normal - <7 mg/g) (%)	60.5	61.31	59.70	Y	Dirichlet	B.3.2.1
Moderate (7-15 mg/g) (%)	23.5	24.23	22.83	Y	Dirichlet	B.3.2.1
High (≥15 mg/g) (%)	16.0	16.57	15.37	Y	Dirichlet	B.3.2.1

Baseline complications and infertility (%)						
Cardiac complications	0	0	0	N	Beta	B.3.2.1
Liver complications	0	0	0	N	Beta	B.3.2.1
Osteoporosis	0	0	0	N	Beta	B.3.2.1
Diabetes	0	0	0	N	Beta	B.3.2.1
Hypogonadism	2.1	3.0	1.36	Y	Beta	B.3.2.1
Splenectomy	31.3	44.16	19.75	Y	Beta	B.3.2.1
Infertility (prevalence in general population, by gender)						
Male	10.1	14.38	6.50	Y	Beta	B.3.2.1
Female	12.5	17.79	8.03	Y	Beta	B.3.2.1
Baseline utilisation						
Blood transfusion						
Annual transfusions per patient	16.4	17.96	14.91	Y	Gamma	B.3.2.1
Annualised unit of RBC transfusions	35.3	38.63	32.12	Y	Gamma	B.3.2.1
Units of blood per transfusion	2.2	3.07	1.39	Y	Gamma	B.3.2.1
ICT regimen distribution (%)						
Deferasirox (DFX)	58	65.5	50.36	Y	Dirichlet	B.3.2.1
Deferiprone (DFP)	6.8	11.13	3.46	Y	Dirichlet	B.3.2.1
Desferrioxamine (DFO)	14.2	19.95	9.28	Y	Dirichlet	B.3.2.1
DFP + DFO	11.1	16.37	6.76	Y	Dirichlet	B.3.2.1
DFP + DFX	4.9	8.75	2.17	Y	Dirichlet	B.3.2.1
DFX + DFO	4.9	8.75	2.17	Y	Dirichlet	B.3.2.1
Clinical inputs:						
Treatment procedure, response, and treatment waning						
Treatment phase (months)	12.00	N/A	N/A	N	N/A	B.3.3.1
Iron normalisation/change phase (months)						
Serum ferritin	48.00	N/A	N/A	N	N/A	B.3.3.1
Myocardial T2*	48.00	N/A	N/A	N	N/A	B.3.3.1
Liver iron concentration	48.00	N/A	N/A	N	N/A	B.3.3.1
Treatment procedure (%)						

Treatment withdrawal	4.0	10.45	0.48	Y	Beta	B.3.3.1
Initial engraftment success rate	100	N/A	N/A	N	Beta	B.3.3.1
Probability of repeated treatment (among those failed initial engraftment)	0	N/A	N/A	N	Beta	B.3.3.1
Second engraftment success rate	100	100	100	Y	Beta	B.3.3.1
Response (after treatment phase) (%)						
Proportion achieve TI	92.6	99.05	80.36	Y	Dirichlet	B.3.3.1
Proportion achieve TR	7.5	19.64	0.95	Y	Dirichlet	B.3.3.1
Transfusion reduction rate	87.6	100	36.41	Y	Beta	B.3.3.1
Proportion with TD	0	0	0	N	Dirichlet	B.3.3.1
Iron chelation therapy (%)						
Adherence to iron chelation therapy	100	100	100	Y	Beta	B.3.3.1
Reduced ICT use for patients with TR during ongoing phase (%)						
Percentage of full ICT use	100	100	100	Y	Beta	B.3.3.1
Iron level change (%)						
Under TI						
Proportion achieving normal iron levels	100	100	80	Y	Dirichlet	B.3.3.1
Proportion achieving low iron levels	0	0	0	N	Dirichlet	B.3.3.1
Complication risk inputs:						
Cardiac complications						
Annual risk (proportion) based on myocardial T2* level (%)						
Myocardial T2* normal	0.3	0.38	0.17	Y	Beta	B.3.3.2
Myocardial T2* low (>20ms - below normal) (%)	1.1	2.52	0.28	Y	Beta	B.3.3.2

Myocardial T2* moderate (10-20 ms) (%)	1.9	5.23	0.22	Y	Beta	B.3.3.2
Myocardial T2* high (<10 ms) (%)	4	10.41	0.59	Y	Beta	B.3.3.2
Liver complications						
Annual risk (proportion) based on liver iron level (%)						
Liver iron concentration (normal)	0.05	0.09	0.03	Y	beta	B.3.3.2
Liver iron concentration (low)	0.06	0.07	0	Y	Beta	B.3.3.2
Liver iron concentration (moderate)	0.06	0.07	0	Y	Beta	B.3.3.2
Liver iron concentration (high)	8.5	21.3	1.3	Y	Beta	B.3.3.2
Osteoporosis						
Monthly incidence (rate) among general (non-TDT) population, by gender and age group						
Male						
<30	0.000022	0.000024	0	Y	Beta	B.3.3.2
30-34	0.000045	0.00004	0	Y	Beta	B.3.3.2
35-39	0.000047	0.0001	0	Y	Beta	B.3.3.2
40-44	0.000047	0.0001	0	Y	Beta	B.3.3.2
45-49	0.000051	0.0001	0	Y	Beta	B.3.3.2
50-54	0.00006	0.0001	0	Y	Beta	B.3.3.2
55-59	0.000073	0.0001	0	Y	Beta	B.3.3.2
60-64	0.000088	0.0001	0	Y	Beta	B.3.3.2
65-69	0.00012	0.0001	0	Y	Beta	B.3.3.2
70-74	0.00021	0.0002	0	Y	Beta	B.3.3.2
75+	0.00036	0.0004	0	Y	Beta	B.3.3.2
Female						
<30	0.000021	0.000023	0	Y	Beta	B.3.3.2
30-34	0.000042	0.000045	0	Y	Beta	B.3.3.2
35-39	0.000052	0.0001	0	Y	Beta	B.3.3.2
40-44	0.000073	0.0001	0.0001	Y	Beta	B.3.3.2
45-49	0.00011	0.0001	0.0001	Y	Beta	B.3.3.2
50-54	0.00016	0.0002	0.0002	Y	Beta	B.3.3.2

55-59	0.00023	0.0002	0.00020	Y	Beta	B.3.3.2
60-64	0.00033	0.0003	0.00030	Y	Beta	B.3.3.2
65-69	0.00048	0.0005	0.00050	Y	Beta	B.3.3.2
70-74	0.00067	0.0007	0.0007	Y	Beta	B.3.3.2
75+	0.0010	0.0010	0.0010	Y	Beta	B.3.3.2
Increased risk associated with transfusion status (rate ratio)						
TI	1.00	1.43	0.65	Y	Gamma	B.3.3.2
TR	13.99	19.99	9.06	Y	Gamma	B.3.3.2
TD	26.98	38.54	17.46	Y	Gamma	B.3.3.2
Diabetes						
Annual risk for normal iron levels (%)						
Serum ferritin or myocardial T2* (normal)	0.05	0.64	0.29	Y	Beta	B.3.3.2
Risk equation of non-normal iron levels						
Intercept	-8.02	N/A	N/A	N	N/A	B.3.3.2
Serum ferritin (moderate or high)	2.69	N/A	N/A	N	N/A	B.3.3.2
Myocardial T2* (moderate or high)	2.96	N/A	N/A	N	N/A	B.3.3.2
Age	0.10	N/A	N/A	N	N/A	B.3.3.2
Hypogonadism						
Annual risk for normal iron levels (%)						
Serum ferritin or myocardial T2* (normal)	0	0	0	N	Beta	B.3.3.2
Risk equation of non-normal iron levels						
Intercept	-4.42	N/A	N/A	N	N/A	B.3.3.2
Serum ferritin (high)	1.06	N/A	N/A	N	N/A	B.3.3.2
Myocardial T2* (moderate or high)	1.36	N/A	N/A	N	N/A	B.3.3.2
Age	0.10	N/A	N/A	N	N/A	B.3.3.2
Splenectomy (%)						
Risk under TI	0	0	0	N	Beta	B.3.3.2
Risk under TR	0	0	0	N	Beta	B.3.3.2
Risk under TD	0	0	0	N	Beta	B.3.3.2
Other conditions:						

Infertility						
Increased risk of infertility related to treatments (prevalence ratio)						
Exa-cel						
Male	1.24	1.73	0.75	Y	Normal	B.3.3.2
Female	1.57	2.19	0.95	Y	Normal	B.3.3.2
Fertile age (years; applied to males and females)						
Starting age	16.00	N/A	N/A	N	N/A	B.3.3.2
End age	51.00	N/A	N/A	N	N/A	B.3.3.2
Cost inputs:						
Drug or transplant costs						
Exa-cel						
Acquisition price	[redacted]	[redacted]	[redacted]	N	N/A	B.3.5
Discount	[redacted]	[redacted]	[redacted]	N	N/A	B.3.5
Transplant-related costs						
Pre-transplant costs (exa-cel)						
Pre-transplant screening and fertility preservation	£3,483	N/A	N/A	N	N/A	B.3.5
Mobilisation						
Total mobilisation costs	[redacted]	[redacted]	[redacted]	Y	Gamma	B.3.5
Mobilisation HRU						
Mobilisation cycles	1.2	N/A	N/A	N	N/A	B.3.5
G-CSF daily dose (µg/kg)	£0	N/A	N/A	N	N/A	B.3.5
G-CSF length (days)	£0	N/A	N/A	N	N/A	B.3.5
Plerixafor daily dose (mg/kg)	0.24	N/A	N/A	N	N/A	B.3.5
Plerixafor length (days)	3	N/A	N/A	N	N/A	B.3.5
Mobilisation costs						
G-CSF cost per unit	£53	N/A	N/A	N	N/A	B.3.5
G-CSF unit strength (µg)	300	N/A	N/A	N	N/A	B.3.5
Plerixafor cost per unit	£4,880	N/A	N/A	N	N/A	B.3.5

Plerixafor unit strength (mg)	£24	N/A	N/A	N	N/A	B.3.5
Hospitalisation for harvesting procedure	£5,375	N/A	N/A	N	N/A	B.3.5
Myeloablation						
Total myeloablation costs	£0	£0	£0	Y	Gamma	B.3.5
Myeloablation HRU						
Busulfan daily dose (mg/kg)	3.75	N/A	N/A	N	N/A	B.3.5
Myeloablation length (days)	4.0	N/A	N/A	N	N/A	B.3.5
Number of busulfan administrations	4.0	N/A	N/A	N	N/A	B.3.5
Myeloablation costs (scenario only; assumed included in SCT costs in base case))						
Busulfan cost per unit	£169.18	N/A	N/A	N	N/A	B.3.5
Busulfan unit strength (mg)	60	N/A	N/A	N	N/A	B.3.5
Cost of busulfan administration	£314	N/A	N/A	N	N/A	B.3.5
Number of additional transfusions	2	N/A	N/A	N	N/A	B.3.5
Other pre-transplant costs (exa-cel)						
Other pre-transplant costs						
Exa-cel	See Pre-transplant costs (exa-cel)	N/A	N/A	N	N/A	B.3.5
Additional costs for transplantation						
Hospitalisation costs for procedure (exa-cel)	£26,602	£37,998	£17,215	Y	Gamma	B.3.5
Post-transplant monitoring (exa-cel)						
Number of years of post-transplant monitoring	15.00	N/A	N/A	N	N/A	B.3.5
Monthly post-transplant monitoring cost						

Year 1	£99.8	£143	£65	Y	Gamma	B.3.5
Year 2	£99.8	£143	£65	Y	Gamma	B.3.5
Year 3	£82.0	£117	£53	Y	Gamma	B.3.5
Year 4	£82	£117	£53	Y	Gamma	B.3.5
Year 5+	£82	£117	£53	Y	Gamma	B.3.5
Blood transfusion and iron chelation costs						
Blood transfusion						
Monthly blood transfusion costs	£823	N/A	N/A	N	N/A	B.3.5
Cost per RBC unit	£238	£340	£154	Y	Gamma	B.3.5
Cost per procedure	£90	£128	£58	Y	Gamma	B.3.5
Staff time	£49	N/A	N/A	N	N/A	B.3.5
Disposables	£41	N/A	N/A	N	N/A	B.3.5
DFO						
Cost per unit	£4.66	N/A	N/A	N	N/A	B.3.5
mg per unit	500.00	N/A	N/A	N	N/A	B.3.5
Daily dose (mg/kg)	40.00	55.68	24.32	N	Normal	B.3.5
Dose per week	5.00	N/A	N/A	N	N/A	B.3.5
Administration cost per time	£0	N/A	N/A	N	N/A	B.3.5
DFX						
Cost per unit	£4.20	N/A	N/A	N	N/A	B.3.5
mg per unit	90.00	N/A	N/A	N	N/A	B.3.5
Daily dose (mg/kg)	21.00	29.39	20.61	N	Normal	B.3.5
Dose per week	7.00	N/A	N/A	N	N/A	B.3.5
Administration cost per time	£0	N/A	N/A	N	N/A	B.3.5
DFP						
Cost per unit	£1.30	N/A	N/A	N	Gamma	B.3.5
mg per unit	500.00	N/A	N/A	N	N/A	B.3.5
Daily dose (mg/kg)	87.50	121.79	53.20	N	Normal	B.3.5
Dose per week	7.00	N/A	N/A	N	N/A	B.3.5
Administration cost per time	£0	N/A	N/A	N	N/A	B.3.5
Phlebotomy during normalisation/change phase (for exa-cel)						
Monthly costs	£10	£15	£7	Y	Gamma	B.3.5
Cost per procedure	£5	N/A	N/A	N	N/A	B.3.5

Frequency per week	0.50	0.71	0.32	Y	Gamma	B.3.5
Complication and other condition costs						
Complications						
Cardiac complications (year 1; monthly)	£625	£893	£404	Y	Gamma	B.3.5
Cardiac complications (year 2+; monthly)	£322	£460	£208	Y	Gamma	B.3.5
Liver complications (year 1; monthly)	£259	£370	£168	Y	Gamma	B.3.5
Liver complications (year 2+; monthly)	£259	£370	£168	Y	Gamma	B.3.5
Osteoporosis (year 1; monthly)	£691	£986	£447	Y	Gamma	B.3.5
Osteoporosis (year 2+; monthly)	£38	£54	£25	Y	Gamma	B.3.5
Diabetes (year 1; monthly)	£486	£694	£314	Y	Gamma	B.3.5
Diabetes (year 2+; monthly)	£486	£694	£314	Y	Gamma	B.3.5
Hypogonadism (year 1; monthly)	£53	£75	£34	Y	Gamma	B.3.5
Hypogonadism (year 2+; monthly)	£53	£75	£34	Y	Gamma	B.3.5
Splenectomy (one time)	£0	N/A	N/A	N	Gamma	B.3.5
Other conditions						
Infertility (IVF once off)						
Female	£2,632	£3,759	£1,703	Y	Gamma	B.3.5
Infertility - recurring (monthly storage of sperm of oocyte)						
Male	£19	£26	£12	Y	Gamma	B.3.5
Female	£19	£26	£12	Y	Gamma	B.3.5
Disease management costs						
Cost for HRU						
Cost per inpatient visit	£1,241	N/A	N/A	N	N/A	B.3.5
Cost per day case visit	£839	N/A	N/A	N	N/A	B.3.5

Cost per outpatient visit	£209	N/A	N/A	N	N/A	B.3.5
Cost per ER visit	£276	N/A	N/A	N	N/A	B.3.5
TI						
Monthly disease management costs	£35	£50	£23	Y	Gamma	B.3.5
Number of inpatient visits per month	0.00	N/A	N/A	N	N/A	B.3.5
Number of day case visits per month	0.00	N/A	N/A	N	N/A	B.3.5
Number of outpatient visits per month	0.17	N/A	N/A	N	N/A	B.3.5
Number of ER visits per month	0.00	N/A	N/A	N	N/A	B.3.5
TR						
Monthly disease management costs	£103	£148	£67	Y	Gamma	B.3.5
Number of inpatient visits per month	0.00	N/A	N/A	N	N/A	B.3.5
Number of day case visits per month	0.02	N/A	N/A	N	N/A	B.3.5
Number of outpatient visits per month	0.38	N/A	N/A	N	N/A	B.3.5
Number of ER visits per month	0.01	N/A	N/A	N	N/A	B.3.5
TD						
Monthly disease management costs	£172	£245	£111	Y	Gamma	B.3.5
Number of inpatient visits per month	0.01	N/A	N/A	N	N/A	B.3.5
Number of day case visits per month	0.04	N/A	N/A	N	N/A	B.3.5
Number of outpatient visits per month	0.58	N/A	N/A	N	N/A	B.3.5

Number of ER visits per month	0.02	N/A	N/A	N	N/A	B.3.5
AE costs						
One time AE costs						
Exa-cel	£0	N/A	N/A	N	Gamma	B.3.5
SoC	£0	N/A	N/A	N	Gamma	B.3.5
Monthly costs for recurring AEs						
Exa-cel	£0	N/A	N/A	N	Gamma	B.3.5
SoC	£2.39	£3.4	£1.5	Y	Gamma	B.3.5
Terminal costs						
Once-off terminal costs	£12,397	£17,708	£8,022	N	Gamma	B.3.5
TI						
Absenteeism	0%	N/A	N/A	N	N/A	B.3.5
Presenteeism	0%	N/A	N/A	N	N/A	B.3.5
TR						
Absenteeism	10%	N/A	N/A	N	N/A	B.3.5
Presenteeism	17%	N/A	N/A	N	N/A	B.3.5
TD						
Absenteeism	20%	N/A	N/A	N	N/A	B.3.5
Presenteeism	34%	N/A	N/A	N	N/A	B.3.5
Patient out-of-pocket costs						
Out-of-pocket costs as percentage of health state costs	0%	N/A	N/A	N	N/A	B.3.5
Other indirect costs (monthly)						
TI	£0	N/A	N/A	N	Gamma	B.3.5
TR	£0	N/A	N/A	N	Gamma	B.3.5
TD	£0	N/A	N/A	N	Gamma	B.3.5
Monthly patient productivity costs						
TI	£0	N/A	N/A	N	Gamma	B.3.5
TR	£0	N/A	N/A	N	Gamma	B.3.5
TD	£0	N/A	N/A	N	Gamma	B.3.5
Monthly caregiver burden costs						
TI	£0	N/A	N/A	N	Gamma	B.3.5
TR	£0	N/A	N/A	N	Gamma	B.3.5

TD	£0	N/A	N/A	N	Gamma	B.3.5
Utility inputs:						
Health state utilities						
TI	0.93	0.95	0.91	Y	Beta	B.3.4
TR	0.75	0.78	0.73	Y	Beta	B.3.4
TD	0.73	0.75	0.69	Y	Beta	B.3.4
Age- and gender-dependent utility adjustment						
Intercept	0.95	N/A	N/A	N	N/A	B.3.4
Male	0.02	N/A	N/A	N	N/A	B.3.4
Age (years)	0.00	N/A	N/A	N	N/A	B.3.4
Age2	0.00	N/A	N/A	N	N/A	B.3.4
Disutilities						
Complication- and infertility-related disutilities						
Cardiac complications	-0.11	-0.09	-0.14	Y	Beta	B.3.4
Liver complications	-0.11	-0.09	-0.13	Y	Beta	B.3.4
Osteoporosis	-0.08	-0.05	-0.11	Y	Beta	B.3.4
Diabetes	-0.06	-0.04	-0.09	Y	Beta	B.3.4
Hypogonadism	-0.03	-0.02	-0.05	Y	Beta	B.3.4
Splenectomy	0.00	0	0	N	Beta	B.3.4
Infertility	-0.06	-0.05	-0.063	Y	Beta	B.3.4
Transplantation-related disutilities						
Treatment with exa-cel in transplant year	-0.11	-0.13	-0.08	N	N/A	B.3.4
Engraftment failure in transplant year	-0.40	-0.48	-0.32	Y	Beta	B.3.4
Iron chelation therapy-related disutilities						
Receiving oral ICT	0.00	0.00	0	Y	Beta	B.3.4
Receiving subcutaneous ICT	-0.10	-0.12	-0.08	Y	Beta	B.3.4
TI + oral ICT	0.93	N/A	N/A	N	N/A	B.3.4
TI + subcutaneous ICT	0.83	N/A	N/A	N	N/A	B.3.4
TR + oral ICT	0.75	N/A	N/A	N	N/A	B.3.4
TR + subcutaneous ICT	0.65	N/A	N/A	N	N/A	B.3.4
TD + oral ICT	0.73	N/A	N/A	N	N/A	B.3.4

TD + subcutaneous ICT	0.63	N/A	N/A	N	N/A	B.3.4
Treatment with exa-cel	0.62	0.67	0.57	Y	Beta	B.3.4
Mortality inputs:						
Transplant-related mortality (instant mortality %)						
Exa-cel	0	0	0	Y	Beta	B.3.3.4
Engraftment failure						
Exa-cel	25.0	30.0	20.0	Y	Beta	B.3.3.4
Transfusion status-dependent mortality						
Standardised mortality tion(SMR)						
TI	1.25	1.50	1.00	Y	Normal	B.3.3.4
TR	2.35	2.82	1.88	Y	Normal	B.3.3.4
TD	3.45	4.14	2.76	Y	Normal	B.3.3.4
Complication-dependent mortality						
Annual risk (probability; disease-specific mortality) (%)						
Cardiac complications	13.0	23.29	5.39	Y	Beta	B.3.3.4
Osteoporosis (on and after 65 years old)	0.0	N/A	N/A	N	N/A	B.3.3.4
SMR						
Liver complications	1.00	N/A	N/A	N	N/A	B.3.3.4
Diabetes	1.50	1.80	1.20	Y	Normal	B.3.3.4
Hypogonadism	1.00	N/A	N/A	N	N/A	B.3.3.4
Instant risk (probability %)						
Splenectomy (operative mortality within 30 days)	1.6	2.29	0.97	Y	Beta	B.3.3.4
Infertility-dependent mortality						
SMR						
Male	1.00	N/A	N/A	N	N/A	B.3.3.4
Female	1.00	N/A	N/A	N	N/A	B.3.3.4
AE inputs:						
Monthly AE rate for recurring AEs (SoC only)	1.14%	N/A	N/A	N	N/A	B.3.3.5

Key: CI, confidence interval; Y, Yes, N, No

B.3.10.2. Assumptions

Table 51: Key model assumptions

Model parameters	Assumptions
Rate of iron level change	• The iron level change was assumed to occur at a constant rate during this phase in the base-case. • During ongoing phase, patients would remain at the same transfusion status and iron level as the end of iron normalisation/change phase.
Life-long complications	Once a complication occurs, the patient will have the complication until death. Complication risks are assumed to be independent of each other given the lack of data to inform joint probability of multiple complications
Mortality	Mortality is assumed to be affected by age, gender, transfusion status, TDT-related complications, transplantation, and engraftment failure (exa-cel only). Among patients with TI, baseline mortality was assumed to be 25% higher than the age/gender matched general population cohort.
AEs	For exa-cel, all AEs associated with the transplant or drug infusion were assumed to occur in the hospital and thus are captured in transplantation-related hospitalisation costs and disutilities.
Use of SoC	Patients on SoC receive lifelong RBC transfusion and ICT. Patients on other treatments could switch to receive SoC in the following cases: • If they withdrew from any of the stem-cell therapies (i.e., exa-cel) • If they failed any of the stem-cell therapies (i.e., exa-cel)
Treatment withdrawals and treatment failures impact on pre-transplant and drug/transplant costs (stem-cell therapies only)	If patients withdrew from any of the stem-cell therapies (i.e., exa-cel), it was assumed that they withdrew after mobilisation and apheresis (exa-cel). Therefore, myeloablation, other pre-transplant costs, and drug/transplant costs would not be applied to these patients. If patients failed stem-cell therapies, they would incur full mobilisation, apheresis, myeloablative conditioning, other pre-transplant, and drug/transplant costs.

Post-transplant costs	Post-transplantation monitoring is assumed to last for up to 15 years after the transplantation procedure and incur monitoring costs. This is based on clinical expert feedback.

B.3.11 Base-case results

B.3.11.1. Base-case incremental cost-effectiveness analysis results

The base case cost-effectiveness results are presented in Table 52 to Table 54. NICE considers inequality or unfairness in the distribution of health to be an important factor in decision-making (9). In section B.3.9 we summarise a DCEA that was conducted to quantify the distribution of health inequalities in TDT and the potential impact on exa-cel. We therefore report, as a co-base case, the ICERs including modifiers to the incremental costs and incremental QALYs based on appropriate DCEA methodology.

Justification for a 1.5% discount rate in the base case, based on the criteria laid out in the NICE methods guide, has been provided in Table 30.

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Table 52: Base-case results (1.5% discount rate)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER with severity modifier
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted incremental results								

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DCEA. Distributional cost-effectiveness analysis

Table 53: Scenario analysis (3.5% discount rate)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER with severity modifier
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted incremental results								

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DCEA. Distributional cost-effectiveness analysis

Table 54: Net-health benefit (1.5% discount rate)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Standard of care	[redacted]	[redacted]				
Exa-cel			[redacted]	[redacted]	[redacted]	[redacted]
Severity-weighted NHB						
DCEA-weighted NHB						
DCEA & severity-weighted NHB						

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

Table 55: Net-health benefit (3.5% discount rate)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Standard of care	[redacted]	[redacted]				
Exa-cel			[redacted]	[redacted]	[redacted]	[redacted]
Severity-weighted NHB						
DCEA-weighted NHB						
DCEA & severity-weighted NHB						

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit; Distributional cost-effectiveness analysis

B.3.12 Exploring uncertainty

Extensive sensitivity analyses were carried out including Probabilistic sensitivity analyses (PSA), one-way deterministic sensitivity results (OWSA) and scenario analyses.

B.3.12.1. Probabilistic sensitivity analysis

The PSA was run with 1000 iterations, by which time the running ICER had stabilised based on a caterpillar plot. In each PSA simulation run, the relevant severity modifier was captured (including no modifier where relevant) and QALYs reweighted accordingly. To enable incorporation of age in the severity-modified PSA, the upper age was restricted to 50 (the upper limit likely in clinical practice). The results reported here represent thus represent the reweighted results. The reweighting can be switched off in the PSA sheet of the model if desired.

The ICER from the PSA with the base case discount rate of 1.5% was [redacted] compared with [redacted] in the deterministic base case. This demonstrates that there is low uncertainty and high confidence in the results of the model.

The ICER from the PSA with a discount rate of 3.5% was [redacted] compared with [redacted] in the deterministic base case.

When employing the base-case discount rate of 1.5%, exa-cel had a [redacted] probability of being cost-effective vs. SoC at the willingness to pay (WTP) threshold of £20,000 per QALY and a [redacted] probability of being cost-effective vs. SoC at the WTP threshold of £30,000 per QALY.

At a discount rate of 3.5%, exa-cel had a [redacted] probability of being cost-effective vs. SoC at the WTP threshold of £20,000 per QALY and a [redacted] probability of being cost-effective vs. SoC at the WTP threshold of £30,000 per QALY.

Table 56: PSA results (1.5% discount rate)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER with severity modifier
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted incremental results				[redacted]		[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DCEA. Distributional cost-effectiveness analysis
Note: Simulations are only DCEA/severity-modified where applicable to the simulation run.

Table 57: PSA results (3.5% discount rate)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER with severity modifier
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted incremental results				[redacted]		[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DCEA. Distributional cost-effectiveness analysis
Note: Simulations are only DCEA/severity--modified where applicable to the simulation run.

Figure 23: Cost-effectiveness acceptability curve, 1.5% discount rate (DCEA and severity modified)

DCEA. Distributional cost-effectiveness analysis

Figure 24: Cost-effectiveness acceptability curve, 3.5% discount rate (DCEA and severity modified)

DCEA. Distributional cost-effectiveness analysis

Figure 25: Cost-effectiveness acceptability curve, 1.5% discount rate (severity modified)

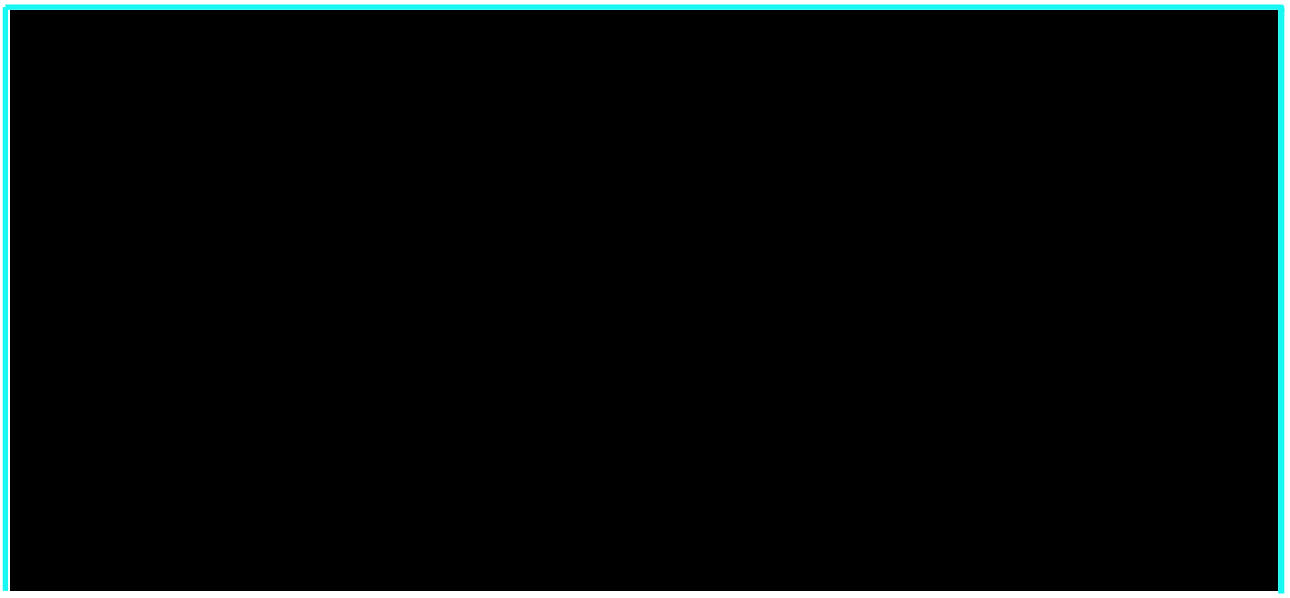


Figure 26: Cost-effectiveness acceptability curve, 3.5% discount rate (severity modified)

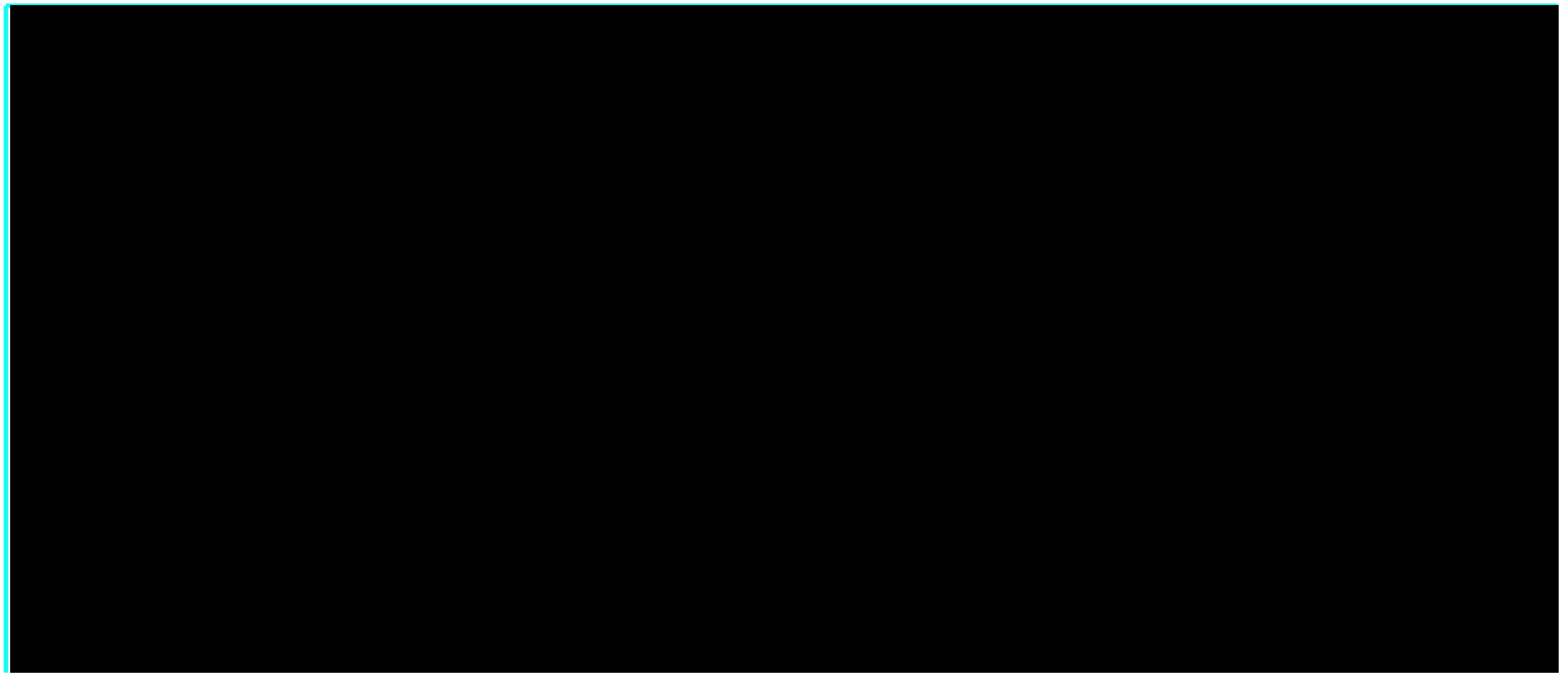
B.3.12.2. Deterministic sensitivity analysis

In each Deterministic sensitivity analysis (DSA) scenario, the relevant severity and/or DCEA modifier was captured (including no modifier where relevant) and QALYs and/or costs reweighted accordingly. The results reported here thus represent the reweighted results only where applicable. The reweighting can be switched off in the DSA sheet of the model if desired.

At the base case discount rate of 1.5%, the most sensitive parameters in the OWSA were the frequency of cardiac complications and their mortality, the frequency of blood transfusion, the proportion of patients achieving TI, the patient weight ratio vs. the general population and patient age, the length of iron normalisation, and the proportion of patients achieving of iron normalisation. Utility values for TI and TD disease were also relatively impactful.

At a discount rate of 3.5%, the most sensitive parameters in the OWSA were the frequency of cardiac complications, utility value for TD disease, the frequency of blood transfusion, the proportion of patients achieving TI, the disutility of receiving ICT, hypogonadism, and osteoporosis, and the annual risk of liver complications associated with liver iron level.

Figure 27: OWSA results, 1.5% discount rate (severity and DCEA modified)



Note: Simulations are only DCEA/severity-modified where applicable to the simulation run.

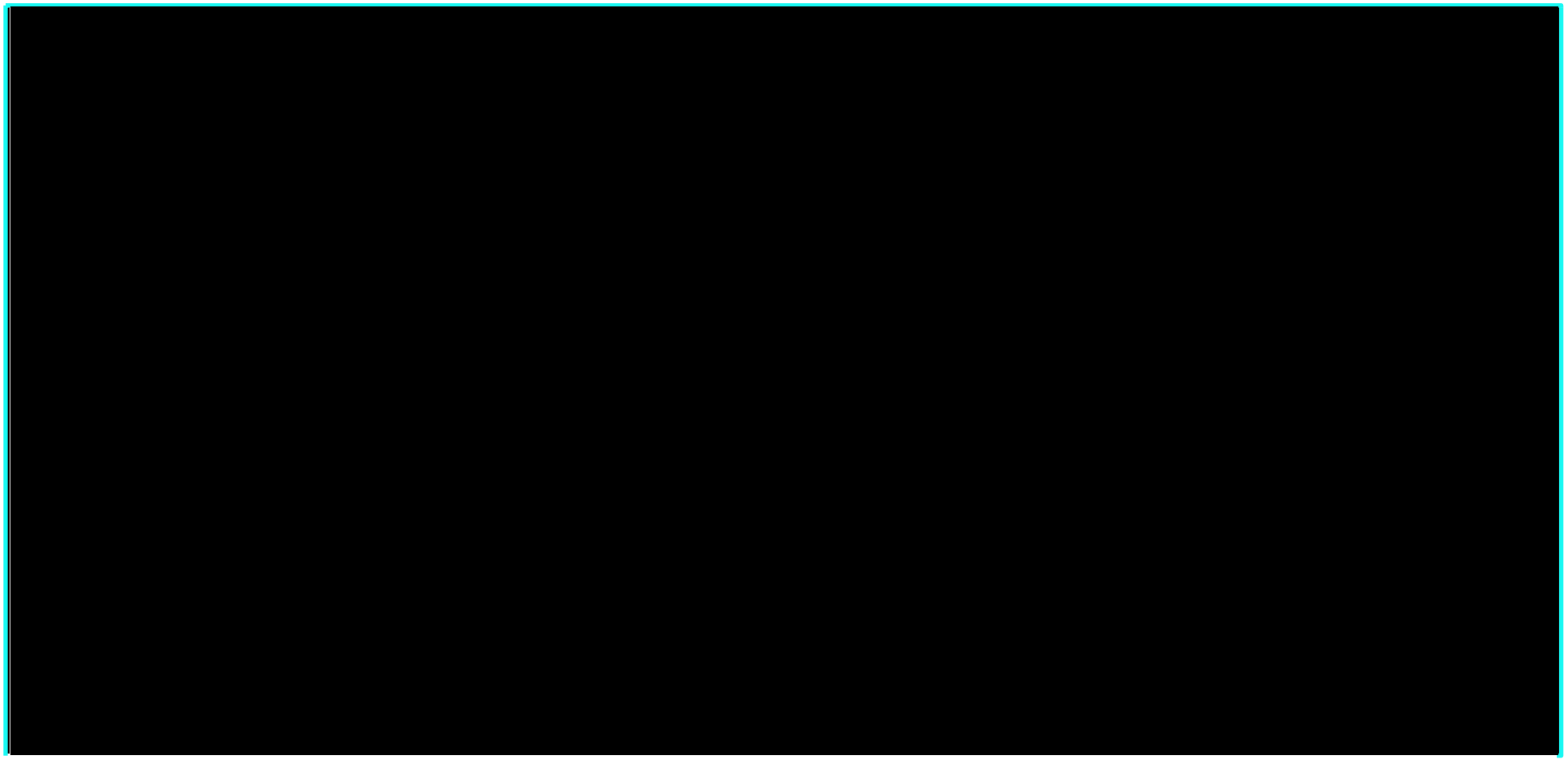
Figure 28: OWSA results, 3.5% discount rate (severity and DCEA modified)

Note: Simulations are only DCEA/severity--modified where applicable to the simulation run.

Figure 29: OWSA results, 1.5% discount rate (severity modified)

Note: Simulations are only severity-modified where applicable to the simulation run.

Figure 30: OWSA results, 3.5% discount rate (severity modified)



Note: Simulations are only severity-modified where applicable to the simulation run.

B.3.12.3. Scenario analysis

In each scenario, the relevant severity and/or DCEA modifier was captured (including no modifier where relevant) and QALYs and/or costs reweighted accordingly. The results reported here thus represent the reweighted results only where applicable. The reweighting can be switched off in the DSA sheet of the model if desired.

At the base case discount rate of 1.5%, the most impactful scenarios included adjusting the TI patients SMR from 1.25 to 2, which increased the ICER to [redacted], and including societal benefits which reduced the ICER to [redacted]

At a discount rate of 3.5%, the most impactful scenarios were included adjusting the TD patients SMR from 3.45 to 2, which increased the ICER to [redacted], and including societal benefits which reduced the ICER to [redacted].

Table 58: Results of scenario analyses, 1.5% discount rate (with severity-modifier and DCEA)

Base case assumption	Scenario assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case results		[redacted]	[redacted]	[redacted]
TI patients have 0% risk of developing complications after iron normalisation	TI patients have 1.25x risk of general population of developing complications after iron normalisation	[redacted]	[redacted]	[redacted]
Iron-normalisation takes 4 years	Iron-normalisation takes 5 years	[redacted]	[redacted]	[redacted]
Interaction between disutilities of complications is multiplicative	Interaction between disutilities of complications is additive	[redacted]	[redacted]	[redacted]
Carer utility is excluded	Carer utility is included	[redacted]	[redacted]	[redacted]
Interaction between mortality from different complications is multiplicative	Interaction between mortality from different complications is additive	[redacted]	[redacted]	[redacted]
SMR of 3.45 for TD patients	SMR of 2 for TD patients	[redacted]	[redacted]	[redacted]
SMR of 1.25 for TI patients post-exa-cel	SMR of 2 for TI patients post-exa-cel	[redacted]	[redacted]	[redacted]
Additional AE costs are excluded	Additional AE costs are included	[redacted]	[redacted]	[redacted]
Societal benefits are excluded	Societal benefits are included			

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Note: Scenarios are only severity/DCEA-modified where applicable to that scenario.

Table 59: Results of scenario analyses, 3.5% discount rate (with severity-modifier and DCEA)

Base case assumption	Scenario assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case results		[redacted]	[redacted]	[redacted]
TI patients have 0% risk of developing complications after iron normalisation	TI patients have 1.25x risk of general population of developing complications after iron normalisation	[redacted]	[redacted]	[redacted]

Iron-normalisation takes 4 years	Iron-normalisation takes 5 years	[redacted]	[redacted]	[redacted]
Interaction between disutilities of complications is multiplicative	Interaction between disutilities of complications is additive	[redacted]	[redacted]	[redacted]
Carer utility is excluded	Carer utility is included	[redacted]	[redacted]	[redacted]
Interaction between mortality from different complications is multiplicative	Interaction between mortality from different complications is additive	[redacted]	[redacted]	[redacted]
SMR of 3.45 for TD patients	SMR of 2 for TD patients	[redacted]	[redacted]	[redacted]
SMR of 1.25 for TI patients post-exa-cel	SMR of 2 for TI patients post-exa-cel	[redacted]	[redacted]	[redacted]
Additional AE costs are excluded	Additional AE costs are included	[redacted]	[redacted]	[redacted]
Societal benefits are excluded	Societal benefits are included			

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Note: Scenarios are only severity/DCEA-modified where applicable to that scenario.

Table 60: Results of scenario analyses, 1.5% discount rate (with severity-modifier only)

Base case assumption	Scenario assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case results		[redacted]	[redacted]	[redacted]
TI patients have 0% risk of developing complications after iron normalisation	TI patients have 1.25x risk of general population of developing complications after iron normalisation	[redacted]	[redacted]	[redacted]
Iron-normalisation takes 4 years	Iron-normalisation takes 5 years	[redacted]	[redacted]	[redacted]
Interaction between disutilities of complications is multiplicative	Interaction between disutilities of complications is additive	[redacted]	[redacted]	[redacted]
Carer utility is excluded	Carer utility is included	[redacted]	[redacted]	[redacted]
Interaction between mortality from different complications is multiplicative	Interaction between mortality from different complications is additive	[redacted]	[redacted]	[redacted]
SMR of 3.45 for TD patients	SMR of 2 for TD patients	[redacted]	[redacted]	[redacted]

SMR of 1.25 for TI patients post-exa-cel	SMR of 2 for TI patients post-exa-cel	[redacted]	[redacted]	[redacted]
Additional AE costs are excluded	Additional AE costs are included	[redacted]	[redacted]	[redacted]
Societal benefits are excluded	Societal benefits are included	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Note: Scenarios are only severity/DCEA-modified where applicable to that scenario.

Table 61: Results of scenario analyses, 3.5% discount rate (with severity-modifier only)

Base case assumption	Scenario assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case results		[redacted]	[redacted]	[redacted]
TI patients have 0% risk of developing complications after iron normalisation	TI patients have 1.25x risk of general population of developing complications after iron normalisation	[redacted]	[redacted]	[redacted]
Iron-normalisation takes 4 years	Iron-normalisation takes 5 years	[redacted]	[redacted]	[redacted]
Interaction between disutilities of complications is multiplicative	Interaction between disutilities of complications is additive	[redacted]	[redacted]	[redacted]
Carer utility is excluded	Carer utility is included	[redacted]	[redacted]	[redacted]
Interaction between mortality from different complications is multiplicative	Interaction between mortality from different complications is additive	[redacted]	[redacted]	[redacted]
SMR of 3.45 for TD patients	SMR of 2 for TD patients	[redacted]	[redacted]	[redacted]
SMR of 1.25 for TI patients post-exa-cel	SMR of 2 for TI patients post-exa-cel	[redacted]	[redacted]	[redacted]
Additional AE costs are excluded	Additional AE costs are included	[redacted]	[redacted]	[redacted]
Societal benefits are excluded	Societal benefits are included			

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Note: Scenarios are only severity/DCEA-modified where applicable to that scenario.

B.3.13 Subgroup analysis

No relevant subgroups have been identified who are likely to benefit more or less from exa-cel treatment or have greater or less cost-effectiveness.

B.3.14 Benefits not captured in the QALY calculation

As discussed in section B.3.4, any use of the EQ-5D (instead of the vignettes used in the base case) to underpin decision-making may risk underestimating the benefits of treatment with exa-cel:

- Patients are likely to have adapted to their condition, leading to high baseline EQ-5D values and introduction of a ceiling effect on the QALY gain;
- The EQ-5D, lacking a fatigue domain, may fail to capture one the key factors that leads to detrimental HRQoL in TDT.

A large proportion of the TDT population eligible for exa-cel is adolescents. The reference case analysis does not capture the benefits on education of reduced absence from school due to the need for regular RBC transfusions and improved concentration while at school due to reduced fatigue. These are likely to have knock-on consequences for the future success and employment of adolescents with TDT.

Similarly, omission of carer utility from the reference case ignores the substantial burden of parents of adolescents and young adults with TDT, such as support with education and daily activities including attendance of healthcare services.

The base case does not capture any productivity benefits such as improved employment rates of adults. A survey of UK patients indicated significant challenges with employment including (155):

- Time off for transfusions and appointments;
- Fatigue felt before transfusions and treatment;
- Lack of awareness amongst employers and colleagues;
- Lack of flexible working hours;
- Uncertainty whether or not to disclosure to employers;

- Pain as a result of thalassaemia;
- Mobility issues

The model does not capture any benefit to the NHS of improving blood stocks and blood transfusion services due to the reduced need from exa-cel treated patients.

Finally, we have presented a DCEA that incorporates the general public's preferences with respect to health inequalities and demonstrates quantitatively how treatment with exa-cel could potentially reduce existing inequality or unfairness in the distribution of health within the TDT population. Incorporation of the DCEA results as part of decision-making would mitigate any benefits on reducing inequality not captured in the reference-case analysis.

B.3.15 Validation

B.3.15.1. Validation of the cost-effectiveness analysis

A comprehensive model validation was performed in which the internal validity, face validity, and external validity of the model was assessed.

Several internal quality control procedures were undertaken to verify the results of the de novo cost-effectiveness model. All source inputs and calculations in the Excel model were generated by one researcher and verified by another independent researcher to ensure accuracy. Quality control also included a line-by-line audit of the Visual Basic for Applications (VBA) code used in the model. In addition, the model structure, setting, assumptions, input, and data were reviewed by experienced health economists who have extensive experience in model construction.

Face validity was assessed by comparing the model's predicted survival output with real-world estimates of survival reported in the literature. Since limited data about survival is available for exa-cel, face validity was assessed for the SoC arm. A retrospective cohort analysis conducted in the HES database reported the median age of death among 612 patients with TDT in the UK to be 45 years (1). Another analysis conducted in the CPRD-HES databases from 2008-2019 found the mean age of death in 237 patients with TDT was approximately 55 years (2, 3).The model projections for survival (mean age at death) for patients with TDT receiving SoC in this analysis is estimated to be 50.38 years, which is within the range of plausible survival estimates from these aforementioned contemporary UK studies.

For SoC, the undiscounted life-years (LYs) and discounted QALYs predicted by ERG's analysis of beti-cel model (LYs: 37.79 years; QALYs: 15.48 years) are both greater than the estimates in the current model (LYs: [redacted] years; QALYs: [redacted] years). Multiple factors may have contributed to the difference, including a different starting age (21.4 years in current model vs. an unreported range of values in the beti-cel simulation model) and the approach for modelling mortality (life tables in the current model vs. Gompertz curve in the beti-cel simulation model). The exact reasons are hard to determine given the differing model structures (Markov cohort in the current model vs DICE simulation in the beti-cel model).

Further external validation of the model compared to UK sources were conducted (see Appendix J.1.1).

B.3.16 Interpretation and conclusions of economic evidence

This de novo economic evaluation examined the cost-effectiveness of exa-cel in TDT. The model predicted that, over a lifetime horizon, patients treated with exa-cel had a substantial increase in estimated survival of [redacted] compared to SoC. Patients treated with exa-cel experienced approximately 451.84 less RBC transfusions over the lifetime horizon compared to patients treated with SoC. Further, the lifetime burden of TDT-related complications was projected to be substantially lower for patients treated with exa-cel compared to those treated with SoC. Over a lifetime horizon, the incremental costs associated with treating with exa-cel compared to SoC was £[redacted] , which yielded an ICER of £[redacted] per discounted QALY gained.

Data for exa-cel was informed by the ongoing CLIMB THAL-111 trial (publicly available data presented at EHA 2022), which included 44 patients with TDT ages 12 to 35 years (121). The trial population is considered to be representative of the population expected to be treated for TDT in the UK. At the time of the data cut, 25 out of 27 patients with TDT were transfusion free following exa-cel infusion. Exa-cel may provide a breakthrough solution for patients for whom a HLA-matched related HSC donor is not available. Exa-cel may provide a breakthrough solution for patients for whom a HLA-matched related HSC donor is not available.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Summary of Information for Patients (SIP)

June 2023

File name	Version	Contains confidential information	Date
ID4015_Exa-cel_TDT_SIP_FINAL [noCON]	1.0	No	29/06/2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Exagamglogene autotemcel (or exa-cel for short). The brand name is confidential but is mentioned in B.1.2 of the main submission (Document B).

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Beta-thalassaemia in patients aged 12 years or older who need regular blood transfusions, do not have a family relative with matching blood stem cells to give to them, and who are eligible to have a stem cell transplant using their own blood stem cells (known as an autologous stem cell transplant).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

A Marketing Authorisation Application was sent to the Medicines and Healthcare products Regulatory Authority (the organisation that gives companies the legal right to sell medicines in the UK) in December 2022. Once approved, exa-cel can be given to patients in the UK. Further details are in section B.1 of the main submission (Document B).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Vertex has supported the UK Thalassaemia Society with some of their work on creating educational resources for families impacted by beta-thalassaemia.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
Beta-thalassaemia is an inherited blood disorder caused by a mutation in a gene responsible for making haemoglobin, the protein that carries oxygen in red blood cells (1). This results in patients suffering from chronic severe anaemia. People with transfusion-dependent beta-thalassaemia need lifelong regular blood transfusions and removal of excess iron in the blood (known as chelation therapy) to survive (1); on average, patients with this condition need to have 17 transfusions per year - or every 3 weeks. Patients and their families experience severe disruption to their lives; approximately 30% of patients are unemployed or unable to work full time because of their condition. Patients live with pain and tiredness in between transfusions. Low haemoglobin levels also lead to reduced oxygen delivery to organs and tissues, which limits patients' growth and causes paleness, small muscle size, jaundice (yellowing of the skin), and skeletal changes due to the bone marrow expanding to try and make more red blood cells. Iron chelation therapy also causes side effects including stomach sickness, and can be unpleasant for patients to take. Beta-thalassaemia is thought to affect around 288,000 people worldwide (2). People who live with this disease are more likely to die earlier than the general population and are more likely to develop other severe illnesses such as heart conditions, diabetes, liver disease and osteoporosis (weak, fragile bones).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
In the UK, all pregnant women are offered a blood test to screen for beta-thalassaemia. All newborn babies are offered screening as part of the newborn heel prick blood spot screening programme that is usually performed when they are 5 days old. (3) Patients will not need to have any new diagnostic tests to be treated with exa-cel.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed: • What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP. • Please also consider: o if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data. o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.
People with transfusion-dependent beta-thalassaemia receive lifelong blood transfusions – usually approximately 2 units of blood over a period of 3 hours, once every 3 weeks, or about 17 times per year. Transfusions do not cure beta-thalassaemia but can provide temporary relief of the anaemia. However, patients still often experience fatigue and pain in the days and weeks before their next transfusion. The extra blood that patients receive raises their iron levels because of the extra haemoglobin, so patients also need to take daily doses of 'iron chelating therapy' to remove the extra iron from their blood. The only treatment available that can cure beta-thalassaemia is a stem cell transplant from a matched related donor (a process known as an 'allograft'); however this is only available to a very small group of patients - approximately 20%.

2d) Patient-based evidence (PBE) about living with the condition

Context: • **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials. In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

A series of patient interviews and focus groups conducted in the UK and US provides evidence of the psychological impact beta-thalassaemia can have on patients and caregivers. They found that the limited ability to carry out activities of daily living and contribute to family life can lead to a profound psychological impact on morale and self-esteem of patients with beta-thalassaemia. Other commonly reported psychological symptoms include depression, anxiety, stress and worries about the future (4).

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Exa-cel works by increasing the production of a special type of haemoglobin called haemoglobin F (*foetal haemoglobin* or HbF), which is produced in all developing babies before birth. Haemoglobin F normally stops being produced soon after birth, but with exa-cel the production of haemoglobin F is turned back on. Having more haemoglobin F increases overall haemoglobin levels in the body and has been shown to improve the production and function of red blood cells. This can mean that people with beta-thalassaemia may not need blood transfusions.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Exa-cel is not intended to be used in combination with any other medicines. However, there are some medications that are used in the process of preparing a patient to receive exa-cel. The full procedure is described below in 3c), but, briefly, the additional medicines are used as follows:

- A *mobilisation* medicine is injected into a vein (*intravenous* infusion) to move the patient's blood stem cells from the bone marrow into the blood stream. This involves a group of medicines known as *granulocyte-colony stimulating factors*, including filgrastim and plerixafor.
- A *conditioning* medicine is injected into the patient to remove the stem cells from the bone marrow, so that they can be replaced with the modified cells in exa-cel. This involves busulfan – a type of medicine that is often used against cancer as part of *chemotherapy*.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Exa-cel is a one-time gene therapy. It is made specifically for each patient, using the patient's own blood stem cells. Blood stem cells are cells that can turn into other blood cells including red cells, white cells and platelets. The cells are taken from the patient, then are genetically modified and they are given back to the same patient as a stem cell transplant.

Exa-cel can only be given in an authorised treatment centre (specialised hospital) by doctors with experience in stem cell transplants, and in the treatment of patients with blood disorders such as beta-thalassaemia.

STAGE 1: Before exa-cel treatment, a doctor will give the patient a *mobilisation* medicine into a vein (*intravenous* infusion). This medicine moves blood stem cells from the bone marrow into the blood stream. The blood stem cells are then collected in a machine that separates the different blood cells (this is called *apheresis*). This entire process may happen more than once. Each time, it takes about one week.

At this stage, 'rescue cells' are also collected and stored at the hospital. These are the patient's existing blood stem cells and are kept untreated just in case there is a problem in the treatment process.

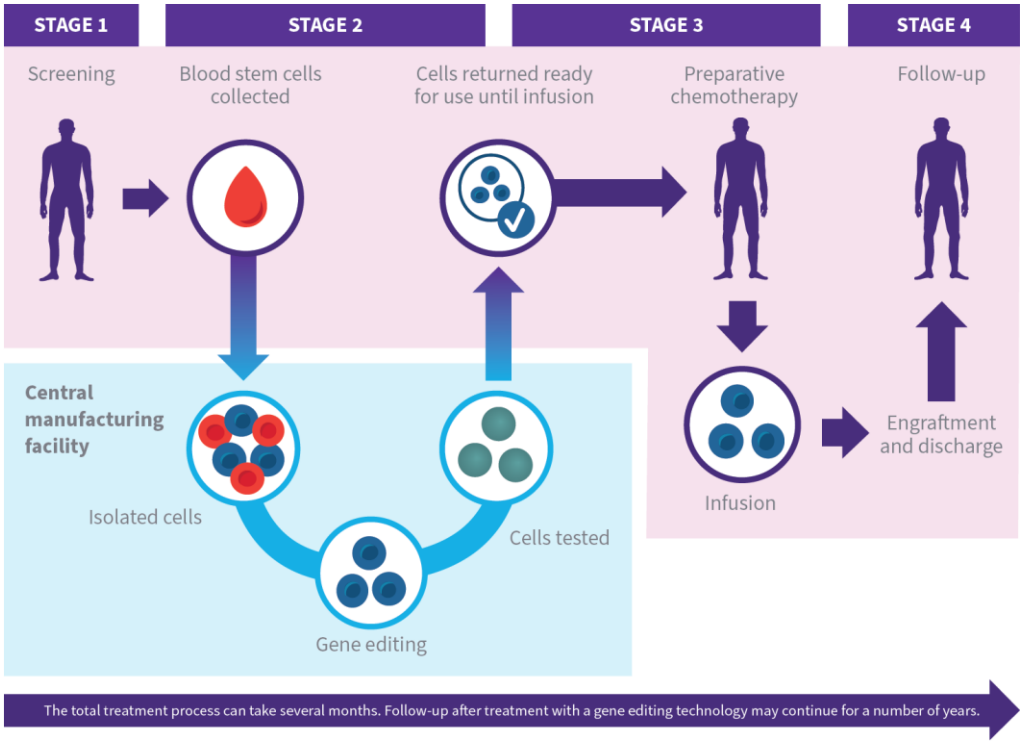
STAGE 2: After they are collected, the patient's blood stem cells will be sent to the manufacturing site where they are used to make exa-cel. It may take up to 6 months from the time the cells are collected to manufacture and test exa-cel before it is sent back to the patient's doctor.

STAGE 3: Shortly before the patient has their stem cell transplant, the doctor will give them a *conditioning* medicine into a vein (*intravenous infusion*) for a few days in hospital. This will prepare the patient for treatment by clearing cells from the bone marrow, so they can be replaced with the modified cells in exa-cel. After the patient is given this medicine, their blood cell levels will go very low. For this step the patient will need to stay in the hospital until after the exa-cel infusion.

STAGE 4: One or more vials of exa-cel will be given into a vein (*intravenous infusion)* over a short period of time.

After the exa-cel infusion, the patient will stay in hospital so that the healthcare team can closely monitor their recovery. This can take approximately 2 months, but times can vary. A doctor on the team will decide when the patient can go home.

The below picture shows all the steps needed for patients to receive treatment with exa-cel: (5, 6)



3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

CLIMB THAL-111 (previously known as CTX001-111) is an ongoing trial to assess the safety and efficacy of a single dose of exa-cel in patients aged 12-35 years with transfusion-dependent beta-thalassaemia. This study planned to dose approximately 45 patients with exa-cel and took place in 13 study centres across the USA, Canada, UK, Germany, and Italy.

This was an open-label, single-arm trial, meaning that both the patients and trial staff knew what treatment was being given, and all patients received exa-cel.

The treatment stages of the trial are described in 3c) above.

The ‘primary outcome’ of CLIMB THAL-111 was the number of patients who maintained average haemoglobin of at least 9 g/dL, without any further blood transfusions for at least 12 months in a

row any time after exa-cel infusion. This outcome was known as 'transfusion independence at 12 months' or 'TI12'.

CLIMB THAL-111 also measured how many cells showed the genetic edit made by the exa-cel process and whether this was kept up over time. The change in haemoglobin concentration and haemoglobin F concentration from the beginning of the trial ('baseline') was also measured.

Changes in patient-reported outcomes over time were also measured.

Each patient will be asked to take part in a long-term follow-up trial called CLIMB-131. This will continue to follow patients for up to 15 years after they received their exa-cel infusion.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Of the 48 patients with beta-thalassaemia who had received exa-cel by the time the trial data were analysed in September 2022, more than half (58.3%) had genotypes associated with severe disease, beta-zero/beta-zero or other beta-zero-like severe genotypes. At the time of the data cut, 27 beta-thalassaemia patients could be measured for the primary and key secondary endpoint.

- 24/27 (88.9%) achieved the primary endpoint of transfusion-independence for at least 12 consecutive months (TI12) and the secondary endpoint of transfusion-independence for at least 6 consecutive months (TI6) with a mean weighted haemoglobin of at least 9 g/dL. On average, patients were transfusion-independent for 20.5 months, and the longest single period of transfusion independence was 40.7 months.
    - Of the 3 patients who did not achieve transfusion independence, one patient has since stopped transfusions and has been transfusion-free for 2.9 months; the remaining 2 patients have had substantial reductions (80% and 96%) in transfusion volume from baseline.

- Increases in total haemoglobin occurred early within the first few months and were maintained over time. In the analysis of all patients who received exa-cel, average total haemoglobin was ≥11g/dL at Month 3 and ≥12g/dL from Month 6 onward with foetal haemoglobin present across all cells.

- The average number of genes showing the desired exa-cel edit was stable over time in bone marrow and peripheral blood, indicating successful permanent editing in the long-term blood cell-producing ('haematopoietic') stem cells.

- Patients also had clinically significant improvements in patient-reported outcomes.

https://crisprmedicinenews.com/press-release-service/card/positive-results-from-pivotal-trials-of-exa-cel-for-transfusion-dependent-beta-thalassemia-and-sever/

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

When considering the impact of beta-thalassaemia on patients' quality of life (QoL), it is important to consider the fact that generic tools, such as the EuroQol-5D, are not able to accurately reflect the disease burden for a number of reasons, including the fact that EuroQol-5D measures a patient's quality of life on a single day, rather than over time, so may not capture the challenges associated with transfusions, particularly tiredness (fatigue) and pain, if the survey is not completed on the appropriate day.

According to a patient survey that assessed validity of EuroQol-5D in beta-thalassaemia, key reported symptoms that occurred at least half of the time over the past 3 months were tiredness/fatigue, weakness, pain/discomfort, shortness of breath and tachycardia (fast heartbeat). Patients found the questions to not always be relevant and the descriptive system too simple because of how often their symptoms changed. Patients suggested that an improved survey would ask about their average experiences with beta-thalassaemia rather than on a single day (7).

In addition, given that beta-thalassaemia is a chronic condition that patients live with from birth, there is a response shift and ceiling effect seen with quality of life outcomes reported; that is, patients get used to their condition as the 'status quo' and so the differences between better days and worse days in their health are not properly picked up. This makes the quality of life for people with beta-thalassaemia to look at least as good as the general population, which is not accurate. This was clearly shown in the Zynteglo (betibeglogene autotemcel) appraisal [ID968] where the company reported that patients in their clinical trial were returning quality of life values at baseline nearing the population average for the UK, as measured by EuroQol-5D.

The humanistic impact on caregivers and families of patients with beta-thalassaemia is substantial. Parents and caregivers have to make considerable time sacrifices related to treatment schedules (including transportation and preparation for treatment) and care for individuals with beta-thalassaemia. In addition, parents of patients with beta thalassaemia often report feeling worried about their child's future and experience feelings of guilt and self-blame due to the hereditary nature of the condition. Caregivers of patients with TDT highlight increased frequency of depression and anxiety as main contributing factors to their reduced quality of life.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where

possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

All patients in the trial successfully 'engrafted' - made new white blood cells (known as 'neutrophils') and platelets - after receiving exa-cel.

The safety profile of exa-cel was similar to when busulfan is given as 'conditioning treatment' to remove blood cells from patients before they have a stem cell transplant. The most common side effects reported in the trial were: lower levels of white blood cells (sometimes with a fever - febrile neutropaenia), headache, inflammation of the stomach or spleen (stomatitis), lower levels of platelets (thrombocytopaenia), nausea, anaemia, increased heart rate or blood pressure, and inflammation or redness of the mouth lining (mucosal inflammation).

Two TDT patients had serious adverse events considered related to exa-cel. One patient had three serious adverse events considered related to exa-cel, and one serious adverse event of idiopathic pneumonia syndrome that was considered related to both exa-cel and busulfan. All four serious adverse events happened during the engraftment period and have resolved. One patient had SAEs of delayed neutrophil engraftment and thrombocytopenia, both of which were considered related to exa-cel and busulfan, and both serious adverse events have resolved.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Exa-cel can provide a one-time functional 'cure' to patients with beta-thalassaemia and create a disease-free state of being. Once a patient successfully engrafts new white cells and platelets, exa-cel is expected to continue to work for the rest of a patient's life as there is no known way in which the edited cells can become unedited.

As a result of the increased foetal haemoglobin levels and haemoglobin blood concentration following exa-cel infusion, patients will experience less anaemia and fatigue associated with low haemoglobin. Elimination of the need for regular blood transfusions means that patients do not need to organise their family, personal, social, educational and/or professional lives around regular hospital appointments, and can avoid the pain and anxiety associated with the transfusion procedure – much of which is not properly captured by standard quality of life assessments.

Freedom from regular blood transfusions also means that patients will be able to stop taking iron chelation medicines that are needed to remove excess iron from the transfused blood they receive; these medicines cause many side effects in their own right and patients find them unpleasant to take. The removal of the need to take this chronic medication can also save a lot of 'out of pocket' costs for patients who do not receive financial help with paying for their prescriptions.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Exa-cel treatment is given to patients by way of a stem cell transplant. As this is an intensive and lengthy treatment that puts great strain on the human body, it is only suitable for patients who are physically fit enough to withstand the procedure and safely recover. This means that some people with beta-thalassaemia will not be able to have the treatment.

If the mobilisation process does not collect enough stem cells from the blood at the first attempt, the patient may need to return to hospital for the procedure to be repeated.

The conditioning process that prepares a patient to receive exa-cel removes all stem cells from the body, which temporarily stops the patient's immune system from working. It is at this point that patients may experience a number of side effects because their temporary lack of an immune system means they are unable to fight off any infections or illnesses.
This procedure may also leave them patients unable to have children, so before they start treatment they will need to discuss potential options with a doctor. This could include storing eggs and/or sperm to use in the future.

The overall treatment process takes place over many months and involves a lot of travel between home and the treatment centre. Once the conditioning medicine is given to a patient they will need to stay in hospital until after they have recovered from the transplant. This can take around 2 months, so patients will miss out on their education or paid work during that time, and may feel lonely. Parents, guardians and/or other family members caring for the patient may also have to spend time and money travelling long distances to visit their loved one during this time.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Structure of the economic model

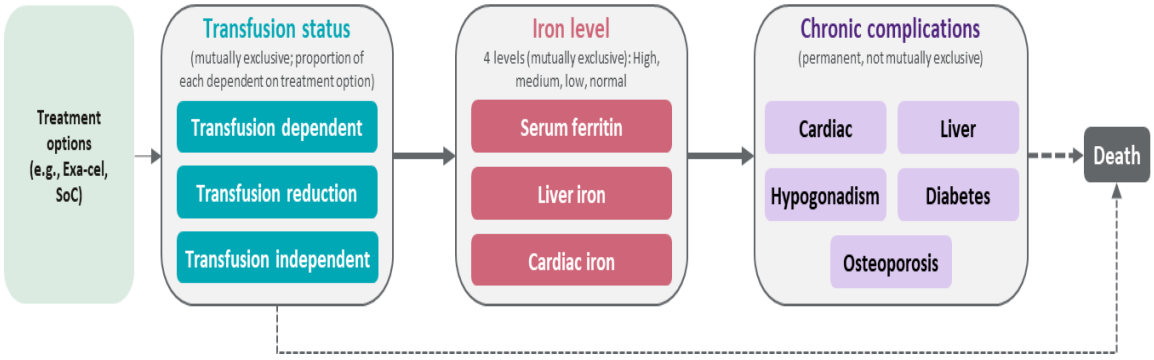
The economic model uses a 'Markov' structure, which shows the different ways in which a patient's health can change throughout the rest of their life based on the number of blood transfusions they need after having either exa-cel or other treatments for beta-thalassaemia.

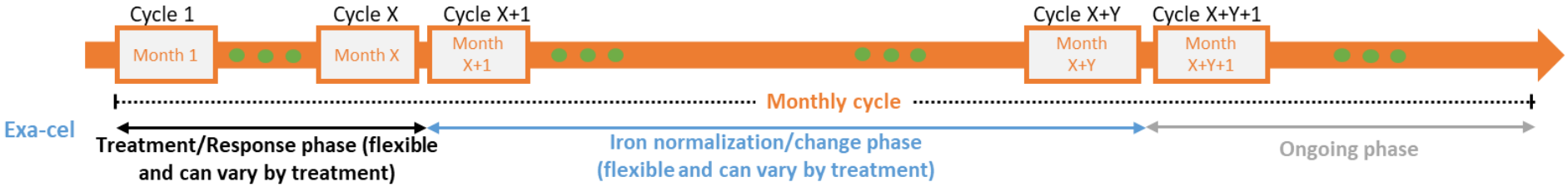
In the model, following treatment with either exa-cel or an alternative option, patients can either stop having transfusions (reflecting successful treatment) and go on to have normal iron levels; or they can reduce the number of transfusions needed (partially successful treatment) and go on to have medium iron levels, or they can continue to need regular transfusions (unsuccessful treatment) and have high iron levels. For each of these outcomes patients will have certain levels of iron in their blood . Afterwards, the model goes on to show different diseases and complications that any of the patients could develop – regardless of how they responded to their beta-thalassaemia treatment.

Overall, the model aims to show the natural history and outcomes that beta-thalassaemia patients experience in the real world.

Patients who successfully stop having transfusions after exa-cel treatment and stop taking iron chelation therapy are assumed to live as long as the general population, with a similar risk of developing serious long-term diseases.

The below diagrams show the model phases and how they are linked together:





Transfusion status	• TD	• TD, TR, or TI, based on treatment response and treatment waning effect	
Iron level	• Baseline level	• Based on transfusion status; change constantly over time or at the end of this phase	• Based on transfusion status
Phase specific procedures	•Mobilization, apheresis, and conditioning •Transfusion received by all patients •ICT received by all patients	• No transfusions for patients in TI, reduced transfusion received by patients in TR, and regular transfusion received by patients in TD •ICT received by all patients	•Regular transfusion received by patients in TD; reduced transfusion received by patients in TR; no transfusions for TI patients •Full dose ICT received by patients in TD and TR and not received by patients in TI
Phase specific events	•Treatment withdraw, engraftment failure, complications, and infertility	•Complications and infertility	
Factors that impact mortality	•Transfusion status, transplantation, complications, infertility, and age	•Transfusion status, transplantation, complications, infertility, and age	

Trial outcomes that feed into the economic model

The model uses the following outcomes from the clinical trial:

- Length of exa-cel treatment
- Age of patients at the start of treatment
- Number of transfusions per patient at the start of treatment
- Number of patients who stop taking exa-cel
- Number of patients who successfully make new blood cells after their stem cell transplant
- Response to exa-cel treatment – no further blood transfusions needed, fewer transfusions needed, or no change to number of transfusions needed
- Risk of death due to exa-cel treatment procedure
- Rate of serious side effects after exa-cel treatment

The starting patient age in the model is just over 21 years. The trial provided 12 months' worth of outcomes data and the model extrapolated this to estimate survival and quality of life over the course of a lifetime (79 further years, so that patients could remain in the model up until 100 years of age).

Other pieces of data used in the model came from published articles, previous NICE appraisals of beta-thalassaemia treatments, and assumptions from clinical experts in treating beta-thalassaemia.

As a replacement for blood transfusions and iron chelation therapy, exa-cel is expected to reduce the number of days patients need to attend hospital for the day to receive transfusions for their beta-thalassaemia. This means that more supplies of blood will be available to the health system, and more chair or bed spaces will be available for patients needing transfusions for other conditions.

Although the model does not 'reverse' any damage that patients have already developed from living with beta-thalassaemia, it is assumed that because exa-cel successfully treats this condition, patients will have similar risks to the general population of developing ageing-related illnesses; and therefore, a positive impact on the health service.

As the trial has been running for only a few years, the model uses the data collected to date, along with published data and expert opinion, to guess how long patients will be able to remain free of blood transfusions; whether the increased blood haemoglobin and haemoglobin F concentrations will be maintained; whether the engrafted white cells and platelets will be sustained; or if there could be any side effects associated with exa-cel in the future.

The long-term follow-up study (CLIMB-131) mentioned in section 3d) above will provide further information on these uncertainties in the future.

The modelled cost-effectiveness results included a number of features designed to more fully reflect that exa-cel is for treating beta-thalassaemia patients would otherwise die or have a very severely impaired life. These features are summarised below:

The lower discount rate of 1.5% on future costs and health effects

- This is to reflect that exa-cel is for beta-thalassaemia patients that would otherwise die or have a very severely impaired life. In a UK study looking at the burden of illness in beta-thalassaemia patients, their mortality rate (how often patients died) was more than five times that of the general population, and patients on average died at the age of 55 years. Patients with TDT not only have poor daily quality of life compared with the general population but are also at risk of developing severe complications over the course of their lifetime. These include heart-related (cardiac) and liver complications, as well as diabetes;

these illnesses not only make patients more sick than the general population but also bring a higher risk of death. Another study of UK TDT patients found that more than three-quarters had at least one co-morbidity (another illness alongside their beta-thalassaemia), more than half suffered from two of more, and over a third of patients suffered from three or more (8, 9).

- Beta-thalassaemia patients on current standard of care treatment have a limited life span and a high risk of co-morbidities affecting many organs in their body. They also have to manage the impact of regular transfusion and iron chelation, including tiredness, and pain (7).

- Exa-cel is likely to restore patients to full or near-full health. Patients treated with exa-cel will live longer, be less likely to have co-morbidities (both thalassaemia/anaemia-related and iron overload related) and they will no longer need transfusion or iron chelation, which are hugely burdensome treatments. They will have improved quality of life and reduced tiredness, pain, plus more time released, more likely to return to work.

- The benefits of exa-cel as a one-time gene editing therapy are expected to remain. Clinical opinion suggests that if the treatment effect is maintained at 2 years there is no reason to think that it would then decrease.

Severity modifier

In addition to the 1.5% discount rate, the economic model also includes a 'modifier' that considers two factors:

a) how many future years of living in good health (known as 'quality-adjusted life-years', commonly shortened to 'QALYs') beta-thalassaemia patients would lose with current standard treatments compared to someone who doesn't have beta-thalassaemia. **This is known as the 'absolute shortfall'.**

b) what proportion (this could be a percentage) of the patient's future quality-adjusted life-years are lost because they have beta-thalassaemia. **This is known as the 'proportional shortfall'.**

Improvements in fatigue may not be captured because the EuroQol-5D tool does not have a domain that asks patients about this. Also, because patients have likely got used to their condition (as they have lived with it since birth), they may report high baseline values and will have a 'ceiling effect' on the quality of life gain that makes it look much smaller than it actually is.

A large proportion of the beta-thalassaemia population eligible for exa-cel is children aged 12-17 years old. The standard analysis does not capture the benefits on education of reduced absence from school due to the need for regular transfusions and improved concentration while at school due to reduced tiredness. These are likely to have knock-on consequences for the future success and employment of adolescents with beta-thalassaemia.
Similarly, omission of carer utility from the reference case ignores the substantial burden of parents of adolescents and young adults with beta-thalassaemia, such as support with education and daily activities including attendance of healthcare services.

The base case does not capture any productivity benefits such as improved employment rates of adults. A survey of UK patients indicated significant challenges with employment including (10):

- Time off for transfusions and appointments;
- Fatigue felt before transfusions and treatment;
- Lack of awareness amongst employers and colleagues;
- Lack of flexible working hours;
- Uncertainty whether or not to disclosure to employers;
- Pain as a result of thalassaemia;
- Mobility issues

The model does not capture any benefit to the NHS of improving blood stocks and blood transfusion services due to the reduced need from exa-cel treated patients.

Finally, the model presents a new method called a 'Distributional Cost Effective Analysis'. This is a method that demonstrates how exa-cel treatment could potentially reduce existing inequality or unfairness in the distribution of health within the beta-thalassaemia population. As noted in the UK burden of illness study, people with beta-thalassaemia are overrepresented in the bottom 2 groups (out of 5) for social and economic deprivation.

The results of the economic analysis are confidential, but are discussed in sections A.12 and B3.11 of the main submission.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Exa-cel is the first medicine in the world to be made using the Nobel Prize-winning CRISPR/Cas-9 technology that acts as a kind of 'genetic scissors' to accurately edit genes at the exact desired location. It offers a one-time treatment that allows patients with beta-thalassaemia to achieve a disease-free state by treating the underlying cause of the disease. By removing the need for blood transfusions and iron chelation therapy, exa-cel is expected to reduce the number of new illnesses that these treatments often cause. This means that patients will not need to regularly attend medical appointments

AS discussed in section 3f) above, exa-cel brings patients many QALY benefits that cannot be captured in the economic model but are important to be considered.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Data published by the National Haemoglobinopathy Registry (NHR) in 2021 indicates that almost half of beta-thalassaemia patients in the UK are of Pakistani and South Asian ethnicity. The UK burden of illness study found that just over half of beta-thalassaemia patients were South Asian (9); and the UK Thalassaemia Society estimates that 79% of babies born with beta-thalassaemia in the UK each year are born to Asian parents from India, Pakistan and Bangladesh (11, 12).

In addition, there is a shortage of ethnically matched blood stocks available to treat patients of ethnic-minority heritage and ensure optimal treatment outcomes. This is important as mismatched blood can be rejected by the patient's immune system and cause severe illness.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on the exa-cel clinical data and the methods used in the economic analysis: https://crisprmedicinenews.com/press-release-service/card/positive-results-from-pivotal-trials-of-exa-cel-for-transfusion-dependent-beta-thalassemia-and-sever/

https://www.rff.org/publications/explainers/discounting-101/#:~:text=Discounting%20is%20the%20process%20of,discounting%20measures%20this%20relative%20value.

https://mtechaccess.co.uk/nice-hta-decision-modifier/

https://pubmed.ncbi.nlm.nih.gov/25908564/

https://www.york.ac.uk/che/research/equity/economic_evaluation/

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/

- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Allogeneic stem cell transplant – a form of treatment in which a patient receives stem cells from a healthy human donor.
Allograft – see *allogeneic* above.
Apheresis – a machine-led process that separates out the different blood stem cells
Autologous stem cell transplant – a form of treatment in which a patient's own stem cells are removed from their blood and treated before being infused back into the patient.
Autograft – see *autologous* above.
Co-morbidity – any illness that affects patients alongside their beta-thalassaemia.
Conditioning – see *myeloablation* below.
Engraftment – the process in which stem cells given to a patient in a transplant take hold into the bone marrow and start to make new blood cells.
Erythrocyte – a red blood cell.
EuroQol-5 Dimension – a survey that asks patients to mark how they are – generic, preference-based measure of HRQoL in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
Haematopoietic – the process of creating blood cells.
Haemoglobin – a protein in red blood cells that carries oxygen round the body and gives red cells their colour.
Mobilisation –
Myeloablation – a method of decreasing bone marrow activity. Also known as *myeloablative conditioning.*
Neutrophil – a kind of white blood cell.
Platelet – a small type of cell that helps the body to form clots to stop bleeding.
Red blood cell – a type of blood cell that is made in bone marrow and found in the blood. Red cells contain a protein called haemoglobin, which carries oxygen from the lungs to all parts of the body. Red cells are also known as *erythrocytes.*
White blood cell – a type of cell found in the blood that helps the body to fight off infections and illnesses.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis. 2010;5:11.
2. Biffi A. Gene Therapy as a Curative Option for β-Thalassemia. N Engl J Med. 2018;378:1551-2.
3. Public Health England. Sickle cell and thalassaemia (SCT) screening: programme overview. 2013.

4. Li N, Drahos J, Boateng-Kuffour A, Calvert M, Levine L, Dongha N, et al., editors. Health-Related Quality of Life and Disease Impacts in Adults With Transfusion-Dependent β-Thalassemia - Preliminary Results From the Global Longitudinal Survey. ASH; 2022; New Orleans, LA.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Clarification questions

[July 2023]

File name	Version	Contains confidential information	Date
ID4015_exa-cel_TDT_clarification_response [CON]	1.0	Yes	03/08/2023

Section A: Clarification on effectiveness data

Exa-cel

A1. Priority Question: Please provide the following details about the exa-cel manufacturing process:

- **What was the mean time (or typical times) between stem cell collection and exa-cel infusion?**
- **How many manufacturing facilities currently exist and in which countries are they located?**
- **In the CLIMB THAL-111 trial was exa-cel delivered as it would be in real-world practice? i.e from a thawed frozen product, or was it delivered as a fresh product? If the latter, please present any data which demonstrate that the frozen product is as efficacious as the fresh product.**

Company response

- Typically, it will take 5-6 months from the cell cycle collection to patients being infused exa-cel. Some patients may require more than 1 round of apheresis, which must be spaced apart by several weeks.
- [redacted] One site in the UK (Roslin, Scotland) is approved for clinical use and awaiting approval for commercial use. A second site in the US (Tennessee, Charles River Labs) is approved for clinical use and awaiting approval for commercial use.
- Exa-cel was delivered as it would be in real-world practice. Exa-cel vial(s) were stored at the site in the frozen state at a temperature of ≤ -135°C until just before the scheduled infusion. Exa-cel vial(s) were thawed as per local site standard operating procedures and infused within 20 minutes of thaw.

Systematic review

A2. Priority Question: It is stated in the appendix that the full reference list of excluded studies of the systematic review will be provided at clarification stage. Please provide this list, with reasons for exclusion for each study.

Company response

The full list of excluded studies at data extraction from the clinical SLR can be found in Table 1.

Table 1: List of excluded studies at data extraction

Lead author, year	Title	Reason for exclusion
Original SLR		
Alpendurada, 2012	Effects of combined deferiprone with deferoxamine on right ventricular function in thalassaemia major	Population out of scope
Bartlett, 1990	Long-term trial with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1). II. Clinical observations	Population out of scope
La Nasa, 2005	Unrelated donor stem cell transplantation in adult patients with thalassemia	Population out of scope
Ladis, 2010	Deferasirox administration for the treatment of non-transfusional iron overload in patients with thalassaemia intermedia	Population out of scope
Miyazawa, 2008	A safety, pharmacokinetic and pharmacodynamic investigation of deferasirox (Exjade, ICL670) in patients with transfusion-dependent anemias and iron-overload: a Phase I study in Japan	Population out of scope
Pisciotto, 1986	Clinical trial of young red blood cells prepared by apheresis	Population out of scope
Pootrakul, 2004	Labile plasma iron (LPI) as an indicator of chelatable plasma redox activity in iron-overloaded beta-thalassemia/HbE patients treated with an oral chelator	Population out of scope
Pootrakul, 2003	Clinical trial of deferiprone iron chelation therapy in beta-thalassaemia/haemoglobin E patients in Thailand	Population out of scope
Chuansumrit, 2016.	Safety profile of a liquid formulation of deferiprone in young children with transfusion-induced iron overload: a 1-year experience	Population out of scope
Isgro, 2010	Immunohematologic reconstitution in pediatric patients after T cell-depleted HLA-haploidentical stem cell transplantation for thalassemia	Population out of scope
Kaur, 2022	Efficacy of packed red blood cell transfusions based on weight versus formula in thalassemic children: An open-label randomized control trial	Population out of scope
Saleh, 2016	A randomized trial on the safety and efficacy of early start of iron chelation therapy with deferiprone in newly diagnosed children with transfusion dependent thalassemia	Population out of scope

Torcharus, 1993	High transfusion in children with beta-thalassemia/Hb E: clinical and laboratory assessment of 18 cases	Population out of scope
al-Refaie, 1992	Efficacy and possible adverse effects of the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1) in thalassemia major	Intervention out of scope
Bernardo, 2008	Treosulfan-based conditioning regimen for allogeneic haematopoietic stem cell transplantation in patients with thalassaemia major	Intervention out of scope
Bourantas,1997.	Administration of high doses of recombinant human erythropoietin to patients with beta-thalassemia intermedia: a preliminary trial	Intervention out of scope
Boutouyrie-Dumont, 2013	The safety, tolerability, pharmacokinetics and pharmacodynamics of FBS0701, an iron chelator in development, in phase I studies of healthy volunteers and patients with transfusional iron overload	Intervention out of scope
Cohen, 1984	Clinical trial of young red cell transfusions	Intervention out of scope
Dore, 1996	Serum transferrin receptor levels in patients with thalassemia intermedia during rHuEPO administration	Intervention out of scope
Elalfy,2014.	Role of vitamin C as an adjuvant therapy with different iron chelators in young beta-thalassemia major patients: Safety and efficacy in relation to tissue iron overload	Intervention out of scope
Goldberg, 2011	The palatability and tolerability of deferasirox taken with different liquids or food	Intervention out of scope
Smith,2019.	Preliminary results of a phase 1/2 clinical study of zinc finger nuclease-mediated editing of BCl11a in autologous hematopoietic stem cells for transfusion-dependent beta thalassemia	Intervention out of scope
Ashayeri, 2016	Efficacy of deferasirox (Exjade) versus osveral in treatment of iron overload in patients with beta-thalassemia major in Iran; a non-randomized controlled trial	Intervention out of scope
Adhikari, 1995	Efficacy and safety of oral iron chelating agent deferiprone in beta-thalassemia and hemoglobin E-beta thalassemia	Outcome out of scope
Alpendurada, 2010	Effect of myocardial iron removal on right ventricular function: Insights from a randomized, placebo controlled, double-blind trial in thalassemia major	Outcome out of scope
Aycicek, 2014	Efficacy of deferasirox in children with beta-thalassemia: single-center 3 year experience	Outcome out of scope
Benso, 1995	Growth velocity monitoring of the efficacy of different therapeutic protocols in a group of thalassaemic children	Outcome out of scope
Bertaina, 2017.	The use of BPX-501 donor T cell infusion (with inducible caspase 9 suicide gene) together with HLA-haploidentical stem cell transplant to treat children with hemoglobinopathies and erythroid disorders	Outcome out of scope
Borgna-Pignatti, 1997	Evaluation of a new method of administration of the iron chelating agent deferoxamine	Outcome out of scope
Calvaruso, 2015	Deferiprone versus deferoxamine in thalassemia intermedia: Results from a 5-year long-term Italian multicenter randomized clinical trial	Outcome out of scope

Cavazzana, 2014	Outcomes of gene therapy for beta-thalassemia major via transplantation of autologous hematopoietic stem cells transduced ex vivo with a lentiviral beta globin vector	Outcome out of scope
Chirnomas, 2009	Deferasirox pharmacokinetics in patients with adequate versus inadequate response	Outcome out of scope
Chuansumrit, 2016	Correlation between liver iron concentration determined by magnetic resonance imaging and serum ferritin in adolescents with thalassaemia disease	Outcome out of scope
Cianciulli, 1994.	Early detection of nephrotoxic effects in thalassemic patients receiving desferrioxamine therapy	Outcome out of scope
Das, 2017	Evaluation of renal function with technetium-99m diethylene-Triamine-pentaacetate acid scintigraphy in patients with beta-Thalassemia	Outcome out of scope
Eshghi, 2011	Efficacy and safety of Iranian made Deferasirox (Osveral)in Iranian major thalassemic patients with transfusional iron overload: A one year prospective multicentric open-label non-comparative study	Outcome out of scope
Flynn, 1973	Proceedings: 5-year controlled trial of chelating agents in treatment of thalassaemia major	Outcome out of scope
Galanello, 2005	Evaluation of ICL670, a once-daily oral iron chelator in a phase III clinical trial of beta-thalassemia patients with transfusional iron overload	Outcome out of scope
Galaverna, 2019.	Alpha/beta T-cell depleted Haploidentical HSCT followed by infusion of donor lymphocytes transduced with inducible caspase9 gene is safe and effective for patients with erythroid disorders	Outcome out of scope
Galia, 2003	Potential myocardial iron content evaluation by magnetic resonance imaging in thalassemia major patients treated with Deferoxamine or Deferiprone during a randomized multicenter prospective clinical study	Outcome out of scope
Gaziev, 1999	Second marrow transplants for graft failure in patients with thalassemia	Outcome out of scope
Gaziev, 2016	Optimal Outcomes in Young Class 3 Patients With Thalassemia Undergoing HLA-Identical Sibling Bone Marrow Transplantation	Outcome out of scope
Hashmi, 2004.	Allogeneic bone marrow transplantation in beta-thalassaemia--single centre study	Outcome out of scope
Huang, 2016	Psychometric evaluation of clinical outcomes assessments in a phase II trial	Outcome out of scope
Hussain, 1998	Subcutaneous infusion and intramuscular injection of desferrioxamine in patients with transfusional iron overload	Outcome out of scope
Kulozik, 2021.	Interim results of betibeglogene autotemcel gene-additiontherapy in pediatric patients with transfusion-dependent beta-thalassemia (TDT) treated in the Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies	Outcome out of scope
Lefrere, 1989	Risk of HIV infection in polytransfused thalassaemia patients	Outcome out of scope
Li, 2000	Early iron reduction programme for thalassaemia patients after bone marrow transplantation	Outcome out of scope

Lin, 2019	Therapeutic mechanism of combined oral chelation therapy to maximize efficacy of iron removal in transfusion-dependent thalassemia major - a pilot study	Outcome out of scope
Lucas, 2000	A trial of deferiprone in transfusion-dependent iron overloaded children	Outcome out of scope
Maggio, 2020	Evaluation of the efficacy and safety of deferiprone compared with deferasirox in paediatric patients with transfusion-dependent haemoglobinopathies (DEEP-2): a multicentre, randomised, open-label, non-inferiority, phase 3 trial	Outcome out of scope
Matsui, 1994.	Critical comparison of novel and existing methods of compliance assessment during a clinical trial of an oral iron chelator	Outcome out of scope
Modell, 1982	Survival and desferrioxamine in thalassaemia major	Outcome out of scope
Olivieri, 1993.	Oral iron chelation with 1,2-dimethyl-3-hydroxypyrid-4-one (L1) in iron loaded thalassemia patients	Outcome out of scope
Olivieri, 1990.	Evaluation of the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1) in iron-loaded patients	Outcome out of scope
Oved, 2018	Outcomes of unrelated donor peripheral stem cell transplantation for patients with non-malignant hematologic disorders using two partial t cell depletion strategies	Outcome out of scope
Pennell, 2010.	Continued improvement and normalization of myocardial T2*In patients with beta-thalassemia major treated with deferasirox (Exjade) for up to 3 years	Outcome out of scope
Platis, 2004	Glucose metabolism disorders improvement in patients with thalassaemia major after 24-36 months of intensive chelation therapy	Outcome out of scope
Pongtanakul, 2012	Twice daily dosing of deferasirox significantly improves clinical efficacy in transfusion dependent thalassemias who were inadequate responders to standard once daily dose	Outcome out of scope
Pope, 1997	Salivary measurement of deferiprone concentrations and correlation with serum levels	Outcome out of scope
Porter, 2009	Assessment of safety in patients receiving longer-term iron chelation therapy with deferasirox who had achieved serum ferritin levels of <1000 ng/mL during the study course	Outcome out of scope
Rienhoff, 2011	A phase 1 dose-escalation study: Safety, tolerability, and pharmacokinetics of FBS0701, a novel oral iron chelator for the treatment of transfusional iron overload	Outcome out of scope
Santamaria, 1994	The effect of transfusion on pulmonary function in patients with thalassemia major	Outcome out of scope
Sebastian, 2020	PIH17 Efficacy, Tolerability And Medication Adherence Of Twice-Daily Dosing Schedule Of Deferasirox In Transfusion-Dependent Paediatric Beta-Thalassemia Patients: A Randomized Controlled Study	Outcome out of scope
Seif El Dien, 2013	Deferoxamine-induced dysplasia-like skeletal abnormalities at radiography and MRI	Outcome out of scope

Shenoy, 2018.	Unrelated Donor Transplantation in Children with Thalassemia using Reduced-Intensity Conditioning: The URTH Trial	Outcome out of scope
Song, 2014	Combined versus monotherapy or concurrent therapy for treatment of thalassaemia	Outcome out of scope
Taher, 2017	New film-coated tablet formulation of deferasirox is well tolerated in patients with thalassemia or MDS: Results of the randomized, phase II eclipse study	Outcome out of scope
Taher, 2017	Improved patient-reported outcomes with a film-coated versus dispersible tablet formulation of deferasirox: Results from the randomized, phase II eclipse study	Outcome out of scope
Taher, 2017	Predicting serum ferritin levels in patients with iron overload treated with the film-coated tablet of deferasirox during the eclipse study	Outcome out of scope
Taher, 2017.	New film-coated tablet formulation of deferasirox is well tolerated in patients with thalassemia or lower-risk MDS: Results of the randomized, phase II ECLIPSE study	Outcome out of scope
Taher, 2017	Mediation by patient-reported outcomes on the association between film-coated versus dispersible formulations of deferasirox and serum ferritin reduction: A post hoc analysis of the eclipse trial	Outcome out of scope
Taher, 2018.	Mediation by patient-reported outcomes of the association between filmcoated or dispersible formulations of deferasirox and serum ferritin reduction: A post hoc analysis of the eclipse trial	Outcome out of scope
Taher, 2016	New film-coated tablet formulation of deferasirox is well tolerated in patients with thalassemia or MDS: Results of the randomized, phase II E.C.L.I.P.S.E. study	Outcome out of scope
Taher, 2016.	Improved patient-reported outcomes with a film-coated versus dispersible tablet formulation of deferasirox: Results from the randomized, phase II E.C.L.I.P.S.E. study	Outcome out of scope
Taher, 2017	New film-coated tablet formulation of deferasirox is well tolerated in patients with thalassemia or myelodysplastic syndromes: results of the randomized, phase ii eclipse study	Outcome out of scope
Taher, 2017	Improved patient-reported outcomes with a film-coated versus dispersible tablet formulation of deferasirox: Results from the randomized, phase II eclipse study	Outcome out of scope
Taher, 2018	Patient-reported outcomes from a randomized phase II study of the deferasirox film-coated tablet in patients with transfusion-dependent anemias	Outcome out of scope
Tamaddoni, 2010	Comparison between deferoxamine and combined therapy with deferoxamine and deferiprone in Iron overloaded thalassemia patients	Outcome out of scope
Tan, 1993.	A prospective study on the use of leucocyte-filters in reducing blood transfusion reactions in multi-transfused thalassemic children	Outcome out of scope
Unal, 2009.	Deferasirox monotherapy maintains the good cardiac iron status in thalassemic patients	Outcome out of scope

Viprakasit, 2018	An open-label, multicenter, single-arm, phase ii study assessing patient preference for the deferasirox film-coated tablet compared to the reference dispersible tablet formulation: The jupiter study	Outcome out of scope
Vitrano, 2014	Deferiprone versus deferoxamine in thalassemia intermedia: Results from 5-year long-term italian multi-center randomized clinical trial	Outcome out of scope
Vlachaki, 2007	Peripheral blood haematopoietic progenitor cells in patients with beta thalassaemia major receiving desferrioxamine or deferiprone as chelation therapy	Outcome out of scope
Wali, 2004	Study of intermittent intravenous deferrioxamine high-dose therapy in heavily iron-loaded children with beta-thalassemia major poorly compliant to subcutaneous injections	Outcome out of scope
Walters, 2017	A phase 3 study to evaluate safety and efficacy of lentiglobin gene therapy for transfusion-dependent beta-thalassemia in patients with non-beta0/beta0 genotypes: The northstar-2 (HGB-207) trial	Outcome out of scope
Walters, 2021	Updated Results of a Phase 1/2 Clinical Study of Zinc Finger Nuclease-Mediated Editing of BCL11A in Autologous Hematopoietic Stem Cells for Transfusion-Dependent Beta Thalassemia	Outcome out of scope
Wang, 2006	Comparison of oral and subcutaneous iron chelation therapies in the prevention of major endocrinopathies in beta-thalassemia major patients	Outcome out of scope
Yesilipek, 2015.	Safety and efficacy of deferasirox in beta-thalassemia major patients after hematopoietic stem cell transplantation: Baseline data of a phase II, multi-center, single-arm, prospective study	Outcome out of scope
Harmatz, 2007	Phase Ib clinical trial of starch-conjugated deferoxamine (40SD02): a novel long-acting iron chelator	Outcome out of scope
Keikhaei, 2011	Combined and alternative iron chelator drugs in treatment of thalassemia major	Outcome out of scope
Lal, 2009.	Safety of combined chelation therapy with deferasirox and deferoxamine in transfusion-dependent thalassemia	Outcome out of scope
Piga, 2015.	Luspatercept (ACE-536) increases hemoglobin and decreases transfusion burden and liver iron concentration in adults with beta-thalassemia: Preliminary results from a phase 2 study	Outcome out of scope
Brittenham, 1994.	Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major	Study design out of scope (SLR, MA/NMA, Case report)
Cakan, 2021	Erythrocyte transfusion restored heart rate variability in children with thalassemia major	Study design out of scope (SLR, MA/NMA, Case report)
Cancado, 2009.	Efficacy and safety of deferasirox (EXJADE) in patients with transfusion- dependent anemias:	Study design out of scope (SLR,

	Preliminary results from the first, retrospective, Multicenter Brazilian Study	MA/NMA, Case report)
Cassinerio, 2012	Cardiac iron removal and functional cardiac improvement by different iron chelation regimens in thalassemia major patients	Study design out of scope (SLR, MA/NMA, Case report)
Chang, 1945	The long-term efficacy and tolerability of oral deferasirox for patients with transfusion-dependent beta-thalassemia in Taiwan	Study design out of scope (SLR, MA/NMA, Case report)
Cheung, 2008	Effect of deferasirox (ICL670) on arterial function in patients with beta-thalassaemia major	Study design out of scope (SLR, MA/NMA, Case report)
Christoforidis, 2007	Four-year evaluation of myocardial and liver iron assessed prospectively with serial MRI scans in young patients with beta-thalassaemia major: comparison between different chelation regimens	Study design out of scope (SLR, MA/NMA, Case report)
Elalf6, 2016	Impact of age and type of underlying disease on long-term safety and efficacy in patients with transfusional hemosiderosis treated with deferasirox: Results from a 3-year non-interventional study (SENTINEL)	Study design out of scope (SLR, MA/NMA, Case report)
Farmaki, 2010	Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major	Study design out of scope (SLR, MA/NMA, Case report)
Farmaki, 2011	Oral chelators in transfusion-dependent thalassemia major patients may prevent or reverse iron overload complications	Study design out of scope (SLR, MA/NMA, Case report)
Fassos, 1994.	Urinary iron excretion depends on the mode of administration of the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one in patients with homozygous beta-thalessemia	Study design out of scope (SLR, MA/NMA, Case report)
Garadah, 2011	The impact of two different doses of chelating therapy (deferasirox) on echocardiographic tissue Doppler indices in patients with thalassemia major	Study design out of scope (SLR, MA/NMA, Case report)
Ghavamzadeh, 2017	Outcomes of co-transplantation of mesenchymal stem cells and hematopoietic stem cells compared to hematopoietic stem cell transplantation alone in -thalassemia patients	Study design out of scope (SLR, MA/NMA, Case report)
Graziano, 1978.	Chelation therapy in beta-thalassemia major. I. Intravenous and subcutaneous deferoxamine	Study design out of scope

		(SLR, MA/NMA, Case report)
Hussein, 2013	Risk adopted allogeneic hematopoietic stem cell transplantation using a reduced intensity regimen for children with thalassemia major	Study design out of scope (SLR, MA/NMA, Case report)
Jaing, 2007	Transplantation of unrelated donor umbilical cord blood utilizing double-unit grafts for five teenagers with transfusion-dependent thalassemia	Study design out of scope (SLR, MA/NMA, Case report)
Karakas, 2016	Cardiac and hepatic iron assessment by MR imaging in patients with beta thalassemia: Single center experience	Study design out of scope (SLR, MA/NMA, Case report)
Karimi, 2015	Efficacy of Deferasirox (Exjade) in Modulation of Iron Overload in Patients with beta-Thalassemia Intermedia	Study design out of scope (SLR, MA/NMA, Case report)
Klaihmon, 2017	Normalized levels of red blood cells expressing phosphatidylserine, their microparticles, and activated platelets in young patients with beta-thalassemia following bone marrow transplantation	Study design out of scope (SLR, MA/NMA, Case report)
Kolnagou, 2011	Efficacy, compliance and toxicity factors are affecting the rate of normalization of body iron stores in thalassemia patients using the deferiprone and deferoxamine combination therapy	Study design out of scope (SLR, MA/NMA, Case report)
Kwiatkowski, 2020.	Long-term efficacy and safety of betibeglogene autotemcel gene therapy for the treatment of transfusion-dependent beta-thalassemia: Results in patients with up to 6 years of follow-up	Study design out of scope (SLR, MA/NMA, Case report)
Magri, 2008	Early impairment of myocardial function in young patients with beta-thalassemia major	Study design out of scope (SLR, MA/NMA, Case report)
Miniero, 1998.	Cord blood transplantation (CBT) in hemoglobinopathies. Eurocord	Study design out of scope (SLR, MA/NMA, Case report)
Pepe, 2006	Evaluation of the efficacy of oral deferiprone in beta-thalassemia major by multislice multiecho T2*	Study design out of scope (SLR, MA/NMA, Case report)

Scaramellini, 2020	A holistic approach to iron chelation therapy in transfusion-dependent thalassemia patients with serum ferritin below 500 mug/L	Study design out of scope (SLR, MA/NMA, Case report)
Smith, 2011	Effect of deferiprone or deferoxamine on right ventricular function in thalassemia major patients with myocardial iron overload	Study design out of scope (SLR, MA/NMA, Case report)
Sodani, 2009	Purified T-depleted, CD34+ peripheral blood and bone marrow cell transplantation from haploidentical mother to child with thalassemia	Study design out of scope (SLR, MA/NMA, Case report)
Totadri, 2015	The deferiprone and deferasirox combination is efficacious in iron overloaded patients with beta-thalassemia major: A prospective, single center, open-label study	Study design out of scope (SLR, MA/NMA, Case report)
Uaprasert, 2017	Vascular and hemostatic alterations associated with pulmonary hypertension in beta-thalassemia hemoglobin e patients receiving regular transfusion and iron chelation	Study design out of scope (SLR, MA/NMA, Case report)
Wankanit, 2018	Acute Effects of Blood Transfusion on Insulin Sensitivity and Pancreatic beta-Cell Function in Children with beta-Thalassemia/Hemoglobin E Disease	Study design out of scope (SLR, MA/NMA, Case report)
Agarwal, 1991	Efficacy and safety of 1-2, dimethyl-3-hydroxypyrid-4-one (L1) as an oral iron chelator in patients of beta thalassaemia major with iron overload	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Athanassiou-Metaxa, 2004	Combined chelation therapy with deferiprone and desferrioxamine in iron overloaded beta-thalassemia patients	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Borgna-Pignatti, 1989.	Survival in thalassemia with conventional treatment	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)

Duca, 2018	Non-transferrin-bound iron and oxidative stress during allogeneic hemopoietic stem cell transplantation in patients with or without iron overload	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Kilinc, 1994	Echocardiographic findings in thalassemia major	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Maggio, 2012	Long-term use of deferiprone significantly enhances left-ventricular ejection function in thalassemia major patients	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Martin, 2006	Deferasirox versus deferoxamine [6]	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Pati, 1999	Deferiprone (L1) associated neutropenia in beta thalassemia major: an Indian experience	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Peng, 2006	Report on the proceedings of the 15th International Conference on Oral Chelation (ICOC) in the treatment of thalassemia and other diseases at Taichung, Taiwan, April 22-26, 2005	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Pongtanakul, 2013	Twice daily deferasirox significantly improves clinical efficacy in transfusion dependent thalassaemias who were inadequate responders to standard once daily dose	Publication type out of scope (Narrative reviews, editorials,

		letters, notes, commentaries)
Rego, 1998.	Dose-dependent pulmonary syndrome in patients with thalassemia major receiving intravenous deferoxamine [2]	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Salehifar, 2017	Efficacy of oral deferasirox by twice-daily dosing in patients with transfusion-dependent beta-thalassaemia	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Taher, 2019.	Influence of patient-reported outcomes on the treatment effect of deferasirox film-coated and dispersible tablet formulations in the ECLIPSE trial: A post hoc mediation analysis	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Taher, 2019.	Predicting serum ferritin levels in patients with iron overload treated with the film-coated tablet of deferasirox during the ECLIPSE study	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Vitrano, 2019	Long-term sequential deferiprone and deferasirox therapy in transfusion-dependent thalassaemia patients: a prospective clinical trial	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Voskaridou, 2010	Treatment with deferasirox (Exjade) effectively decreases iron burden in patients with thalassaemia intermedia: results of a pilot study	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Voskaridou, 2011	Deferasirox effectively decreases iron burden in patients with double heterozygous HbS/beta-thalassemia	Publication type out of scope (Narrative

		reviews, editorials, letters, notes, commentaries)
Cavazzana, 2014.	Outcomes of gene therapy for s thalassemia major via transplantation of autologous hematopoietic stem cells transduced ex vivo with a lentiviral sa T87Q globin vector	Study design out of scope (SLR, MA/NMA, Case report)
Yesilipek, 2016	A phase 2, multicenter, single-arm study to evaluate safety and efficacy of deferasirox after hematopoietic stem cell transplantation in children with beta-thalassemia major	Study design out of scope (SLR, MA/NMA, Case report)
Clinical SLR update		
Koctekin, 2023	Optical coherence tomography angiography findings in transfusion-dependent beta-thalassemia patients with and without splenectomy	Outcome out of scope
Shastry, 2023	Role of Thromboelastogram in monitoring the activation of the coagulation pathway and assessing the associated risk factors for hypercoagulable state in transfusion dependent thalassemia patients	Study design out of scope
Sanpakit, 2023	Outcomes of Hematopoietic Stem Cell Transplantation in Pediatric Patients with Transfusion-Dependent Thalassemia in Thailand	Study design out of scope
Chapchap, 2023	Cardiac iron overload evaluation in thalassaemic patients using T2* magnetic resonance imaging following chelation therapy: a multicentre cross-sectional study	Population out of scope
Meena, 2023	Study of growth differentiation factor-15 in polytransfused children with β-thalassemia	Outcome out of scope
Koçtekin, 2023	Evaluation of Color Discrimination Ability in Patients with Transfusion Dependent Beta Thalassemia by Farnsworth Munsell 100 Hue Test	Outcome out of scope
Ansari, 2022	Evaluation of the combination therapy of hydroxyurea and thalidomide in β-thalassemia	Population out of scope
Narula, 2022	Prospective case control studyon prevalence of anxiety disorders in chronically transfused thalassemia patients of age group 8-18 years and their parents	Outcome out of scope
Darvishi, 2022	Amlodipine: Can act as an antioxidant in patients with transfusion-dependent β-thalassemia? A double-blind, controlled, crossover trial	Outcome out of scope
Handattu, 2022	Metabolic bone disease in children with transfusion-dependent thalassemia	Outcome out of scope
Agrawal, 2022	Optimum dose of oral folic acid supplementation in transfusion-dependent thalassemia: a randomized controlled trial	Outcome out of scope
Pramanik, 2022	Safety and efficacy of lenalidomide in patients with transfusion dependent E-beta thalassemia refractory to hydroxyurea	Outcome out of scope
Parakh, 2022	COVID-19 pandemic and care of transfusion-dependent patients of thalassaemia: Experience from a paediatric centre in North India	Population out of scope

Teawtrakul, 2022	Red blood cell alloimmunization and other transfusion-related complications in patients with transfusion-dependent thalassemia: A multi-center study in Thailand	Study design out of scope
AlHousni, 2022	Adrenal dysfunction in Omani children live with transfusion dependent beta-thalassemia: a routine assessment is recommended	Population out of scope
Padeniya, 2022	Frequency of hereditary hemochromatosis gene (Hfe) variants in Sri Lankan transfusion-dependent beta-thalassemia patients and their association with the serum ferritin level	Study design out of scope
Pepe, 2022	National networking in rare diseases and reduction of cardiac burden in thalassemia major	Study design out of scope
Gupta, 2022	Comparison of the effects of calcium channel blockers plus iron chelation therapy versus chelation therapy only on iron overload in children and young adults with transfusion-dependent thalassemia: A randomized double-blind placebo-controlled trial	Population out of scope
Jamalpoor, 2022	Effect of narration and painting methods on the self-concept of children with thalassemia major before and three months after intervention: a randomised clinical trial	Outcome out of scope
Song, 2022	Quality of life in children with beta-thalassemia major: a cross-sectional study in China	Outcome out of scope
Delaporta, 2022	Real-world data on the use of luspatercept in greek patients with transfusion dependent thalassemia	Study design out of scope
Meloni, 2022	Heart failure in thalassemia major: time for new cardiovascular magnetic resonance markers?	Outcome out of scope
Tricta, 2022	Early-start deferiprone in infants/young children with transfusion-dependent beta thalassemia: evidence for iron shuttling to transferrin-randomized, double-blind, placebo-controlled trial (START)	Population out of scope
Kattamis, 2022	Real-world complication burden and disease management in transfusion-dependent adults with beta-thalassemia (β-thal) in Greece: final results of the epidemiological cross-sectional Ulysses study	Study design out of scope
Silwal, 2022	Evaluation of portal venous system in post splenectomised beta-thalassemic children: A prospective study in a tertiary care hospital	Outcome out of scope
Sasiprapha, 2022	Efficacy and safety of inhaled nitrite in addition to sildenafil in thalassemia patients with pulmonary hypertension: A 12-week randomized, double-blind placebo-controlled clinical trial	Outcome out of scope
Locatelli, 2022	Betibeglogene autotemcel gene therapy for non–β(0)/β(0) genotype β-thalassemia	Copy duplicate from original SLR
Boulad, 2022	Lentiviral globin gene therapy with reduced-intensity conditioning in adults with β-thalassemia: a phase 1 trial	Outcome out of scope
Panachiyil, 2022	Efficacy and tolerability of twice-daily dosing schedule of deferasirox in transfusion-dependent paediatric beta-thalassaemia patients: a randomized controlled study	Population out of scope

Ahmed, 2022	Early detection of iron overload cardiomyopathy in transfusion dependent thalassemia patients in Sulaymaniyah city, Iraq	Study design out of scope
Mahato, 2022	Prospective observational assessment of the thyroid profile in patients of thalassemia with multiple blood transfusions and high serum ferritin	Outcome out of scope
El-Shanshory, 2022	Al-hijamah (the triple S treatment of prophetic medicine) significantly increases CD4/CD8 ratio in thalassemic patients via increasing TAC/MDA ratio: a clinical trial	Outcome out of scope
Kittipoom, 2022	The long-term efficacy of deferiprone in thalassemia patients with iron overload: real-world data from the registry database	Population out of scope
Althanoon, 2022	The assessment of the incidences of ocular toxicity and ocular findings caused by iron-chelating compound	Outcome out of scope
Habbash, 2022	Endocrine complications and the effect of compliance with chelation therapy in patients with beta thalassemia major in eastern province of Saudi Arabia	Outcome out of scope
Rao, 2022	Comparative efficacy and safety of oral iron chelators and their novel combination in children with thalassemia	Population out of scope
Mousaid, 2022	Hemoglobinopathies and dilated cardiomyopathy at the CHU Ibn Rochd-Casablanca	Population out of scope
Hong, 2022	BK virus nephropathy of native kidney after hematopoietic stem cell transplantation	Population out of scope
Yanislava, 2023	Association of GDF15 levels with body mass index and endocrine status in beta-thalassaemia.	Outcome out of scope
Mehta, 2023	Immunosuppression boost with mycophenolate mofetil for mixed chimerism in thalassemia transplants.	Study design out of scope
Fahime, 2022	Evaluation of immune system in patients with transfusion-dependent beta-thalassemia in Rasoul-e-Akram Hospital in 2021: A descriptive cross-sectional study.	Outcome out of scope
Rafati, 2022	Two trade names of deferasirox (Osveral R and Exjade R) in reduction of iron overload parameters in major beta-thalassemia patients: A randomized open labeled clinical trial.	Copy duplicate from original SLR
Kulkarni, 2022	Endothelial activation and stress index-measured pre-transplantation predicts transplantation-related mortality in patients with thalassemia major undergoing transplantation with thiotepa, treosulfan, and fludarabine conditioning.	Study design out of scope

A3. Page 73 and 74 of the appendix describe the results of the risk of bias assessment of the BELIEVE trial. It is stated the evidence was judged to be 'low to moderate', but Table 68 suggests the highest, most positive judgement was given to all domains. Please clarify which issues led to a low to moderate risk of bias result.

Company response

As the EAG alludes to, this is a mistake in the original reporting of the ITC. The reviewer has interpreted two 'no' responses to result in a low to moderate quality of evidence, where on both occasions the response of 'no' was actually a positive (i.e. study groups were not mismatched, and there was no evidence that more outcomes were measured than reported). On the basis of responses provided, the conclusion should have been that BELIEVE is a high-quality study.

A4. Priority Question: Page 11 of 23 of the document *Data on file ITC report* refers to a SLR called *Exagamglogene autotemcel (exa-cel) for Patients with Transfusion-dependent Beta Thalassemia and Severe Sickle Cell Disease: Report on Systematic Literature Review for Indirect Treatment Comparison (Vertex Pharmaceuticals Inc., 18 November, 2022a*. Please provide this SLR report.

Company response

Please find the requested report submitted alongside our clarification response. Note that the SLR was conducted for the ITC feasibility and therefore the content of the report was fit-for-purpose and did not describe all extracted data from the prioritised studies, nor all studies identified within the SLR. The ITC Feasibility Short Report is a compendium to the SLR report and provides additional information on the prioritised studies with regard to feasibility for conducting ITC vs exa-cel.

CLIMB trials

A5. Priority Question: P47 of the submission states that the CLIMB THAL-111 trial will be analysed using a group sequential testing procedure. Please supply:

a) **A full description of the design of this procedure, including boundary conditions, the alpha-spending process and justification for choosing the interim analyses.**

b) **Please explain why interim analysis 1 (IA1) was not performed.**

c) **Please state whether any trial stopping rules were met or boundary conditions reached at IA2, and whether statistical adjustments were made to analysis to account for the interim nature of the analysis.**

Company response

a. The CLIMB THAL-111 protocol stipulated that three IAs may be performed following a group sequential testing procedure in the expanded study to allow for early evaluation of efficacy. The actual alpha spending was to be based on the information available at the interim analysis (IA). The first IA was to be conducted when approximately 17 subjects had been followed for at least 16 months after receiving exa-cel. The second IA was to be conducted when approximately 24 subjects have been followed for at least 16 months after receiving exa-cel. The third IA was to be conducted when approximately 30 subjects have been followed for at least 16 months after receiving exa-cel. At each interim, the primary analysis for the primary and the key secondary endpoints will be based on subjects who were infused with exa-cel with at least 16 months of follow-up at the time of analysis (Primary Efficacy Set). Operating characteristics of the efficacy boundaries for primary and key secondary endpoints are presented in Table 2.

Table 2 Operating Characteristics of Efficacy Boundaries for Primary and Key Efficacy Endpoints

Analysis Stage	Efficacy Boundary	Boundary in Response Rate (95% CI)	Probability of Crossing Efficacy Boundaries Under Different True Response Rates (*p1*)[a]

			p1=80%	*p1=85%*	*p1=90%*
IA 1	14/17	82.4% (56.6%, 96.2%)	54.9%	75.6%	91.7%
IA 2[b]	18/24	75.0% (53.3%, 90.2%)	81.1%	94.3%	99.3%
IA 3	22/30	73.3% (54.1%, 87.7%)	87.1%	97.2%	99.8%
Final	31/45	68.9% (53.4%, 81.8%)	97.5%	99.8%	>99.9%
Overall power			98.0%	99.9%	>99.9%

a. Marginal probability of crossing the efficacy boundary at a specific interim analysis or final analysis.
b. IA1 was not conducted, the alpha planned for this IA was recovered for the subsequent analysis and the primary and key secondary endpoints was to be considered as statistically significant if the corresponding 1-sided P value was <0.01416.

b. During earlier interaction with health authorities, the feedback the Company received is that the overall data package is not adequate to assess the risk/benefit based on IA1. Therefore, a decision was made not to perform IA1. Since this decision is not related to study data or study conduct, from a statistical perspective, we can recover the unused alpha corresponding to IA1, as described in our response to A1a.

c. As described, IA1 was not conducted, therefore, the primary and key secondary endpoints were considered as statistically significant if the corresponding 1-sided P value was <0.01416. The prespecified efficacy boundary for IA2 was crossed and overwhelming efficacy is considered established for exa-cel (1, 2).

A6. On p65 it is stated that incomplete/missing data were not imputed, unless otherwise specified. How many patients had incomplete or missing data (and for which outcomes?)

Company response

There was no missing data for the primary and key secondary endpoints. With regards to other secondary endpoints, there was a minimal amount of missing data for allelic editing and haemoglobin F (HbF). No imputation was done for missing data. A descriptive summary was performed using all available data.

A7. When are the results for the June 2023 data cut expected to be available?

Company response

As agreed at the clarification call, the Company has submitted a report detailing the most recent data cut (April 2023) to NICE and the EAG. Further details for timing of delivery of an updated economic model incorporating this data have been shared with NICE (updated analysis to be shared on 11th August).

A8. Please state how many patients had IVS-I-5 mutations.

Company response

In CLIMB THAL-111, at the time of IA2 there were a total of [redacted] patients in the FAS with an IVS-I-5 mutation, including [redacted]. [redacted] of these patients had completed the RBC transfusion washout period and were transfusion independent (TI) for a range of [redacted] – [redacted] months, starting 60 days after the last RBC transfusion for post-transplant support or TDT disease management (1, 2). [redacted]

The Company note that this was a key topic in the ERG report for betibeglogene autotemcel (beti-cel), where the ERG state that 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*.'.

We emphasise that in this sub-population, where beti-cel was less likely to achieve transfusion independence, exa-cel treatment has resulted in transfusion independence in [redacted] past the RBC transfusion washout period, with a range of [redacted] – [redacted] months, starting 60 days after the last RBC transfusion for post-transplant support or TDT disease management.

A9. Priority Question: For Figure 33 in the appendices, please provide pre-enrolment stage data i.e. numbers of patients who were identified/invited/screened but not enrolled (with reasons for not being enrolled).

Company response

For CLIMB THAL-111, 13 patients were screened who did not meet eligibility criteria and were never enrolled. 8/13 were due to high liver/cardiac iron content; 2/13 were due to high direct bilirubin, 2/13 due to ineligible genetic background, 1/13 due to

autoimmune related haemolysis. Further information is provided as a supplement to our clarification response (4).

A10. Please present data for the first three columns of Table 25 (Overview of AEs before and after exa-cel infusion and overall) for the CLIMB SCD-121 trial.

Company response

As requested, an overview of the AEs experienced by patients in CLIMB SCD-121 and CLIMB-131 in the safety analysis set is presented below in Table 3.

Table 3: Overview of AEs before and after exa-cel infusion (CLIMB SCD-121 and CLIMB-131, SAS)

Visit	Enrolment to <exa-cel[a] (n=[redacted])	Exa-cel to M24[a] (n=35)	Enrolment to M24 (n=[redacted])
Patients with exa-cel infusion, n	[redacted]	35	[redacted]
Patients with busulfan dosing, n	[redacted]	35	[redacted]
Patients with any AEs, n (%)	[redacted]	35 (100.0)	[redacted]
Patients with AEs related or possibly related to exa-cel, n (%)	[redacted]	12 (34.3)	[redacted]
Patients with AEs related or possibly related to busulfan, n (%)	[redacted]	35 (100.0)	[redacted]
Patients with Grade 3 or 4 AEs	[redacted]	34 (97.1)	[redacted]
Patients with SAEs	[redacted]	14 (40.0)	[redacted]
Patients with SAEs related or possibly related to exa-cel	[redacted]	0	[redacted]
Patients with SAEs related or possibly related to busulfan	[redacted]	4 (11.4)	[redacted]
Patients with AEs leading to study discontinuation	[redacted]	0	[redacted]
Patients with AEs leading to death	[redacted]	1 (2.9)[b]	[redacted]

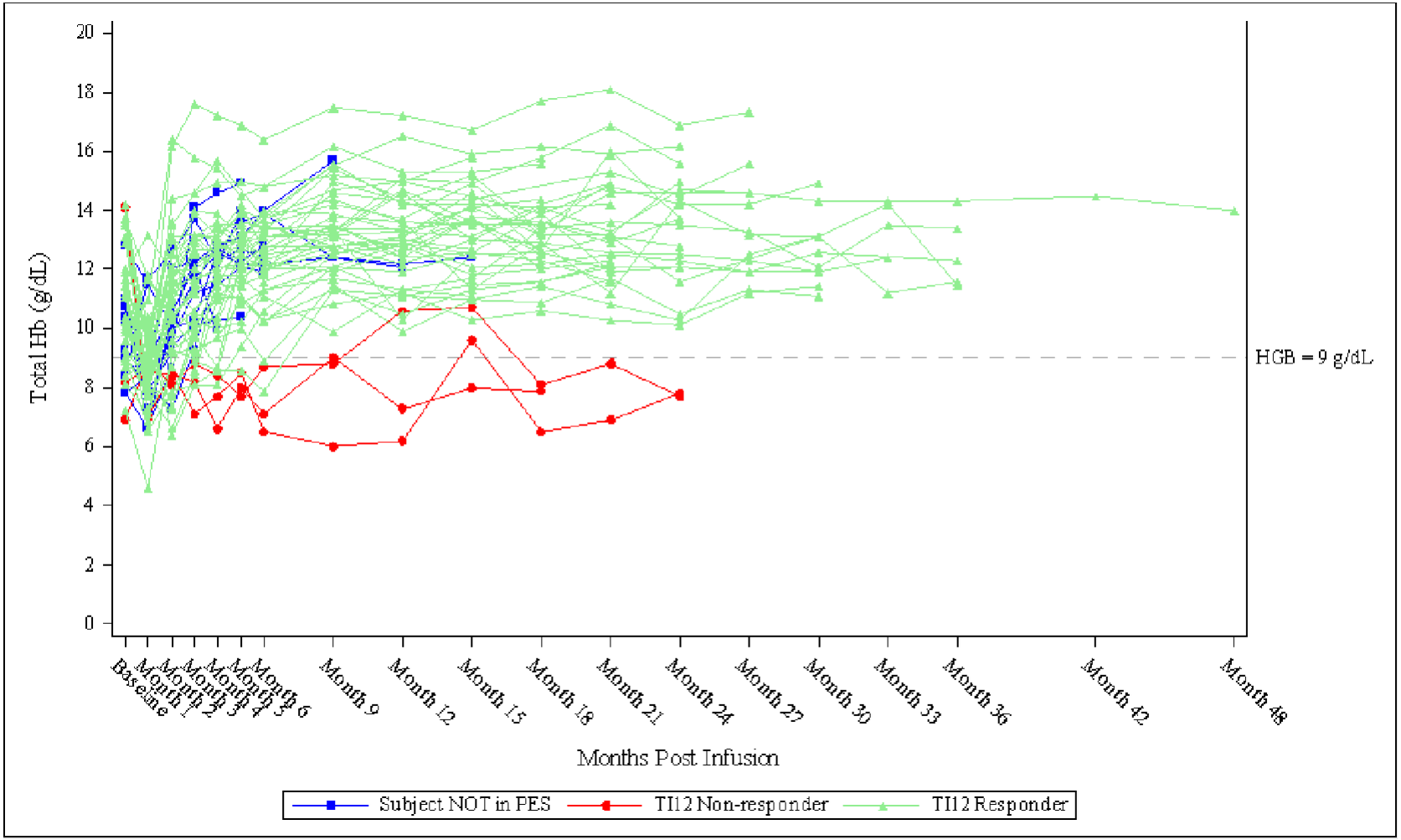
Key: AE: adverse event; exa-cel: exagamglogene autotemcel; M: month, SAE: serious adverse event; SAS: safety analysis set.
Notes: AEs were coded using MedDRA Version 25.0. The Safety Analysis Set included [redacted] patients. Percentages were calculated as n/N1×100 within each interval, unless otherwise specified. When summarising number and percentage of patients for each study interval, a patient with multiple events within a category and study interval was counted only once in that category and study interval.
[a]Study intervals: Enrolment to <exa-cel: enrolment to the day before exa-cel infusion; Exa-cel to M24: day of exa-cel infusion to M24 visit or end of study visit; Enrolment to M24: enrolment to M24 visit or end of study visit.
[b]One death, from respiratory failure due to COVID-19, was not considered to be related to exa-cel.
Source: Table 14.3.1.1.1b, CLIMB-131 CSR (1); EHA 2023 slides (5).

A11. Priority Question: Please replicate Figure 19 for the outcomes change in foetal haemoglobin concentration over time and change in total haemoglobin concentration over time (separate graphs for each outcome).

Company response

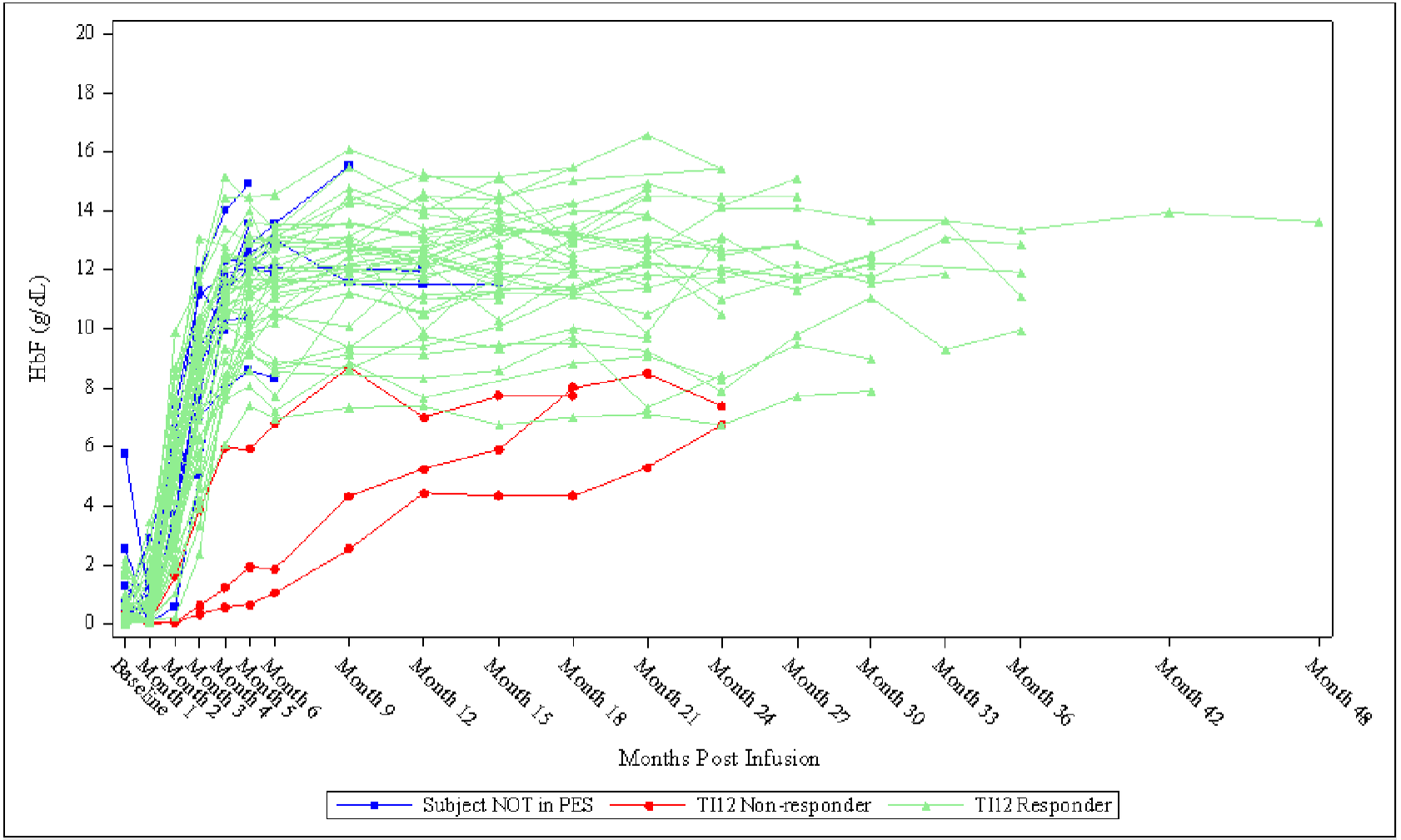
Figures presenting the outcomes change in total haemoglobin concentration over time and fetal haemoglobin concentration on an individual basis over time are available for IA2. However, these do not categorise patients based on whether they achieved transfusion independence at month 12 (see Figure 14.2.3.1, and Figure 14.2.4.1 of the IA2 CSR). Although the data presented in this form is not available for IA2, it is available for the more recent data-cut, d120. As such, although where possible we refer only to IA2 throughout our response to avoid confusion, the Company feel that these figures from D120 best address the EAG request. Furthermore, given that they are presented over time, trends can be visualised at the time of IA2 if preferred. Figure 1 presents the total haemoglobin concentration data per individual, categorised by achievement of the primary outcome. Figure 2 provides the same for fetal haemoglobin. Whilst data from the most recent data cut (D120) is provided as a separate document, with the agreement that our response be informed by IA2, we do note that at D120, all patients are TI, with a range of 0.3 to 48.1 months, starting 60 days after the last RBC transfusion, including those that were TI12 non-responders (3).

Figure 1: Individual total haemoglobin (g/dL) over time (CLIMB THAL-111 & CLIMB-131, FAS)



Key: FAS: Full Analysis Set; Hb: haemoglobin; PES: Primary Efficacy Set; TDT: transfusion dependent β-thalassemia; TI12: maintaining a weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation in CLIMB THAL-111. Analysis visit was used in the figure.
Source: Figure 4, interim D120 report (3).

Figure 2: Individual fetal haemoglobin (g/dL) over time (CLIMB THAL-111 & CLIMB-131, FAS)



Key: FAS: Full Analysis Set; HbF: fetal haemoglobin; PES: Primary Efficacy Set; TDT: transfusion dependent β-thalassemia; TI12: maintaining a weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation in CLIMB THAL-111. Analysis visit was used in the figure.
Source: Figure 5, interim D120 report (3).

A12. Please add baseline data to the top of Appendix table 75 (i.e. as has been done for Table 74).

Company response

As highlighted in Section B.2.6.2.5. of the company submission, the first timepoint of evaluation for allelic editing in the bone marrow was Month 6. Data on the allelic editing in the bone marrow was not collected at baseline. At Month 6 (first timepoint of evaluation), the mean (SD) proportion of alleles with intended genetic modification in the CD34+ cells of the bone marrow was 77.85% (11.72%), which is consistent with allelic editing in the drug product. The mean proportion of alleles with the intended genetic modification in the CD34+ cells of the bone marrow remained stable at Month 12 (≥68%) onward (1, 2).

A13. Priority Question: On page 84 of the company submission it is stated that data from CLIMB THAL-111 and CLIMB-131 indicates favourable changes in iron overload. Please provide a formal statistical analysis of change in: i) Serum ferritin levels, ii) liver iron content, and iii) cardiac T2* to support this assertion.

Company response

A reduction in iron overload is known to occur slowly, over two to four years following successful allogeneic stem cell transplantation, because of the body's homeostatic process for iron metabolism and removal may require many months to process (6, 7). The iron-normalisation/change phase was assumed to be 4 years, based on clinical expert opinion.

As described in the CS, patients with a cardiac T2* <10 msec by MRI or left ventricular ejection fraction (LVEF) <45% by echocardiogram, were excluded from CLIMB THAL-111. Similarly, there were a number of exclusion criteria relating to advanced liver disease, including 'liver iron content (LIC) ≥15 mg Fe/g dry weight on R2 magnetic resonance imaging of liver, unless liver biopsy within 3 months before or at screening showed no evidence of bridging fibrosis or cirrhosis'. As a result of these eligibility criteria, patients had normal cardiac T2* and LIC scores at baseline, which remained at a similar level over time.

Biomarker data for serum ferritin level indicate favourable changes in iron overload and support the anticipated role of exa-cel in preventing further progression of end-organ damage (Table 4).

These findings are consistent with that observed in subjects with TDT after allo-SCT and are supportive of a beneficial treatment effect on iron accumulation (6). It is expected that further reduction in iron overload leading to prevention of end organ damage and overall improvement in survival will be observed with additional follow-up and this endpoint is assessed in the long-term follow-up CLIMB-131.

Table 4: Summary of Serum Ferritin Level and Change from Baseline at Each Visit (FAS)

Visit	Statistic	Total (n=48)
Baseline	n	48
	Mean (SD)	[redacted]
Month 1	n	[redacted]
	Mean (SD)	[redacted]
Change at Month 1	Mean (SD)	[redacted]
Month 2	n	[redacted]
	Mean (SD)	[redacted]
Change at Month 2	Mean (SD)	[redacted]
Month 3	n	[redacted]
	Mean (SD)	[redacted]
Change at Month 3	Mean (SD)	[redacted]
Month 4	n	[redacted]
	Mean (SD)	[redacted]
Change at Month 4	Mean (SD)	[redacted]
Month 5	n	[redacted]
	Mean (SD)	[redacted]
Change at Month 5	Mean (SD)	[redacted]
Month 6	n	[redacted]
	Mean (SD)	[redacted]
Change at Month 6	Mean (SD)	[redacted]
Month 9	n	[redacted]
	Mean (SD)	[redacted]
Change at Month 9	Mean (SD)	[redacted]
Month 12	n	[redacted]
	Mean (SD)	[redacted]
Change at Month 12	Mean (SD)	[redacted]
Month 15	n	[redacted]
	Mean (SD)	[redacted]
Change at Month 15	Mean (SD)	[redacted]
Month 18	n	[redacted]
	Mean (SD)	[redacted]

Change at Month 18	Mean (SD)		[redacted]	
Month 21	n			
	Mean (SD)		[redacted]	
Change at Month 21	Mean (SD)		[redacted]	
Month 24	n			
	Mean (SD)		[redacted]	
Change at Month 24	Mean (SD)		[redacted]	

Note: Change relative to baseline values.
Source: Climb THAL-111 IA2 CSR (2).

A14. Priority Question: Appendix D Figure 33 states that 9 patients had been mobilised but have not yet received exa-cel infusion. Please explain why they have not yet received infusion, and supply waiting time data (which may be ongoing) from mobilisation to infusion for all patients who started mobilisation.

Company response

As explained in Figure 3 and Table 10 of the CS, patients receiving exa-cel go through a four-step process. Stem cell mobilisation marks the start of Stage 2 of the exa-cel treatment procedure. Post-mobilisation, Stage 2 also involves the collection of stem cell cells and the subsequent manufacturing of the exa-cel product. Once the manufactured product is returned to the study site, Stage 3 of the process is initiated, which begins with the patient undergoing myeloablative conditioning (Stage 3A) prior to infusion with exa-cel (Stage 3B). As a result, at the time of the IA2 data cut-off (dated 6th September 2022), the 9 mobilised patients enrolled onto CLIMB THAL-111 who had not yet received exa-cel were between Stage 2 and Stage 3B of the exa-cel treatment process.

To best address this question, we note that at the time of D120 (April 2023), 6 of 9 patients who started mobilisation and were not dosed with exa-cel at IA2 had subsequently received exa-cel infusion. Of the three remaining patients, one patient withdrew consent and discontinued from CLIMB THAL-111, while two patients have not yet been dosed with exa-cel despite beginning mobilisation. No subject has discontinued after starting busulfan conditioning or after exa-cel infusion in CLIMB THAL-111 or discontinued from CLIMB-131 (3).

A15. Priority Question: Please clarify the transfusion status (TI12 Y/N) of Patient 002 at the IA2 data cut-off. On page 70, which provides information on

the three patients in the PES who had not achieved TI12 at the time of IA2 data cut-off, it is stated that the patient [redacted] did not receive any further RBC transfusion starting 14.5 months after exa-cel infusion through the most recent IA2 data-cut for a duration of approximately 4.9 months (includes RBC transfusion washout period and 2.9 months of transfusion free follow-up, with a total follow-up of 19.4 months after exa-cel infusion). These data concur with Figure 14 which shows that patient 002 was receiving transfusions up to shortly before day 450 and was transfusion-free thereafter for around 5 months. However, on p129 it is stated that Subject [redacted] achieved TI despite reaching it later in their treatment journey (14.5 months); this patient is assigned TI status in the model. Please clarify these conflicting data.

Company response

At the time of the IA2 data-cut off, Patient [redacted] did not meet the primary endpoint of the CLIMB THAL-111 study, i.e., was not transfusion independent for 12 consecutive months while maintaining a weighted average haemoglobin ≥9 g/dL starting 60 days after the last RBC transfusion for post-transplant support or disease management. However, the definition for TI12 is not used to define TI status in the economic model. Instead, TI status is defined as those patients who are transfusion-free starting 60 days after the last RBC transfusion for post-transplant support or disease management. Considering that Patient [redacted] was transfusion-free for 2.9 months post-RBC transfusion washout period (10.3 months at D120), this patient has been assigned TI status in the economic model. Therefore, the data presented on pages 70 and 129 of the company submission are not conflicting.

Section B: Clarification on cost-effectiveness data

Note: based on the EAG feedback we have received during clarification questions, we have updated the DCEA health opportunity costs shares, general population-level IMD proportions, and IMD-group QALEs values to align with the contemporary reference cited in priority B23. This is discussed further in priority questions B22 and B23. DCEA-weighted economic outcome values have been updated accordingly throughout relevant submission documents. Consequently, all our scenario analysis response tables refer to these updated DCEA modified base cases.

B1. Priority Question: In the terminated NICE appraisal of betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID968], the committee agreed that its preferred approach would include:

- **Use the reference case discount rate for costs and benefits (3.5%).**
- **Use the EAG's preferred approach to utilities, which implied a beta-thalassaemia related morbidity decrement of ~0.1 compared to the general population.**
- **Limit the UK Chart Review population data to match the population in the clinical-effectiveness data.**
- **Set the time to normalisation for cardiac iron and liver iron to 5 years**
- **Incorporate a non-zero mortality rate associated with myeloablative conditioning followed by betibeglogene autotemcel.**

The company's base case fails to acknowledge these preferences and, in most cases, explicitly contradicts the committee's preferred assumptions e.g. adoption of a non-reference case discount rate. Please justify your approach and explain why you feel the committee's previous judgements do not apply to the appraisal of exa-cel.

a) **Please reconsider your preferred base case assumptions in light of the above.**

Company response

The discontinued NICE appraisal of betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID968] concerns a different technology, with different mode of action and under different NICE guidance for the applicability of non-reference-case discounting. Therefore, it is not relevant or appropriate to use appraisal ID968, and the committee's preferred assumptions, as a benchmark against which to measure the exa-cel company submission. However, regarding the EAG's specific queries, we answer as follows:

Discount rate and applicability of non-reference-case discounting for exa-cel:

While Vertex cannot fully comment on whether or not betibeglogene autotemcel met the criteria for the non-reference case discount rate according to the pre-2022 methods guide, exa-cel meets the current criteria for the use of a 1.5% discount rate.

The technology is for people who would otherwise die or have a very severely impaired life.

First, TDT is a condition which severely impacts patients length and quality of life. Without treatment with exa-cel, patients would otherwise die many decades prior to the general UK population of complications relating to their condition, with a mean age of death of 55 in the UK and a crude mortality rate of more than 5 times the matched general population (1.38 v 0.26 per person year) (8, 9). Not only is life expectancy greatly reduced, the quality of that life is also negatively affected, as described in the company submission B.1.3.2.2.

It is likely to restore them to full or near-full health.

As the D120 data shows, 100% of patients treated with exa-cel became transfusion independent. Patients treated with exa-cel will experience improved survival, reduced risk of co-morbidities and they will no longer need to receive transfusions (3). Long-term survival following stem cell transplant in TDT has been shown to be favourable and the majority of risk factors for late deaths would not be relevant to exa-cel (e.g. non-HLA matched donors and/or GvHD) (10).

In addition, by reactivating the production of HbF, exa-cel mimics hereditary persistence of fetal haemoglobin (HPFH), a naturally occurring genetic variation

associated with a benign clinical course (11-13) Patients with HPFH will experience few or no TDT symptoms by mimicking this exa-cel will restore patients to near normal health (13).

The benefits are likely to be sustained over a very long period.

The expected benefits of exa-cel as a one-time gene editing therapy include long-term amelioraton of a life-long disease. There is no known mechanism by which an edited HSC could revert to a wild-type sequence. Edits to the HSPCs are expected to be permanent and durable. HbF is increased in exa-cel due to an edit in the erythroid specific enhancer region of *BCL11A*. This mechanism is not subject to transcriptional control that could occur with gene addition strategies that are driven by exogenous promoters inserted randomly throughout the genome.

The stable, durable allelic editing observed in CLIMB THAL-111 and -131 is consistent with the stability of HbF production over time and indicative that the clinically meaningful effect of elimination of transfusions will persist long-term. Finally, consensus from UK clinical experts was that if there is sustained effect at 2 years there is no reason to believe the effect would wane (given past experience with stem cell transplantation in this indication (10).

While all evidence available indicates the effect of exa-cel will be durable, Vertex has also proposed that a managed access agreement be carried out to further provide evidence of durable effect. Vertex proposes data collection for 3 years on the basis that clinical experts have indicated that if the effect was durable for two years, they would accept the effect as long term. Given the length of the exa-cel treatment journey, an additional year was proposed to maximise data collection. As this would bring the total patient follow-up time to ≥7 years, in addition to all evidence presented, the 1.5% discount rate should apply.

Finally, Vertex is in commercial discussions with NHSE, and approval of exa-cel would not likely expose the NHS to irrecoverable costs.

Utilities

We believe that sufficient evidence has emerged since ID968 to support the inability of the EQ-5D to fully capture the impact of TDT on quality of life. This issue is addressed in our response to question B12.

Chart review population

It is not possible to use the values from the chart review age-matched subgroup as the results of this analysis were not available in unredacted form anywhere within the ID968 committee papers.

Iron normalisation

We have already presented a scenario analysis whereby the iron normalisation period is set to 5 years in our submission tables 58 and 59. This scenario increased the ICER at a 1.5% discount rate by only 5%. However, based on the observed rate of reduction in iron levels in CLIMB-THAL-111 (see response to question A13) we believe 5 years to be an overestimate and 4 years is the appropriate duration.

Mortality rate following myeloablative conditioning and exa-cel

As discussed at the clarification call, while it is possible to apply an instantaneous event rate due to busulfan conditioning in the model, this was intended to capture any mortality observed during the CLIMB-THAL-111 trial observation period. As no mortality has been observed thus far, we have not included any in the model. Furthermore, late mortality effects associated with the transplantation procedure are already captured by an SMR of 1.25 applied to functionally cured patients, in line with that applied during ID968. There are no relevant sources of near-term mortality rate that can be taken from the literature, as we have not been able to identify any evidence for the mortality impact of busulfan monotherapy in the TDT population. The majority of regimens in the literature being utilised within the context of allogeneic stem-cell transplant and comprising combinations of busulfan, cyclophosphamide, fludarabine, treosulfan and anti-thymocyte globulin have low or zero rates of transplant related mortality (14). It would therefore be impossible to separate out the relative contribution to mortality of busulfan monotherapy within these very different transplantation settings.

B2. In the company submission (Tables 58 – 61), scenario analyses are not presented for the results without severity modification. Please provide all scenario analyses for the results without the severity modifier applied.

Company response

Application of the severity modifier is part of the NICE Methods guide and is applicable based on an objective measure of proportional and absolute QALY shortfall. The model has a lookup function that only applies the severity modifier where the required shortfalls have been achieved and this is also true of all sensitivity analyses presented within the dossier. We have presented the unmodified values in the base case as a reference point but felt this unnecessary when presenting sensitivity analyses. Should the EAG wish to see unmodified results it is possible to generate them by setting the severity modifier and DCEA dropdowns to "No" before running simulations in the deterministic sensitivity analysis sheet (DSA).

Population

B3. As outlined in question B1, the committee in ID968 preferred to use values from an age-matched subgroup of the Shah et al. chart review. The company, however, used the full chart review population to inform several parameter values used in the model including baseline iron levels, distribution of iron chelation agents and resource use.

a) **Please justify your approach and comment on the generalisability of the full chart review population to the modelled population.**

b) **For each parameter set where the full chart review population is used as a source of values, please comment on how using the full population (vs an aged-matched population) may bias the results of the economic analysis.**

Company response

a) It was not possible to use the values from the Shah *et al.* age-matched subgroup as the results of this analysis were not available in unredacted form anywhere within the ID968 committee papers. A comparison between the

prevalence of comorbidities at baseline in Shah *et al.* vs. the CLIMB-THAL-11 trial (FAS; IA2 data cut) is shown in Table 5.

Table 5: Comparison of baseline comorbidities Shah 2021 vs. CLIMB-THAL-111

Comorbidity	Prevalence in Shah et al., 2021	Prevalence in CLIMB-THAL-111
Hypogonadotropic hypogonadism/ Hypogonadism	20%/ 7%	2.1%
Splenectomy	20%	31.3%
Osteoporosis	14%	10.4%
Diabetes	13%	6.3%
Liver complications	10% (hepatitis)	0%

Source: Shah *et al*, (2021) (15); CLIMB THAL-111 CSR (2).

Clearly, there was a higher prevalence of baseline complications in the Shah et al. full cohort almost certainly related to the older age of the cohort, with older patients more likely to have had a history of iron overload. This may have resulted in higher quantities of healthcare resource use related to management of comorbidities than a younger cohort. However, as explained in Table 6, this is unlikely to generate a large bias in the ICER.

b) We have tabulated the parameters that use Shah et al., as a source in the base case and commented regarding their likely risk of bias in Table 6.

Table 6: Parameters sourced from Shah et al. and potential biases

Parameter	Potential bias
Baseline iron levels	Addressed in Question B4
Iron chelation therapy (ICT) regimen distribution	In ID968, the EAG ran a scenario using the ICT distribution at baseline from the age-matched subgroup. This led to a reduction in the ICER of Zynteglo vs. SoC of 2.3%, due to a larger proportion of patients in the younger cohort using combination therapy. We therefore consider that use of the full cohort in this present analysis will generate a small bias against exa-cel.
Monthly disease management costs of TD patients	Healthcare resource use from Shah were not used to provide health state costs in ID968. However, the exa-cel model has limited sensitivity to this parameter. If the monthly disease management costs of TD are halved in the model (keeping TR as the average), the base case ICERs (severity and/or DCEA modified) increase by only

	2% at a 1.5% discount rate. There is therefore limited bias from use of the whole cohort for this parameter.

Key: TD, transfusion-dependent; TR, transfusion-reduced.

B4. Priority Question: Pages 84 and 85 in the company submission indicate baseline iron levels recorded in the CLIMB THAL-111 trial. Please explain why these values were not considered in the economic analysis. Please compare the values to the population in the Shah et al chart review.

a) Please present a scenario analysis using baseline iron levels from the CLIMB THAL-111 trial.

Company response

Categorised baseline iron levels had to be obtained via post-hoc analyses which were not completed in time for submission. Proportions at baseline compared with Shah are presented in Table 7 (noting that these were not yet available for the D120 data cut). Shah notably had higher iron levels at baseline, in particular those in the high iron level health states. However, as explained in the dossier section B.3.2.1, the model is not structured to model the natural history of iron overload for SoC patients over their lifetime. Even if it were, no data are available to provide transition probabilities, thus the iron levels at baseline remain constant throughout the model time horizon for SoC patients. As the CLIMB-THAL-111 study excluded patients with high T2* and liver iron concentration at baseline (see answer to A13), using baseline values from CLIMB-THAL-111 would fail to capture the transition of these TD patients to higher iron levels over their lifetime, which would underpredict future iron overload in the SoC arm and bias results against exa-cel.

Furthermore, the median age of the Shah cohort at the end of the observation period was 24, only 3 years older than the CLIMB-THAL-111 cohort, and one quarter of patients in Shah et al. were under the age of 12 vs. 20% over the age of 40 (15). Thus, those older patients with high iron overload are offset by younger patients with likely lower iron overload, and we expect that restriction of Shah to the age group of CLIMB-THAL-111 would result in similar iron levels.

Table 7: Iron overload parameters in Shah et al. vs. CLIMB THAL-111

Parameter	Shah value	CLIMB-THAL-111 value (FAS; IA2 cut, N = 48)
Serum ferritin (%)		
Low (above normal to ≤1,000 ng/ml)	23.0	[redacted]
Moderate (1,000-2,500 ng/ml)	38.8	[redacted]
High (>2,500 ng/ml)	38.2	[redacted]
Myocardial T2* (%)		
Low (>20ms to below normal)	88.2	[redacted]
Moderate (10-20 ms)	11.8	[redacted]
High (<10 ms)	0.0	[redacted]
Liver iron concentration (%)		
Low (above normal to <7 mg/g)	60.5	[redacted]
Moderate (7-15 mg/g)	23.5	[redacted]
High (≥15 mg/g)	16.0	[redacted]

Note 1: the 1,000 threshold was not available, so estimates for 1,000 are based on assuming proportionality between the 500, 1,000 and 1,250 thresholds.
Source: Shah *et al*, (2021) (15); CLIMB THAL-111 CSR (2).

a) Incremental results applying the baseline iron levels from CLIMB-THAL-111 are presented in Table 8. In summary, the impact differs according to the discount rate used; ICERs increase by 3% at a 1.5% discount rate.

Table 8: Scenario analysis using CLIMB-THAL-111 baseline iron levels

Scenario	Incremental costs (unmodified)	Incremental LYG	Incremental QALYs (unmodified)	ICER (DCEA & severity modified)	ICER (severity modified)
Shah baseline values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CLIMB-THAL-111 baseline values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B5. Priority Question: The base-case model assumes a 0% prevalence of osteoporosis and diabetes at baseline despite the prevalence of these conditions being 10.4% and 6.3%, respectively in CLIMB THAL-111.

a) Please provide justification for this assumption.

b) Please present a scenario analysis using the CLIMB THAL-111 baseline prevalence of these complications.

Company response

a) The reasons for exclusion for these comorbidities was already explained in the dossier; the model comorbidity health states can only capture a cumulative incidence, whereas osteoporosis could be treated and reversed following functional cure. We thus felt it more appropriate to capture only newly incident osteoporosis.

With respect to diabetes, we had made an error in the dossier and there were in fact 3 patients with diabetes at baseline in the IA2 FAS (two type 1 and one type 2) and it is likely that these cases were the result of TDT.

b) A scenario analysis including these comorbidities at baseline (10.4% osteoporosis; 6.3% diabetes, respectively) is presented in Table 9. In summary, this did not have a material impact on results, increasing the ICERs by 2%.

Table 9: Scenario analyses including osteoporosis and diabetes at baseline

Scenario	Incremental costs (unmodified)	Incremental LYG	Incremental QALYs (unmodified)	ICER (DCEA & severity modified)	ICER (severity modified)
Osteoporosis and diabetes excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteoporosis and diabetes included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B6. The base case model assumes a 100% adherence to iron chelation therapy. Please provide a justification for this assumption and present a scenario using an appropriate estimate from the literature.

Company response

It was not possible to obtain the proportion of patients on each type of therapy nor their adherence from the CLIMB-THAL-111 trial. Shah et al. report adherence for the entire cohort and not for the age band relevant to exa-cel. We note from ID968 that younger patients in the Shah chart review were more likely to be on combination therapies, which were also associated with high adherence as reported in the Shah supplementary appendix (15). The model applies the iron chelation therapy (ICT) proportions based on the whole Shah cohort and not the younger subgroup, thus is already likely to underestimate ICT costs by assuming a higher proportion on monotherapy. We did not wish to further bias the results by including low, potentially unrealistic adherence values.

Furthermore, as discussed in the response to question B7, the CLIMB THAL-111 cohort had higher transfusion frequency at baseline than the Shah cohort and may represent a somewhat more severe cohort with respect to their transfusion dependence (possibly due to a higher proportion of more severe genotypes, see question B7). The trial cohort is therefore not only more likely to be on combination therapy but is also likely to be more adherent as a result.

In Table 11 we present an analysis applying adherence percentages by ICT regimen according to the values presented in the Shah appendix, reproduced here in Table 10. Adherence by ICT regimen has been added to the *Cohort inputs* sheet under the existing “ICT regimen distribution” section (the scenario is applied by deleting the 100% values applied to the blue override cells). The disutility of subcutaneous ICT was also reduced by the weighted average of non-adherent patients on subcutaneous therapies.

From the results it is evident that this scenario has a minor impact on the ICER, increasing it by 5%.

Table 10: ICT non-adherence frequencies trom Shah et al., 2021

Regimen	Non-adherence (N)	Non-adherence (%)
Deferasirox	30/132	23%
Deferiprone	7/57	12%
Desferrioxamine	7/85	8%
Combination therapy	1/34	3%

Source: Shah *et al* (2021)

Table 11: Scenario assuming Shah et al. adherence to ICT

Scenario	Incremental costs (unmodified)	Incremental LYG	Incremental QALYs (unmodified)	ICER (DCEA & severity modified)	ICER (severity modified)
100% adherence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shah et al. adherence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Furthermore, several published studies have observed that adherence to ICT is associated with the ICT regimen. Specifically, that adherence to oral iron chelators such as deferiprone and deferasirox is higher than adherence to subcutaneous/intravenous desferrioxamine (16). Given the more optimal management of ICT in recent years, and that more than 70% of TDT patients in the UK receive oral iron chelators (15), 100% adherence to iron chelation therapy is considered appropriate.

SoC

B7. Priority Question: The average number of transfusions assumed in the company base case is based on values from the CLIMB THAL-111 trial (FAS population) and assumes patients receive 16.4 transfusions per year and 35.3 units of blood. This is substantially higher than the corresponding values from the Shah et al. chart review.

a) **Please provide relevant individual patient data from the CLIMB THAL-111 trial on the frequency of transfusions and volume of blood received to enable the EAG to understand the distribution of transfusion**

frequency across patients. If this is not possible, please provide a histogram stratifying patients into groups based on the frequency of transfusions/volume of blood received.

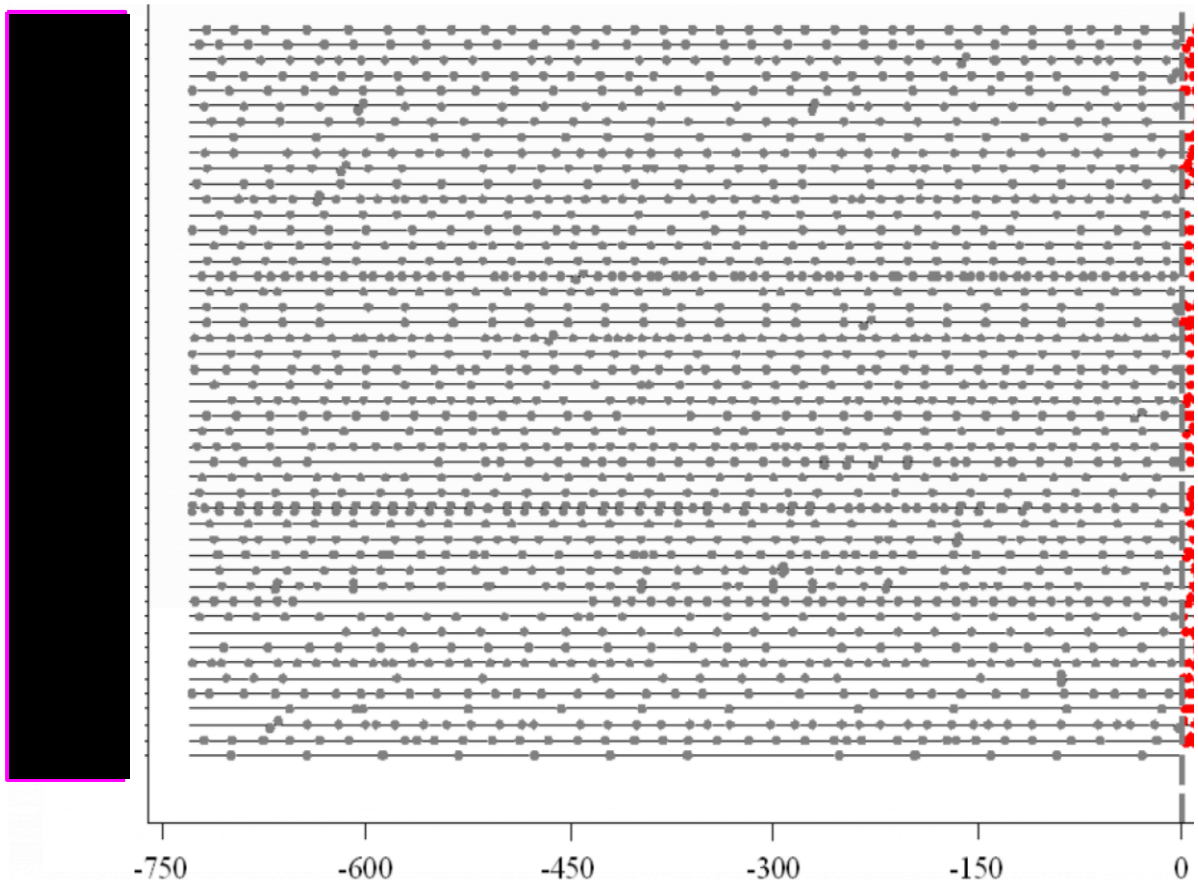
b) **Please comment on the generalisability of the CLIMB THAL-111 trial values to UK practice?**

c) **Please present a scenario analysis in the economic model using values from Shah et al. chart review.**

Company response

a) We are unable to provide the individual patient data, but Figure 3 below should illustrate the distribution of frequency within the study. This figure shows the frequency of transfusions (depicted as grey circles) in the 24 months leading up to treatment with exa-cel, and includes all patients in the FAS at the time of IA2. Patients are ordered by length of follow-up (top = longest follow-up since exa-cel infusion, bottom = shortest).

Figure 3: Frequency of blood transfusions in CLIMB THAL-111 medical history



Source: adapted from Figure 11-4, IA2 CSR (2). Data is presented for the 24 months prior to exa-cel infusion. Each grey circle represents a transfusion episode. *: subjects in the PES.

b) We note that the annualised transfusion frequency was 16.4 per year in CLIMB-THAL-111 (IA2) vs. 13.7 in Shah. Transfusion volumes were (mean) 195.3mL/kg/year in CLIMB-THAL-111 vs. 175.5 mL/kg/year in Shah. One would expect lower transfusion volumes in Shah because 25% of the Shah cohort were aged under 12, but this would not be expected to impact transfusion frequency. Thus, the transfusion burden of patients in CLIMB-THAL-111 does appear to be higher than those in Shah et al. (2021) (15).

In general, more severely affected patients with higher transfusion burden are more likely to opt for gene therapy (see our response to B15), so it is unsurprising that patients in the CLIMB THAL-111 study had higher transfusion burden at baseline than the Shah cohort. There are further reasons why the transfusion frequency from CLIMB THAL-111 is more likely to be generalisable to the population eligible for exa-cel than the Shah et al cohort:

- The genotype proportions are not described in Shah et al. The CLIMB THAL-111 had a low proportion of milder genotypes and there are likely to be larger proportions with milder genotypes and consequently reduced transfusion requirements within the general TDT population.

- In Shah et al, 20% were >40 years old; this population in particular may have had increased numbers of milder genotypes who were needing transfusions as they aged.

- 25% of patients Shah et al. were less than 12 years old and would not have been eligible for the trial.

c) The economic model uses RBC units whereas Shah et al. only reports RBC volumes per kg body weight. As the mean patient weight is not reported in Shah, it isn't possible to convert the volume to RBC units and conduct this scenario.

Exa-cel

B8. Priority Question: Please provide further justification for the assumption of permanent engraftment with exa-cel, and refer specifically to the long-term persistence of HSCT grafts and other gene therapies including betibeglogene autotemcel

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

Company response

The results of treatment with exa-cel are expected to be durable. Following successful engraftment, effects are expected to be lifelong because there is no known mechanism for the edited CD34+ cells to revert to unedited cells. Biologically there is no reason the introduced CRISPR/Cas9 gene edit will not be permanent. Edits to HSPCs are permanent.

HbF is increased in exa-cel due to an edit in the erythroid specific enhancer region of BCL11a. This mechanism is not subject to transcriptional control that could occur with gene addition strategies that are driven by exogenous promoters inserted randomly

throughout the genome. Mean proportion of Hb comprised by HbF increased to 66% at Month 3, with the proportion increasing to and maintained at >87% thereafter, indicating that exa-cel has successfully edited haematopoietic stem cells long-term. In addition, further support for this comes from circulating RBCs; Over 95% of circulating RBCs expressed HbF at Month 6, and this figure remained above 95% through follow-up (1, 2, 5).

Allelic editing data in CD34+ cells of the bone marrow and peripheral blood are indicative of the durable engraftment of edited long-term HSPCs and reflect the permanent nature of the intended edit with % allelic editing in bone marrow and peripheral blood stable throughout. The stable, durable allelic editing observed is consistent with the stability of HbF production over time and indicative that the clinically meaningful effect of transfusion independence will persist long-term.

An extensive body of evidence exists demonstrating sustained efficacy of allo-SCT upon successful engraftment, with allo-SCT considered durable after 1-2 years, after which risk of donor graft rejection / failure has significantly decreased (17-20). Notably, exa-cel uses a patient's own HSPCs, avoiding risks of donor graft rejection / failure (10); no cases of graft rejection / failure have been reported in the CLIMB pivotal trials.

With regards to comparison to beti-cel, there are several important differences to note. Exa-cel uses non-viral, *ex-vivo* CRISPR/Cas9 gene editing to disrupt *BCL11A* expression and restore the natural production of HbF (11). In contrast, beti-cel relies on a viral vector for gene insertion. Exa-cel does not rely on insertion of a functional gene and subsequent transgene overexpression which may result in an imbalanced production of haemoglobin α and β chains. Importantly, due to the non-viral gene editing approach, exa-cel eliminates the risk of insertional mutagenesis, transcriptional deregulation or loss of response. We do however note that at 7 years of follow-up, all patients to achieve TI after treatment with beti-cel in the long-term follow-up study had maintained response (21). In the context of the stated advantages of CRISPR relative to gene insertion, we expect that long-term durability will hold for exa-cel, with no evidence suggesting otherwise.

Consensus from UK clinical experts was that if there is sustained effect at 2 years there is no reason to believe the effect would change (given past experience with stem cell transplantation in this indication) (22).

To summarise, exa-cel, an autologous gene editing therapy, is expected to provide sustained clinical benefits once cells engraft, as demonstrated with allo-SCT. All evidence currently available for CLIMB THAL-111, including allelic editing in the peripheral blood and bone marrow, haemoglobin concentration, HbF %, and transfusion independence data are supportive of this expectation.

a) With respect to diversity of transduced cell lines, as part of allelic monitoring in peripheral blood the company is collecting status of platelets, RBCs and white cell lines to provide information on how the main cell lines are reconstituting. The most recent published data are from EHA 2023 (5).

B9. Priority Question: Figures 18 and 19 in the company submission provide information on the proportion of alleles in CD34+ bone marrow and peripheral blood respectively.

a) Please comment on the clinical interpretation of the proportion of edited alleles following exa-cel transfusion. Were threshold values corresponding to a success/failure prespecified as part of the CLIMB THAL-111 trial? If not, what would the company consider a high or low value for these outcomes?

b) Related to the above, can the company comment on what would represent a clinically significant decline in the proportion of edited alleles (both CD34+ bone marrow and peripheral blood)?

c) Please provide data on the average proportion of edited alleles from the CLIMB THAL-111 trial stratifying patients into groups based on a) whether a patient achieves transfusion independence b) genotype.

Company response

a) Based on the efficiency of bi-allelic modification of CD34+ human haematopoietic stem and progenitor cells (hHSPCs), and an estimate of the

observed improvement in the γ/a-globin ratio in the modified cell populations, one can predict that an optimal outcome haemoglobin concentration ranging from 9 to 11 g/dL might be obtained with long-term engraftment of 16% bi-allelically modified CD34+ hHSPCs based on the unconstrained model and 50% based on the constrained model.

Furthermore, a minimum editing efficiency of 20% based on the unconstrained model to 40% based on the constrained model may lead to a level of haemoglobin in the range of 7 to 9 g/dL, also potentially therapeutically meaningful. This pharmacology model supports an estimated allele editing efficiency of approximately 40% as a minimum threshold for the CLIMB THAL-111.

The following results are from the PES samples from the IA2 datacut. In bone marrow at Month 6 (the first timepoint of evaluation) the mean (SD) proportion of alleles with the intended genetic modification in the CD34+ cells of the bone marrow was [redacted]). This remained stable at month 12 [redacted]) onwards.

In peripheral blood allelic editing was detectable within 1 month after exa-cel infusion. The mean (SD) proportion of alleles with the intended genetic modification in peripheral blood was [redacted] at Month 1 and the mean remained [redacted] from Month 2 onwards. Allelic editing in the peripheral blood is lower than allelic editing in the CD34+ cells of the bone marrow because the peripheral blood included lymphocytes that are derived from the edited CD34+ haematopoietic stem cells (HSCs). With single agent busulfan conditioning lymphocytes are not depleted and this results in a proportion of peripheral blood lymphocytes having been derived prior to therapy from HSCs that were not edited.

The FAS showed similar stable allele editing over time consistent with allelic editing in the bone marrow and peripheral blood to that observed in the PES.

In addition, the high levels of HbF and F cells compared to baseline support that almost all circulating RBCs are derived from edited stem-cells. This is

consistent with the clinical effects of patients with TDT becoming transfusion free.

The trial protocol for CLIMB-111 stated that enrolment would be temporarily suspended for lack of efficacy if the proportion of alleles with intended genetic modification present in peripheral blood was <10% in 3 of the first 12 subjects at 2 consecutive timepoints after neutrophil engraftment. Genetic modification of <10% in peripheral blood was not seen in any of the timepoints after neutrophil engraftment in any of the subjects.

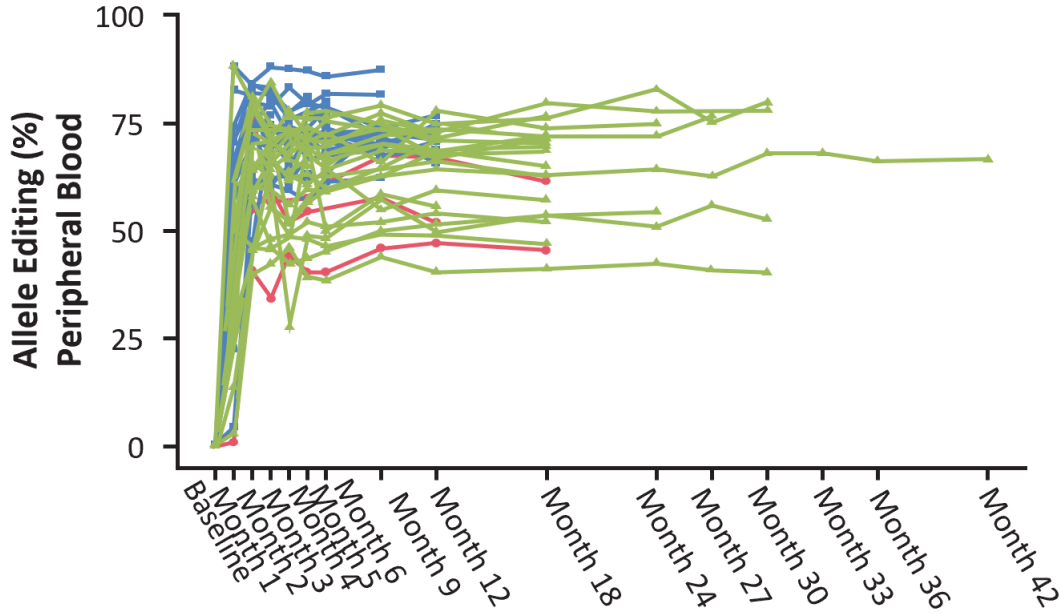
b) There has been no decline in allelic editing over time and percent allele editing in individual subjects, including the 3 subjects in the PES who did not achieve transfusion independence at IA2 was stable over time during the follow-up period through Month 24 (1, 2, 5). The results of treatment with exa-cel are expected to be durable. As the EAG will have been observed from our submitted D120 report, all patients at D120 that had completed the RBC transfusion washout period were transfusion independent (3).

   Bone marrow transplantation in β-thalassemia demonstrates that it is not necessary to completely replace the patient's bone marrow with healthy donor cells to obtain clinical control of the disease. Patients who underwent allogeneic stem cell transplantation and show long-term, persistent mixed chimerism ranging from 10% to 50% of normal donor marrow admixed with the patient's β-thalassemia marrow are often transfusion independent with improved quality of life (23-25). These data support the hypothesis that long-term engraftment with even 10-20% of 'corrected' CD34+ hHSPC may be beneficial.

   Edits to the HSPCs are permanent and durable. Biologically and based on our mechanism, there is no reason the introduced edit will not be permanent. There is no known mechanism by which an edited HSC could convert back to its original sequence.

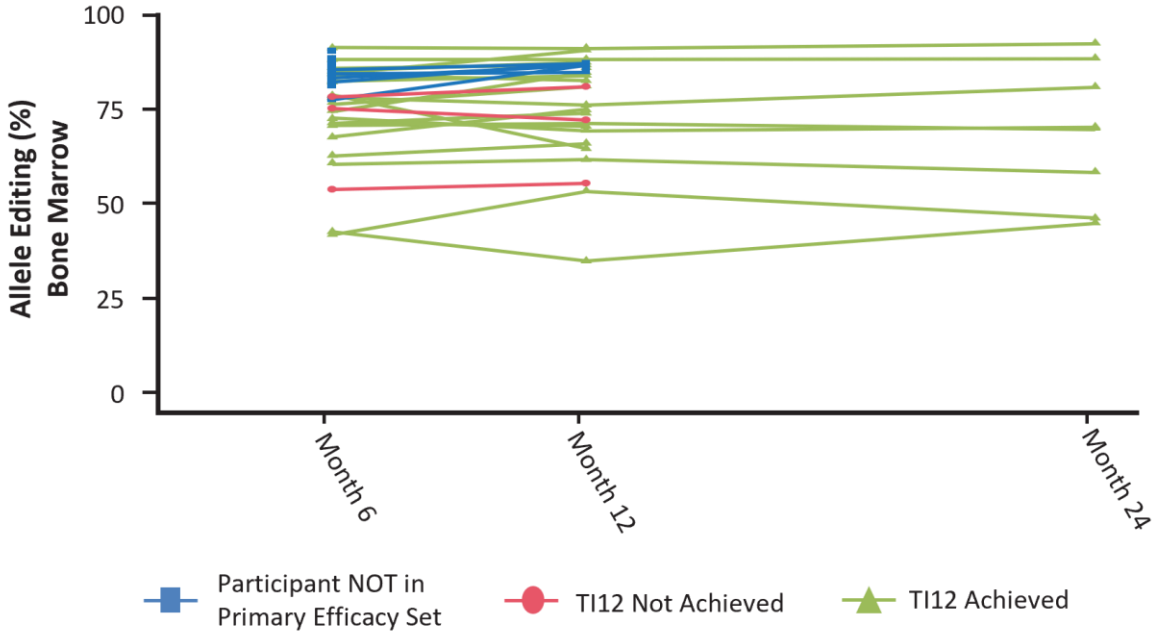
c) Please find allelic editing data stratified by the achievement of TI12 (yes, no) below in Figure 4 and Figure 5.

Figure 4: Allelic editing in peripheral blood stratified by TI (yes, no) (IA2)



TI12, maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion. The evaluation started 60 days after last RBC transfusion for post-transplant support or TDT disease management.

Figure 5: Allelic editing in bone marrow stratified by TI (yes, no) (IA2)



TI12, maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion. The evaluation started 60 days after last RBC transfusion for post-transplant support or TDT disease management.

Data stratified by genotype is not available; however, we do note that all patients at D120 are transfusion independent irrespective of genotype,

[redacted]. Subgroup analysis of the primary endpoint in IA2 shows that the 3 patients who did not achieve TI12 were all β^0/β^0 -like genotype (2) These patients have all achieved TI at D120 and their allelic editing is shown in red in the figures above. This indicates that there is no correlation between allelic editing and those patients who didn't achieve TI12 (3).

Mortality

B10. Priority Question: Reported life years gained in the economic model is substantially shorter for both exa-cel and SoC than for corresponding results reported in the beta-thalassaemia appraisal [ID968] (see company base results). This is despite ostensibly similar assumptions and parameter inputs being used. Further, the modelling of cardiac-related mortality appears to lack face validity and leads to substantially shorter life expectancy even when iron levels are assumed to be normal from cycle 0.

a) **Please explore the difference in reported life years gained and why life expectancy is so much shorter than in the beta-thalassaemia model.**

b) **Please justify your approach to modelling cardiac-related mortality and consider appropriate revisions to model assumptions.**

Company response

a) Our model predicts 29 undiscounted life years (LYs) for the SoC arm vs. 38 LYs in ID968 (the exa-cel and beti-cel arms cannot be compared due to differences in proportions achieving TI). The EAG in ID968 challenged the face validity of the beti-cel model and criticised its overly complex structure, an individual simulation model substantially different to the present Markov structure which could ostensibly generate different results. They also criticised mortality assumptions applied to the model, notably the standardised mortality ratio (SMR), which they considered was derived from a non-contemporary cohort of patients treated with older ICTs associated with poorer compliance (26).

However, Vertex has conducted its own burden of illness study (provided with the submission) in a more contemporary UK cohort which demonstrated excess mortality of 5-6x the matched UK general population, consistent with that observed in the Jobanputra study (26). The mean and median age at death were 55 and 57 years, respectively, demonstrating that outcomes for TDT patients remain poor despite modern ICT therapy. Unlike the beti-cel model, our model was calibrated to predict an SMR and median survival in line with that observed in our burden or illness study and Jobanputra et al., ensuring that our model had external validity (8, 9, 26). We therefore consider any comparisons with the beti-cel model to be irrelevant as the EAG did not have its disposal a contemporary cohort of patients with which to draw relevant comparisons for survival.

b) For clarity, it is not possible to set T2* levels to 'Normal' from cycle 0. The lowest health state at baseline is the T2* Low health state, associated with an annual risk of cardiac complications of 1.1%, hence why there is material ongoing cardiac mortality even when all patients are allocated to the lowest T2* health state at baseline. Only functionally cured patients can transition to the Normal myocardial T2* health state (associated with an annual risk of cardiac complications of 0.3%), at the end of the normalisation period.

   We have checked our cardiac mortality calculations, and these appear to correct valid mortality rates conditional on experienced cardiac morbidity. However, we acknowledge that allowing only the exa-cel arm to achieve normal myocardial T2* levels may lead to a potential bias, therefore we have conducted a number of scenarios including:

   - Setting the Low T2* value to be equal to the Normal T2* value of 0.3%. To ensure that the model continues to predict an overall mortality in line with evidence from Jobanputra et al. and our burden of illness study, we recalibrate the model by increasing the TD SMR of 3.45 to 3.93, delivering an overall SMR of 5.0 for TDT patients vs. the general population. This generates 37 undiscounted LYs in the SoC arm and 46 in the exa-cel arm, but notably predicts a median survival of 60 years for SoC, above the burden of illness median of 57. That is, we assume that

the relative contribution of early cardiac mortality is reduced but that of other morbidities not captured in the model is increased (and the total LYs delivered change due to the shape of the SoC survival curve).

- Setting the Normal T2* value risk of complications to zero, as it could be argued that the risk of complications, impact on QoL, costs and subsequent mortality are already captured within general population estimates. This generates 29 undiscounted LYs in the SoC arm and 47 LYs for exa-cel.

- Assuming a zero risk of complications in both the Normal and Low T2* states and setting the SMR to 4.12 in order to deliver an overall TD SMR of 5. This generates 41 undiscounted LYs in the SoC arm and 55 for exa-cel, but notably predicts a median survival of 65 years, well above the Vertex burden of illness study median of 57.

It can be seen from Table 12 that the ICER decreases by 8% in the first scenario, 18% in the second and 3% in the last

Table 12: Scenario assuming different myocardial iron risks

Scenario	Incremental costs (unmodified)	Incremental LYG	Incremental QALYs (unmodified)	ICER (DCEA & severity modified)	ICER (severity modified)
Base case Low T2* risk (1.1%) & TD SMR of 3.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low T2* risk (0.3%) & TD SMR of 3.93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Zero risk for Normal T2*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Zero risk of complications in Normal and Low T2* & TD SMR of 4.12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse Events

B11. Table 27 of the CS presents data on AEs of Grade 3 or above occurring in >10% of patients after exa-cel infusion.

a) Please explain why costs associated with these AEs are not considered in the economic analysis.

b) Typically, AEs of Grade 3 or above are presented for an incidence of >5% of the patient population. Please update the information in Table 27 to include data on AEs of Grade 3 or above occurring in >5% of patients after exa-cel infusion.

c) Please present data on AEs of Grade 3 or above occurring in >5% of patients after exa-cel infusion that persist up to or occurring after 28 days following exa-cel infusion.

Company response

a) The model delivery costs included the NHS spell cost of autologous stem-cell transplantation (auto-SCT), an HRG code which includes all management costs from 30 days prior to up to the first 100 days post-transplant (27). We selected a 100% inpatient tariff, which would be expected to include any hospitalisations within the first 100 days, whether routine or due to AEs experienced post-transplant. In our submission, we noted that in a post-hoc analysis, [redacted] of CLIMB-THAL-111 patients spent an average of [redacted] days in hospital after having been discharged for the initial procedure. However, we explained that it was unclear whether these represented routine day visits as opposed to hospitalisations and/or whether the readmissions occurred within 100 days of treatment start (which would have been included in the auto-SCT spell cost). We therefore included a scenario whereby [redacted] of patients incurred the cost of a non-elective admission for thalassaemia (trim point 5 days), plus the cost of [redacted] additional days in hospital (thalassaemia spell cost x [redacted]).

We consider this scenario analysis to have adequately captured the cost of any AEs due to exa-cel and/or busulfan, while almost certainly being an

overestimate, given that the post-hoc analysis did not discriminate between routine assessment visits and unplanned hospitalisations.

b) The information presented in Table 27 in the CS has been updated to include data on AEs of Grade 3 or above occurring in >5% of patients after exa-cel infusion (Table 13).

Table 13: Grade 3 or above AEs occurring in >5% of patients after exa-cel infusion (CLIMB THAL-111, FAS

MedDRA Preferred Term, n (%)	Exa-cel to M24 (n=48)
Patients with any Grade 3 or above AEs	**41 (85.4)**
Febrile neutropenia	24 (50.0)
Stomatitis	19 (39.6)
Anaemia	18 (37.5)
Thrombocytopaenia	17 (35.4)
Platelet count decreased	15 (31.3)
Mucosal inflammation	14 (29.2)
Neutrophil count decreased	13 (27.1)
Decreased appetite	11 (22.9)
WBC count decreased	7 (14.6)
Epistaxis	5 (10.4)
Neutropenia	5 (10.4)
Veno occlusive liver disease	5 (10.4)
Hypokalaemia	4 (8.3)
Hypophosphatemia	4 (8.3)
Iron overload	4 (8.3)
Nausea	4 (8.3)
Vomiting	4 (8.3)
Blood bilirubin increased	3 (6.3)
CD4 lymphocytes decreased	3 (6.3)
Haematuria	3 (6.3)
Headache	3 (6.3)
Hypoxia	3 (6.3)

Key: AE: adverse event; exa-cel: Exagamglogene autotemcel; FAS: Full Analysis Set; M: month; WBC: white blood cell.
Notes: AEs were coded using MedDRA Version 25.0. The SAS included 59 patients. Percentages were calculated as n/N1×100. When summarising number and percentage of patients for each study interval, a patient with multiple events within a category and study interval was counted only once in that category and study interval. The table is sorted in descending order of frequency of the exa-cel to M24 column by preferred term.
Source: Table 14.3.2.4.1, CLIMB THAL-111 CSR (2).

c) Unfortunately, it will not be possible to provide these data without a post-hoc analysis, which we will not be able to conduct in time for the clarification response deadline. However, we consider the costs of AEs to have been adequately captured (and definitely overestimated) by the model scenario discussed in part a) and the disutility of AEs to be adequately captured by the disutility of 0.11 that was applied to all patients (not just those with AEs) in the exa-cel cohort for a duration of 1-year post-transplant.

Health-related quality of life

B12. Priority Question: The company state (CS p.88) that *"At baseline, mean (SD) EQ-5D-5L utility index scores in CLIMB THAL-111 were reported to be greater than the average UK population score (0.87 points)".* The company cite Janssen et al. 2019 in support of this statement. However, for the 18 – 24 age group (the age group relevant to the baseline trial population), Janssen report an average utility score of 0.922 (UK - England) indicating that the mean CLIMB THAL-111 baseline EQ-5D scores are below that of the population norm (indicating a modest decrement associated with the condition).

a) **Given the preference in the NICE methods for EQ-5D data elicited from patients with the condition, and the availability of such data from CLIMB THAL-111, please provide further justification for the use of vignettes valued by the general population. Please provide documented evidence supporting any conclusions regarding the inadequacy of the EQ-5D in this population.**

b) **Please update the economic model to include a scenario whereby the model uses the mapped EQ-5D-3L utility values from the CLIMB THAL-111 trial.**

Company response

a) Justification for lack of sensitivity of the EQ-5D and use of vignettes was provided extensively in sections B.1.3.2.2 and B.2.6.2.8. In summary, we believe the EQ-5D to be insensitive because:

- TDT patients have an inherited condition and have experienced chronic symptoms of TDT and its treatment since early childhood. One reason for the high baseline utility values is adaptation, an issue which has been observed with chronic conditions (28).
    - Longer duration of a long-standing illness brings a higher probability of reporting being in Excellent health, and decreases the probability of reporting Poor, Fair and Good health;
    - The likelihood to report Excellent health increases by 8 percentage points for each ten additional years of duration.
- Secondly, the EQ-5D does not have a fatigue domain, a key symptom for TDT patients, particularly in the period preceding their blood transfusion. A recent study demonstrated improved psychometric performance of the EQ-5D-5L in a chronic disease population when a fatigue domain was added (29).
    - 25% of respondents in this study reported full health with a fatigue item added vs. 37% with the unmodified EQ-5D-5L;
    - The EQ-5D-5L Fatigue domain was more strongly correlated with the EQ VAS compared to the EQ-5D-5L.
    - Compared to the unmodified EQ-5D-5L, the extra fatigue item added more explanatory power, especially in the subgroup of respondents with a chronic health condition.

Clearly, a high baseline EQ-5D value brings alongside it issues with ceiling effects, whereby the magnitude of *changes* in quality of life (QoL) from transformative therapies such as exa-cel will fail to be captured. There are multiple real-world examples of a lack of sensitivity of the EQ-5D and/or a ceiling effect:

- A study of 30 patients with TDT from the UK, France, and the US found that EQ-5D-5L does not fully capture important symptoms/functional impacts and therefore lacks face validity in a TDT population given that these patients undergo frequent RBC transfusions and require treatment with ICT, which is associated with poor tolerability (30, 31).

- 74.1% of participants reported that the EQ-5D did not capture important aspects of their experience of living with TDT;
- 29.6% of participants commented that the EQ-5D did not capture how their experience of living with TDT changes depending on where they were in their RBC transfusion cycle;
- 22.2% of respondents reported that fatigue was an important aspect of their experience not captured by the EQ-5D.

- A recent study (published after our QoL SLR search) concluded that the substantial ceiling effect of the EQ-5D suggests it may not be sensitive to QoL impact in TDT (32):
  - In a sample of 23 TDT patients, 9 (43%) participants had EQ-5D-3L utility values of 1 (perfect health).
  - Patients with a wide range of TranQoL scores (a disease-specific quality of life measure for adults and children with thalassaemia major) had EQ-5D utilities of 1, suggesting that the EQ-5D was not sensitive to QoL differences that were detected with the TDT-specific measure.
  - Neither adult nor youth versions of the EQ-5D correlated significantly with the number of days since last blood transfusion.

  Finally, evidence from the CLIMB-THAL-111 study itself supports a ceiling effect for the EQ-5D, where it is evident that a proportion of patients recruited reported utility values of 1 at baseline (at this time we unfortunately have no data on proportions). If the EQ-5D accurately captures QoL, perhaps the most pertinent question is: Why would a TDT patient apparently in full health be willing to risk a burdensome transplantation procedure with an experimental therapy?

b) At the time of the IA2 data cut only 8 patients in the PES had 24 months of follow up data. Utility values earlier than this are unlikely to reflect the utility of a functionally cured patient, given the time needed to recover from the transplant, achieve iron normalisation and cease ICT (time since transplant has been shown to be a key determinant of QoL in TDT (33). The mean utility value

of these 8 patients at 24 months was [redacted] (noting that the baseline age of these 8 patients is unknown, but that the value is well over the population norm for age 18-24). These 8 patients had an increase from baseline of [redacted], suggesting a baseline utility score of [redacted]. We therefore have not conducted this scenario as we consider it to be of little value to the cost-effectiveness analysis, given that the baseline utility values of the IA2 FAS and PES populations were [redacted] and [redacted] respectively, and hence utility gains at final follow-up are likely to be substantially different.

B13. Priority Question: Tables 19, 20 and 21 in the company submission respectively summarise data on EQ-5D, FACT-BMT and FACT-BMT fatigue-related quality of life scores. Please provide a formal statistical analysis (e.g. mixed effects model) of this data analysing change in quality of life scores from baseline.

a) **Please provide the values reported in Tables 20 and 21 including only patients from the PES population.**

Company response

Unfortunately, we do now have the resource available to generate a mixed effects model in time for clarification responses.

a) The requested tables are reproduced from the IA2 CSR below in Table 14 and Table 15.

Table 14: Summary of FACT-BMT scores (CLIMB THAL-111 and CLIMB-131, PES)

Visit	FACT-BMT total score	FACT-G total score	BMTS	FACT-G subscores			
				PWB score	EWB score	FWB score	SWB score
Baseline							
n	22	22	22	22	22	22	22
Mean (SD)	110.7 (20.2)	83.3 (16.0)	27.3 (16.0)	22.0 (6.0)	18.5 (3.8)	20.9 (5.1)	21.9 (4.8)
Median	115.5	85.0	28.0	24.5	20.0	19.5	23.2
Min, Max	68.0, 140.0	53.0, 106.0	15.0, 35.0	9.0, 28.0	11.0, 24.0	11.0, 28.0	10.5, 28.0
Month 12							
n	22	22	22	22	22	22	22
Mean (SD)	118.5 (20.0)	87.6 (15.3)	31.0 (5.3)	24.8 (4.9)	20.8 (2.9)	20.4 (6.4)	21.6 (6.7)
Median	120.3	89.3	31.0	27.0	21.0	21.5	22.5
Min, Max	73.0, 145.0	48.0, 108.0	18.0, 38.0	10.0, 28.0	12.0, 24.0	6.0, 28.0	4.0, 28.0
Month 18							
n	17	17	17	17	17	17	17
Mean (SD)	120.9 (15.8)	89.6 (12.5)	31.3 (4.1)	25.8 (3.5)	20.6 (2.8)	21.0 (5.5)	22.2 (4.4)
Median	127.0	92.0	32.0	27.0	20.0	21.0	22.0
Min, Max	93.0, 143.0	65.0, 106.0	24.0, 39.0	14.0, 28.0	14.0, 24.0	10.0, 28.0	15.0, 28.0
Month 24							
n	8	8	8	8	8	8	8
Mean (SD)	127.4 (15.0)	94.0 (11.4)	33.4 (4.2)	26.0 (2.0)	22.3 (2.3)	23.5 (4.9)	22.3 (5.8)
Median	132.5	97.5	34.5	26.5	23.5	26.0	23.0
Min, Max	102.0, 141.0	77.0, 106.0	25.0, 39.0	23.0, 28.0	18.0, 24.0	15.0, 28.0	14.0, 28.0

Key: BMTS: bone marrow transplantation subscale; EWB: emotional well-being; FACT-BMT: Functional Assessment of Cancer Therapy-Bone Marrow Transplant; FAS; FWB: functional well-being;; PES: Primary Efficacy Set; PWB: physical well-being; SWB: social/family well-being.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation.
Source: Table 11-15, CLIMB THAL-111 CSR (2).

Table 15: Summary of FACT-BMT fatigue related scores (CLIMB THAL-111 and CLIMB-131, PES)

Visit	Question #'1: Lack of energy	Question #35 Tiredness
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Month 12		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Month 18		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Month 24		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Key: PES: Primary Efficacy Set; SD: standard deviation.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation.
Source: Table 11-16, CLIMB THAL-111 CSR (2).

B14. Priority Question: As noted in Question B1, the committee in ID968 preferred to use utility data from a matched population of patients from the UK chart review. This data indicated that the utility of patients with beta-thalassaemia was approximately 0.1 points lower than that of age and sex-matched patients from the general population. Please present an appropriate scenario analysis reflecting the committee's preferences.

Company response

As explained in our response to question B1, values from the chart review subgroup are not published, therefore we are unable to conduct a scenario analysis with ID968 committee preferences. We have conducted a scenario analysis in Table 16 whereby TI patients have a utility of 0.922 (the value provided by the EAG for the matched general population in B12) and TD patients have a utility of 0.822 (0.1 lower than the matched general population), with transfusion-reduced (TR) patients allocated the average of the two. In this scenario, the ICER increases by 22%.

Table 16: Scenario assuming a 0.1 decrement from general population utility

Scenario	Incremental costs (unmodified)	Incremental LYG	Incremental QALYs (unmodified)	ICER (DCEA & severity modified)	ICER (severity modified)
Vignette utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chart review utility decrement of 0.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B15. Priority Question: In the previous NICE appraisal of Zynteglo (ID968), the committee cite the company's patient preference report, where only 37% respondents said they would immediately accept a referral to a transplant specialist for the treatment if offered it, potentially suggesting a preference for the current standard of care, on balance. Please comment on this with reference to the adequacy of current treatment options to maintain a reasonable health-related quality of life.

Company response

Firstly, the Company have significant concerns about the use of this patient preference report to inform deliberations in this appraisal. All that we have available to us is a figure of 37%, which it is clear from the beti-cel committee papers was supposed to be redacted. This raises questions, including:

1. How was this survey conducted, what was the methodology?
2. What was the sample size?
3. Was the population aligned to the beti-cel regulatory label (i.e. excluding the most severe patients [β^0/β^0], who would be eligible for exa-cel)

Beyond our immediate concerns relating to the lack of information on this report, we firmly refute the implied association between willingness to receive beti-cel and adequacy of current treatment options. The decision to receive a highly novel gene therapy (we assume the patient preference report was conducted no later than 2019 based on clarification date, a time when there were no gene therapies available in the

UK, and far less awareness than now) is multi-faceted, and concerns around a highly novel modality, requirement for myeloablative conditioning & impact on fertility, as well as potential insertional mutagenesis are likely contributing factors.

As already stated, beti-cel's regulatory label did not include the most severe form of TDT (β^0/β^0). Based on the limited information provided, we assume these patients did not form part of the patient preference survey (asking patients who would not be eligible whether they would be willing to receive treatment would not appear logical), biasing the response towards less severe patients relative to the population relevant to this appraisal. The severity of CLIMB THAL-111 patients relative to the general TDT population is described in more detail in our response to B7. In addition, at the D120 data cut, 100% of patients were transfusion independent (3).

Whilst this is likely to increase the willingness to receive treatment with exa-cel, based on clinical expert feedback and NHS England's budget impact analysis report, factors including the effects of conditioning on fertility, hesitancy to be the first patients to be treated with a novel modality, and fitness to undergo myeloablative conditioning are all likely to form part of patient considerations; none of which are linked to disease severity.

To summarise, the Company strongly believe that an association cannot be made between willingness to receive beti-cel and adequacy of current treatment. Beti-cel was one of the first gene therapies to be approved in Europe, beti-cel's approved population did not include the most severe form of TDT, and gene therapy carries risk of insertional mutagenesis. These factors will all have played a part in patients' response to this survey, for which we re-iterate we have no reference beyond a mistakenly unredacted figure in the beti-cel committee papers.

B16. A caregiver scenario is applied in which a 0.05 carer utility decrement is applied in the model until the end of the time horizon following patient death. Please provide justification (including relevant precedent from a previous NICE appraisal) to support this approach. In the absence of such a precedent, the EAG suggests this decrement is excluded from the company submission and model.

Company response

Note to the EAG: to remove the death decrement from the caregiver scenario, please set the value in the user defined cell (E72, Utility inputs) to 0.

We would like to confirm that the application of this disutility throughout the time horizon was a modelling error, which has now been corrected. It should only have been applied up to age 26. We therefore present below two scenario analyses in Table 17:

- Where the carer (limited up to age 26) and death disutility is applied
- Where the death disutility is removed

The results of this scenario show that with both the health state and death carer disutilities applied, the ICER decreases by 4%, whereas when only the health state carer disutilities are applied, the ICER decreases by 1%.

Table 17: Scenarios for carer disutilities

Scenario	Incremental costs (unmodified)	Incremental LYG	Incremental QALYs (unmodified)	ICER (DCEA & severity modified)	ICER (severity modified)
No carer disutilities (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state and death-related disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state disutilities only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In HST 7: *Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency*, QALY loss due to death of a child was included in a scenario analysis, assumed to be 9% of the child's QALY loss on death. The disutility was underpinned by the principle that a QoL loss had been observed in bereaved parents in a study by Song et al (2010) (34). The authors in this study compared the quality of

life of 233 couples who had experienced a child death with 229 comparison couples. Quality of life was measured using HUI3. Stratified random sampling was used to select the matched comparison group, using gender, age and education as stratification variables. A multilevel model found that, controlling for demographic factors, bereaved parents HRQL was 0.04 lower than the control group.

Including family QALY loss in HST7 decreased the company's base case ICER from £36,360 to £33,201 and increased incremental QALYs from 13.6 to 14.9. This was not included in the final estimates because the appraisal committee considered that it would *underestimate* the benefit to carers of successful treatment. That is, they were not against the principle of the disutility but did not have the evidence to quantify it, hence they considered the improvement in carer QoL qualitatively in decision-making.

Resource use

B17. In the previous NICE appraisals (ID3980, ID1684) it was noted that micro-costing approaches are likely to underestimate the true costs of administering complex gene therapies and NHSE put forward a tariff to capture these costs of a CAR-T administration. How do the resources associated with the administration of exa-cel compare to other gene therapies such CAR-T therapies? Do the company consider it reasonable to assume that the costs of administering CAR-T cells are broadly representative of those associated with the administration of exa-cel?

a) **Please present scenario analyses reflecting the administration costs applied in i) ID3980 and ii) ID1684.**

Company response

We have identified ID1684 as the now published appraisal TA895 and ID1684 as TA872, the CDF review of TA559. We can see that there were committee discussions regarding a tariff in the three most recently published CAR-T appraisals TA895, TA893 and TA872. The tariff cost of £41,101, apparently agreed in TA872, includes all costs of care from the decision to have CAR T-cell therapy to 100 days after the infusion. This compares with total delivery costs per exa-cel-infused patient totalling

approximately [redacted] in our model (figure taken from the exa-cel trace following removal of exa-cel costs and setting withdrawal to 0%).

Firstly, to refer to the costing approach applied our submission as a 'micro-costing' approach is incorrect; we have applied the spell costs for identical or analogue procedures obtained from NHS reference costs in line with the NICE methods guide, including applying an autologous stem cell transplantation HRG code which we believe to be procedurally a fair analogue of CRISPR-based transplantation, as we explained in our submission and reiterate in this response.

Secondly, having consulted the committee papers for TA895, TA893 and TA872, it appears that the CAR-T tariff proposed by NHSE was itself generated using a prospective micro-costing approach not underpinned by any evidence whatsoever of the actual costs to the NHS of CAR-T administration. This prospective costing appears to have been the subject of further (unpublished) negotiation before agreeing the final cost of £41,101:

- From the TA893 committee papers: "*a CAR-T Finance Working Group used the SmPC for individual products and trial experience of the initial products to establish the individual components of the pathway to build an overall projection of the costs associated with each patient. These overall estimations were then subject to national negotiation discussions between the provider cohort and NHS England to agree an overall tariff, which was considered acceptable to all parties*".

Other points of note:

- Our costs include nearly £10k worth of plerixafor, a high cost drug not routinely commissioned in the NHS.

- According to TA893, the tariff of £41,101 excluded the costs of bridging and conditioning therapy. The former is not relevant to exa-cel administration and the latter is already included within the spell cost of auto-SCT, which includes management costs in the 30 days preceding the SCT and 100 days after it (27). The latter was confirmed to us by an NHS haematologist who carries out SCTs in TDT patients.

- We note that the published NHS reference cost for auto-SCT (100% inpatient stay) is ~£19k for adults (none of the three CAR-T TAs having a paediatric indication) with peripheral blood stem cell harvest costing an additional £5k, totalling approximately £25k for both mobilisation and transplant. It is therefore unclear what the additional ~£15k in the agreed NHSE tariff is paying for, given that emerging real-world evidence demonstrates that the HRU required for CAR-T delivery is less than that required for either allogeneic SCT or autologous SCT (35, 36), including the length of stay required for the procedure:

    - Mean index non-pharmacy cost was lower for CAR T-cell therapy than SCT (mean $41,375 CAR T, $51,778 auto-SCT, $111,594 allo-SCT; p<0.001). Among inpatient-treated patients, the average length of stay (LoS) was shorter for CAR T-cell therapy than for auto-SCT or allo-SCT (mean [median]: 18[15] days CAR T; 21[20] days auto-SCT; 28[26] days allo-SCT; p<0.001) (36).

    - CAR-T treatment required ~ 30% less staff time than allo-SCT (primarily nursing staff) due to fewer chemotherapy cycles, less outpatient visits, and shorter hospital stays (35).

Consequently, we believe that the NHSE tariff is likely to have overestimated CAR-T delivery costs by at least 60% and is an inflated reference point for adult CAR-T services, hence why we felt published NHS auto-SCT reference costs to be a more robust reference point (allo-SCT being inappropriate as it includes administrative costs associated with external donors and the additional morbidities associated with allo-SCT).

The only uncertainty then concerns total length of stay of exa-cel-treated patients vs. auto-SCT patients; our model assumes that length of stay (LoS) is likely to be similar to that of auto-SCT. The trial LoS data (average [redacted] days from infusion to discharge) would be inappropriate, as data are not from the UK and patients are likely to be kept in hospital for longer within the setting of an experimental treatment. The average LoS for allo-SCT and auto-SCT patients in England is 35.5 and 20.1 days, respectively (37).

In order to explore the impact on the ICER, we here present a scenario whereby we assume a LoS more in keeping with the trial. We add the cost of an additional [redacted] days of inpatient stay to the estimated costs (NHS reference cost of an elective admission for thalassaemia, trim point 5 days, plus the additional cost/day of [redacted] additional days, totalling [redacted], as per Table 18). The results of this scenario are presented in Table 19 and had an immaterial impact of 1% on the ICER.

Table 18: Additional hospitalisation cost calculations

HRG code	Unit cost	Trim point (days)[1]	Cost/day	% of cohort
SA11Z Thalassaemia	£2,687	5	£537	[redacted]
Paediatric Thalassaemia with CC Score 1+	£2,539	5	£508	[redacted]
Weighted average cost of [redacted] days	[redacted]			

[1]Trim point from the 2023/25 NHS Payment Scheme: 2023/24 prices workbook,

Table 19: Scenario for additional hospitalisation days

Scenario	Incremental costs (unmodified)	Incremental LYG	Incremental QALYs (unmodified)	ICER (DCEA & severity modified)	ICER (severity modified)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 additional hospitalisation days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) We have not conducted this scenario, given our model currently assumes *higher* delivery costs than those assumed in the CAR-T appraisals.

B18. Priority Question: Please update all drug acquisition costs in the model using up-to-date electronic market information tool (eMIT) costs.

Company response

We understand from our clarification call that there was a discrepancy between the values provided in Appendix K and the main body of the submission. The template table in Appendix K requests the “List price” whereas in the model we use the eMIT

price for busulfan (which is procured in and delivered in hospitals) and the NHS drug tariff price for ICTs (the larger proportion of volumes being dispensed in retail pharmacies, where drugs are procured via a different process to hospital drugs). It would be inappropriate to use eMIT for retail pharmacy drugs, as eMIT reports hospital-sector prices, which may have a different cost to the NHS to those procured by retail pharmacies. We have therefore retained the prices used in the model as per Table 20 below.

Table 20: Unit costs used in the model

Parameter	Presentation	Unit cost	Source
Busulfan	1x 60mg	£169.18	eMIT (July to December 2022)
desferrioxamine (DFO)	10x 500mg	£46.63	NHS drug tariff (June 2023)
deferasirox (DFX)	30x 90mg	£126	NHS drug tariff (June 2023)
Deferiprone (DFP)	100x 500mg	£130	NHS drug tariff (June 2023)

Distributional cost-effectiveness analysis

B19. Priority Question: The submission highlights an equality consideration in relation to ethnicity (Section B.1.4, page 44, Company Submission). The method of distributional cost-effectiveness analysis (DCEA) applied in the submission can be used to illustrate the distribution of health benefits and costs across equity relevant subgroups defined by the analyst.

a) **Please explain and justify why the distributional cost-effectiveness analysis does not explore the distribution across population groups defined on the basis of ethnicity.**
b) **Please explain and justify why the Index of Multiple Deprivation (IMD) based on area of residence was used to define population groups for the DCEA.**
c) **Please explain and justify why the DCEA does not consider an intersectional perspective using subgroups based on ethnicity and IMD.**

Company response

a) TDT disproportionately affects ethnic minorities within the UK. Most ethnic minority groups within the UK are also disproportionately affected by socio-economic deprivation, which is a key determinant of health status (38). TDT patients are more likely to live in a more deprived area of the UK, with 56.2% of TDT patients identified in the Vertex BoI study living in the two most deprived quintiles according to the Index for Multiple Deprivation (IMD) (8, 9). Supported by external expert consultation, we therefore considered socio-economic deprivation to be an adequate proxy which reflects ethnicity. This is because of the disproportionate distribution of TDT prevalence across ethnic minorities whom, in turn, are also most likely to be disproportionately affected by socio-economic deprivation (8, 9). We also judged the available ethnicity data, collated from the CPRD-HES database, to be inadequate for an analysis based on ethnicity in the TDT population. This was because several ethnic minority group data were masked (specifically Black and Mixed ethnicities) which thus creates potential for erroneous results or bias towards different ethnic groups (8, 9).

b) As per our response in a), deprivation was considered a sufficient proxy for representing health inequalities across the treatment and general populations since CPRD-HES ethnicity data were inadequate for analysis in the TDT population. This reasoning is supported by Cookson et al. (2020) (39), which states that directly observing whose health services are affected following expenditure changes is often infeasible due to time and budget constraints. In such cases, analysing secondary data is a suitable approach to identify variables as proxies, for example using the total number of healthcare appointments or episodes or days. This, however, rests on three main assumptions: 1) A unit of utilisation generates the same health regardless of where it takes place in the health system (e.g., by provider type, disease category, geographical location); 2) A unit of utilisation generates the same health regardless of the social characteristics of the recipient; and 3) The social distribution of services affected at the margin is the same as the average social distribution across the health system. Since the CPRD-HES data were disease-specific (i.e., based solely on TDT-patient utilisation), assumptions 1) and 3) can be relaxed, as suggested by Cookson et al. This is especially applicable

given that the CPRD-HES data provided data on a population aligned to the pivotal CLIMB THAL-111 study eligibility criteria (8, 9). On a qualitative level, we were also mindful that the submission of a DCEA alongside the CEA was a novel approach to NICE HTA submissions. As supported by external expert consultation, and over-and-above the quantitative reasons presented above, the use of a single predictor of health inequalities across quintile groups was considered preferable to aid interpretation of the DCEA results. While Vertex acknowledges further research is needed at the national level to evolve these data, it is undeniable that TDT affects ethnic minorities that are also affected by socioeconomic deprivation (8, 9, 38, 40). Therefore, the simplification of assumptions is not only appropriate but perhaps a conservative approach as to the overall impact estimated by the DCEA results.

c) Given the discussion in a) and b), IMD was considered an adequate proxy that sufficiently captured the distribution of health inequalities, within and across treatment and general populations, because most ethnic minority groups are also disproportionately affected by socio-economic deprivation within the UK (8, 9, 38, 40). NHS England specifically identifies IMD quintiles as a means of identifying disadvantaged groups, and as such, our approach is also aligned with other health service priorities and approaches (8, 9, 38, 40) Hence, using IMD as a predictor for health inequality in TDT was considered adequately representative of the disproportionate prevalence of TDT across ethnic minorities. In other words, the disproportionate distribution of TDT prevalence across ethnic minorities was assumed to be captured by socio-economic deprivation too. Moreover, since, in England, there are also health inequalities between different ethnic minority groups (38), subgroup comparisons based on ethnicity were omitted to avoid erroneous results or bias towards different ethnic minority groups. As stated above, this was due to insufficient CPRD-HES data being available for a robust analysis across all TDT ethnic minority groups (8, 9).

B20. Priority Question: Please explain and justify why the distribution of disease by IMD should be considered for this appraisal when it is not part of the NICE Reference Case for other appraisals.

Company response

Principle 9 of NICE's charter aims to reduce health inequalities. Thus, NICE considers inequality or unfairness in the distribution of health to be an important factor in decision-making. Vertex is aware that historically, the fact that a given group of patients have been subject to health inequalities has been considered by committees, and due flexibility has been applied (41, 42). In the past, stakeholders have brought forward qualitative arguments illustrating the impact that health inequalities have on a certain patient population due to their race, which is an important part of the deliberation process, and NICE has accepted these arguments (41). Therefore, Vertex seeks to not only highlight the health inequalities experienced by patients with TDT through qualitative evidence, but also to bring quantitative evidence to bear and make clear the inequalities experienced by these underserved patients.

Prior to submission, Vertex had several productive conversations with the NICE team about our intention to submit this additional evidence with a view to supporting principle 9 of NICE's charter. Vertex welcomed NICE's aim of accounting for health inequalities in its guidance, [redacted]

In addition to NICE's priorities, NHS England has set out its intention to reduce health inequalities as part of its future work. NHS England specifically identifies the IMD as a means of identifying disadvantaged groups, and as such, our approach is aligned with other health service priorities and approaches (43).

Given the emphasis placed on addressing health inequalities across the health service and specifically from NICE, [redacted] we expect this to be taken into account in decision-making.

B21. The submission applies an aggregate distributional cost-effectiveness analysis approach. This approach cannot incorporate equity relevant variation in model inputs, and is usually applied when only summary published results from a cost-effectiveness analysis are available.

a) **Please explain whether any of the cost-effectiveness model inputs could be expected to vary between IMD population groups**

b) **Please justify why a full distributional cost-effectiveness analysis was not undertaken.**

Company response

a) We assume that cost-effectiveness across IMD population groups is constant. We acknowledge that this assumes the use of appropriate methods, including the decision analytic model structure, and that these produce an unbiased estimate of the aggregate population health impacts and costs. It is obviously expected that there will be variation in cost-effectiveness at an individual level. However, accurately capturing the variation in health opportunity costs, utilisation, and thus cost-effectiveness between ethnicity or IMD groups, as discussed in B19 and B28, is challenging within the TDT population, due to data scarcity. The issue of data scarcity and choice of analysis approach has also been compounded by time constraints. Thus, we have focused our analysis on population-level equity-efficiency trade-offs, providing information about the incremental distribution of health effects and opportunity costs for two groups – specifically, programme recipients and everyone else served by the decision-maker. We would like to emphasise that this assumption is supported by CLIMB-THAL-111 data, which found that no relevant subgroups were likely to benefit more or less from exa-cel treatment and, as stated in the dossier submission, would likely not have greater or less cost-effectiveness.

b) Since NICE assess cost-effectiveness at the population level, we presented DCEA results at an aggregate population-level. The decision to conduct an aggregate approach was based on several factors, as discussed in a) above and priority questions B19 and B28. The approach was also supported by external expert consultation given the decision context. Firstly, a fully comprehensive analysis of would desire to incorporate all the social variables

relevant to equity, whether these are by ethnicity, socioeconomic status, geographical region, or others. But, as discussed in Cookson et al. (2020) (39), deciding which causes of inequality are unfair is a question of value rather than of fact. Thus, based on current precedent with NHS institutional practice, we have aligned our analysis with NHS England, which specifically identifies IMD as a means of identifying disadvantaged groups, and as such, our approach is aligned with current health service priorities and approaches. Nevertheless, incorporating a full simulation of socio-economic, ethnic, and other factors associated with health deprivation is, obviously, a preferable approach. As stated in Cookson et al (2020) (39), "… [estimating] only the associations between sociodemographic characteristics and health can overlook the causal pathways that link them together. For example, a gap of ten years in life expectancy between the richest and poorest in a country may be due to low income in childhood causing poor health in adulthood rather than poor health in childhood causing low income in adulthood." However, providing a robust and reliable causal analysis requires sufficiently rich data. Without sufficient data (for example, the issue of masked ethnicity data in the CPRD-HES analysis discussed in priority question B19) it is unlikely that a comprehensive analysis would provide more valid inferences and may, in fact, lead to erroneous allocations to differing groups. Hence, despite the assumption of constant cost-effectiveness across all IMD groups, providing an aggregate estimation, we believe, provides a more reliable estimate of the expectation for the equity-efficiency of exa-cel within the NHS health system.

B22. Priority Question: Please explain why the proportion of the general population by IMD group (Appendix L, Figure 40) is based on the distribution of patients recorded in Hospital Episode Statistics by IMD group in the year 2012-13 from Love-Koh et al 2020.

Company response

This input source was informed via external expert consultation and thus, as confirmed by the external expert during consultation, it was assumed to be the most recent and reliable source for these input values. These values are also the values referenced in Cookson et al. (2020) (39). Please also see priority question B19 for further discussion

on the use of episode statistics. However, we have aligned and updated the base-case with the values from the more recent publication cited by the EAG in B23 below.

B23. Please explain why the cost-effectiveness analysis does not use the most recent estimates of the distribution of quality-adjusted life expectancy (QALE) by IMD quintile (Love-Koh, J., Schneider, P., McNamara, S. et al. Decomposition of Quality-Adjusted Life Expectancy Inequalities by Mortality and Health-Related Quality of Life Dimensions. PharmacoEconomics 41, 831–841 (2023)).

Company response

We were unaware of this publication at the time of the submission. We have updated the IMD-specific QALEs as per the EAG's request. We have also aligned the general population proportions (cells O8:S8, DCEA inputs sheet) with this reference. Please see Table 21 for a tabulation of these changes.

Table 21: Updated input DCEA values (1.5% discount)

Deprivation Group	IMD 1	IMD 2	IMD 3	IMD 4	IMD 5
General Population Shares (%)					
Previous base case (Love-Koh J., et al. 2015) (44)	23.5	20.3	20.3	18.5	17.4
Updated base case (Love-Koh J., et al. 2023) (45)	18.3	20.2	19.9	21.5	20.0
Quality-Adjusted Life Expectancy					
Previous base case (Love-Koh J., et al. 2015) (44)	63.2	67.7	70.0	73.2	75.1
Updated base case (Love-Koh J., et al. 2023) (45)	62.2	65.5	69.5	71.1	73.3

B24. Priority Question: The study by Love-Koh et al. 2020 provides an estimate of the share of opportunity costs by IMD quintile. Please explain why this was

not used to inform the distribution of opportunity costs in the cost-effectiveness analysis.

a) **Please present a scenario analysis using the Love-Koh et al. 2020 estimates of the share of opportunity cost.**

Company response

a) Since TDT patients are high priority patients, we assumed that majority of opportunity costs are borne by lower priority individuals (38). It is also important to acknowledge the wider benefits of exa-cel; it is likely that the treatment will improve individual capabilities such as independence and freedom and thus provide consumption benefits to the wider economy (39). Accurately estimating the health opportunity costs within this treatment population (and not the general population) is also challenging due to data scarcity for TDT patients as well as analytic time and budget constraints. Nevertheless, we provided several opportunity cost scenarios as recommended in Cookson et al. (2020) (39), with varying gradients across each quintile, in the submitted model. However, we have identified and corrected a related cell reference error, which pulled the same health opportunity cost gradient value across all quintile groups rather than the quintile-specific value. Based on the EAG's request, we have also included the values from Love-Koh et al. 2020 in the health opportunity costs gradient as the base-case scenario (46). Please see Table 22 and Table 22 below for a discussion and tabled comparison of these input changes.

Table 22: Health Opportunity Cost Gradient

Deprivation Group	**IMD 1**	**IMD 2**	**IMD 3**	**IMD 4**	**IMD 5**
Health Opportunity cost shares (%)					
Previous base case (Assumption)	20.0	20.0	20.0	20.0	20.0
Updated base case (Love-Koh J., et al. 2020) (46)	14.0	11.9	11.8	8.7	7.5

The DCEA input changes shown in Table 21 and Table 22 result in a 39% decrease in the DCEA-weighted ICER, driven primarily by the updated health opportunity cost values and the slight reduction in QALE shortfall between deprivation groups. See Table 22 below for a comparison of changes in the base-case DCEA-weighted economic results.

Table 23: Comparison of base case DCEA results

Scenario	Inc. costs (DCEA and severity weighted)	Inc. QALYs (DCEA and severity weighted)	ICER (DCEA and severity weighted)	NHB at £20,000 (DCEA and severity weighted)	NHB at £30,000 (DCEA and severity weighted)
Previous base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B25. Please explain why the cost-effectiveness analysis does not use the most recent estimate of the Atkinson inequality aversion parameter. The Atkinson inequality aversion parameter applied is 11, based on an estimate reported in Robson et al. (2017). Robson et al. however, provide an updated estimate of 3.5 in a more recent publication (Robson, Matthew, Owen O'Donnell, and Tom Van Ourti. Aversion to Health Inequality: Pure, Income-related and Income-caused. No. 23-019/V. Tinbergen Institute, 2023).

Company response

We thank the EAG for their comment. We were not aware of this reference at the time of submission.

As noted by the EAG, the value for the aversion to inequality in the exa-cel DCEA was informed by the data from Robson M., et al. 2017 (47). A systematic literature review (SLR) of inequality aversion values for the UK has also been conducted (48). However, the values in the systematic review vary widely, ranging from a low value of 5.76 to a high value of 28.9.

Given the above, the choice of source for an inequality value was made in consultation with an external expert as well as based on the applicability of the study criteria

examined in the systematic literature to the DCEA framework applied in the exa-cel model. From the SLR, study criteria were examined based on whether the focus of the study was an aversion to health inequalities, that the concept of inequality was centred on years of life in full health over the average person's lifetime (YFH; used to calculate QALEs), and if the choice of context for inequality was based on socio-economic group status (i.e., IMD deprivation groups). Based on the recommendations of the external expert and the applicability of the study criteria stated above, a value of 11 was chosen as the most appropriate and robust value for inequality aversion in England. Nevertheless, in the current model setup, the EAG do have the functionality to input a scenario aversion value of 3.5. However, we have several concerns regarding the source of this value and its applicability to the submission.

Firstly, based on our review and interpretation of the paper, the cited source is yet to undergo a full, external peer-review process. It is currently listed as an open-source discussion paper from the Tinbergen Institute (49).

Secondly, the participant sample distribution used in the analysis is skewed towards higher income groups, sampled via an online, volunteer-based survey portal. This skewed income distribution of participants has potential to manifest as collider bias, since the exposure could also be an (indirect) cause of participation. This is especially relevant because the source attempts to adjust for income relative to inequality aversion. Therefore, there is potential for implicit adjustment on the outcome variable and thus that the outcome variable (i.e., inequality aversion) may be truncated at lower aversion values.

We were unable to find adequate discussion on this potential issue and found no detailed discussion on the potential for collider bias. From our reading, the source only refers to the R^2 statistic, derived from the Ordinary Least Squares (OLS) regression applied in the analysis. Although the R^2 statistic is cited as low, this may indicate a poorly fitted model. The authors do not seem to consider this as potential cause for the low R^2 value. The source thus fails to identify the need for robust truncation sensitivity analyses, e.g., by simulating varying participant demographic distributions. Therefore, because the paper does not account for truncation via more robust methods, we believe that there is a high potential of bias in this source's aversion value

that has not been adequately addressed. Hence, we believe that an aversion value of 3.5 should only be considered as a pessimistic scenario value.

B26. Priority Question: Please provide a reference and further justification to explain the approach used to calculate indirect equity weights. In the submitted DCEA these are based on the relative value of the derivative of the Atkinson social welfare of each IMD-quintile-specific baseline QALE to the derivative of the Atkinson social welfare function of the baseline QALE in the least deprived IMD quintile (Appendices, pages 148-149). This approach results in weights equal to or greater than one across all IMD quintiles. Please explain why you have not applied the power functional form to derive weights, $hh_{ii}^{\varepsilon\varepsilon}$.

Company response

As stated in Cookson et al. (2020) (39), in mathematical terms, the choice does not matter: the indifference curves will still give the correct answer. This is because the Equally Distributed Equivalent of Health (EDEH) is an ordinally equivalent, monotonic transformation of the standard Atkinson index of social welfare function - that is, it ranks any health-adjusted life years (HALYs) type distributions in the same order. Changing the function in each IMD group (cells F5:F9, sheet DCEA_weights) to its power functional form derives identical weighting values. Moreover, as highlighted during external expert consultation and as stated in Cookson et al (2020) (39), for communication purposes, it is recommended to assign a health weight of 1 to the best-off subgroup, since this ensures that the incremental equity impact of a 'progressive' programme that disproportionately benefits worse-off groups is positive (so long as the weights are 'progressive', i.e., that is, higher weights are assigned to worse-off groups).

It is also important to be aware that the final weighting of each IMD quintile is primarily driven by the proportion of patients within each IMD quintile group. For example, if the IMD 1 group has a Social Welfare Function weighting of 6.67 at an aversion value of 11 and the proportion of patients within this quintile are 10% (i.e., the prevalence of eligible treatment population within the IMD quintile), the final weighting will only result in a value of $6.67 \times 0.10 = 0.67$. Thus, based on such values and resultant weighting,

this would *decrease* the final incremental QALYs that are allocated to the most deprived quintile. Hence, the IMD-group weightings are appropriately weighted according to the prevalence of the disease within each IMD quintile.

B27. Priority Question: The derived level dependent indirect equity weights are based on aversion to inequality in the level of health across IMD population groups.

a) **Please explain and justify why these indirect equity weights based on aversion to inequality in health levels are applied to the financial opportunity costs rather than the health opportunity costs.**

b) **Please justify why the resultant equity weighted opportunity cost is independent of the cost-effectiveness threshold value.**

c) **Please explain how the equity weighted financial opportunity costs represent opportunity costs in relation to the overall resources available to the NHS.**

Company response

a) We applied indirect equity weights to financial opportunity costs to calculate the DCEA-weighted ICER. Financial opportunity costs represent population-level incremental costs. This approach was applied based on external expert recommendations and the methods described in Cookson et al (2020) (39). However, indirect equity-weights have been applied to health opportunity costs in the DCEA_weights sheet (M77:Q77), which are dynamic values based on the inequality aversion value. Note that the tabular summary of the intervention's health impacts presented in the Base case results sheet (N83:T86) are *unweighted* summary outputs across IMD groups. With regards to the Net Health Benefit (NHB), we used the ratio between the weighted incremental QALY and Costs and unweighted incremental QALY and Costs to calculate the NHB. Since these are proportional, linear changes, the values are equivalent to calculating the weighted patient-level NHB that uses equity-weighted health opportunity costs (i.e., calculating the difference between both weighted Gross Health Benefit and Health Opportunity Costs for each IMD quintile, aggregating these values, and then dividing by the number of patients

in the treatment population). Note that this calculation is dependent on the default cost-effectiveness threshold (cell E6, Base case results sheet). We have also corrected the Net Health Benefit calculation in O142:P143 within the base case results sheet (it was previously calculating Net Monetary Benefit).

b) We have not applied a threshold approach, which explicitly requires the use of health opportunity costs to determine the appropriate threshold weighting value to apply to the cost-effectiveness threshold (39). We did not take this approach based on the feedback received during external expert consultation and the recommendations found in Cookson et al (2020) (39). Please see priority question B28 for a more detailed discussion on the reasons for applying an indirect health weighting approach rather than a threshold weighting approach.

c) Equity-weighted financial opportunity costs are simply the equity-weighted equivalent of the incremental costs between the interventions being compared. In other words, it the is the pure *financial* costs that are potentially forgone which have not yet been transformed onto a health-equivalent scale or trade-off ratio.

B28. Priority Question: In a reference case analysis the NICE cost-effectiveness threshold represents the opportunity cost of programmes displaced by new, more costly technologies. This cost-effectiveness threshold does not consider the distribution of opportunity cost. Please explain and justify whether it is appropriate to compare the presented equity-weighted ICER to the non-equity weighted NICE cost-effectiveness threshold.

Company response

We have applied the DCEA at a general population level – not treatment population level - based on external expert consultation. The reasoning for this is because NICE assess cost-effectiveness according to population-level trade-offs, i.e., this assumes a fixed health care budget requiring explicit health care trade-offs for the general population. Assessing health inequalities and opportunity costs at a population-level is thus consistent with NICE's decision making approach and hence, was considered the most appropriate framework to follow. This was also considered by an external expert to be the more valuable approach to supporting interpretation of the DCEA

results alongside standard CEA outcomes, given NICE's approach to health care decision making (i.e., which consider population-level trade-offs).

It is important to be aware that, by applying indirect equity-weights to the base-case incremental QALYs and costs, the ICER is proportionally weighted. This is equivalent to implicitly increasing the reference-case cost-effectiveness threshold to, as an arbitrary example, £40,000 rather than £30,000.

While a threshold-weighting approach (which explicitly uses health opportunity costs in its calculations) could have been implemented, we reiterate that this was not recommended by external expert opinion and is further supported by discussions found in Cookson et al (2020) (39). Notably, using a threshold weight rests on the implicit assumption that all health benefits accrue to end-of-life patients and all the health opportunity costs fall on non-end-of-life patients. Thus, as stated in Cookson et al. (2020) (39) "… if the decision maker uses a threshold weight instead of [direct] health weighting, then there will be some scenarios where erroneous conclusions are drawn about the desirability of different programmes."

Moreover, accurately estimating the opportunity costs across varying ethnicities and other potential health inequality proxies is challenging within the context of TDT, especially at a treatment population-level; utilisation and ethnicity-specific deprivation data are scarce and thus unreliable for robust inference. As stated in Cookson et al (2020) (39), there are many steps that can be modelled in DCEA and, "… in a particular [decision context it] is a tricky judgment call, requiring consideration of which steps are likely to be important in driving overall distributional consequences as well as analytical resource constraints and data availability." Determining an accurate distribution of opportunity-costs would require a bottom-up analysis over an extended period. This, obviously, incurs extremely high analytical time and resource costs. Given the agreed timelines of this submission between NICE and Vertex, a bottom-up analysis of patient deprivation across varying health inequality proxies was not possible.

Therefore, given the above, comparing an equity-weighted ICER to the NICE reference-case cost-effectiveness threshold(s) is a valid and relevant approach within the decision context of this submission.

B29. Priority Question: The economic model is used to predicted quality-adjusted life years on standard of care in order to inform the shortfall calculation for the severity modifier. Individuals living in more deprived IMD quintiles experience lower quality-adjusted life expectancy than individuals living in less deprived quintiles. The shortfall in QALE between the most deprived and least deprived quintile is 11.9 years (Figure 41, page 142, Appendices).

a) Given the disproportionate representation of the patient population in more deprived IMD quintiles, please explain how far the impact of socioeconomic deprivation is reflected the shortfall calculation.

b) Please provide an estimate of the QALY shortfall relative to an age, gender and IMD matched UK population.

Company response

As per our responses to B30 and B31, we disagree with any attempt by the EAG to remove individual modifiers of the ICER, all of which are independent of one another. The NICE methods guide specifies that "*the expected total QALYs that people living with a condition would be expected to have with current treatment over their remaining lifetime should be subtracted from the total QALYs that the general population with the same age and sex distribution would be expected to have*." There is no request to subtract QALYs representative of population deprivation quintiles, ethnicity, or any other determinant of expected QALYs.

We would like to emphasise the fact that the QALEs presented in Figure 41 [page 142, Appendices] are independent of the severity modifier. These QALEs are the IMD deprivation values used for the Slope Index of Inequality (SII) and the QALE shortfall calculations used in the DCEA – not the severity modifier. Please see priority question B30 for further discussion on this point.

Furthermore, we have seen no examples of where any other company has been asked to base their shortfall on such an analysis. For example, in the recent NICE evaluation of bulevirtide for hepatitis D virus (TA896), which disproportionately affects recent immigrants from a Black African family background in the UK (who additionally must be co-infected with hepatitis B), the shortfall was measured against the general

population . Consequently, we will not provide any analysis of shortfall relative to an age, gender and IMD matched UK population.

B30. Priority Question: The Atkinson inequality aversion parameter in the DCEA is used to reflect a population preference to reduce inequalities in quality-adjusted life expectancy between socioeconomic groups defined on the basis of IMD. Please explain and justify how far these population preferences are separable from severity weights based on absolute and proportionate QALY shortfall.

Company response

The DCEA weights are based on the pre-intervention QALE shortfall between IMD groups. In other words, the QALE shortfall represents the absolute value of relative health inequality between each *general population* IMD group and the least deprived IMD group. Based on the DCEA model framework applied in the submission to NICE, the DCEA shortfall value, therefore, does not represent a disease-specific modifier. In contrast, the severity modifier is based on a QALY shortfall between the treatment population and general population and was estimated using the ScHARR QALY Shortfall Calculator.

It is important to stress to the EAG that the severity modifier is applied post-DCEA weighting. Applying the severity modifier to the base-case incremental QALYs (i.e., pre-DCEA weighting) would overestimate the intervention's effect on population-level health inequality (i.e., the SII would not accurately reflect the change in population-level health inequalities and would most likely overestimate a reduction in health inequalities, post-roll out of the intervention). We also provided the functionality for differential weightings in our submission, in combination or as separated weightings, so that the EAG may assess the full magnitude and impact of the DCEA and severity modifier, as separate or in combination weightings, on the economic results.

B31. Priority Question: The discount rate of 1.5%, severity modifier, and DCEA analysis all reflect societal preferences to place additional value on QALY gains in conditions where there is high unmet need. The application of all three factors together arguably double or even triple counts these societal

preferences. Please justify the approach taken in your base case analysis and why it is appropriate to apply all three adjustments simultaneously.

Company response

We refer the EAG to the NICE methods manual as all of these factors have their own dedicated but independent sections in the manual:

Severity

Severity is presented as a 'decision modifier'; that is, a factor that has not been included in the estimated QALY because it cannot be. The severity modifier captures the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS.

Discount rate

The 1.5% discount rate considers satisfaction of 3 criteria:

- The technology is for people who would otherwise die or have a very severely impaired life.
- It is likely to restore them to full or near-full health.
- The benefits are likely to be sustained over a very long period.

Only the first criterion overlaps with disease severity; the other two criteria are entirely unrelated. The overall objective of the 1.5% discount rate is to avoid penalising those treatments with high upfront (undiscounted) costs but where the QALY gains and cost savings accrue over a long time period and are subject to discounting. In summary, severe diseases may achieve the severity modifier, but only curative advanced cell and gene therapies with high upfront costs are likely to be eligible for a 1.5% discount rate.

Without conducting a review of recent TAs (the severity modifier having only been introduced recently), within the response timeframe we are unable to demonstrate that each of these has been discussed and/or included by committee independently. However, there is precedent to apply both a QALY modifier and a 1.5% discount rate

in the Highly Specialised Technology (HST) appraisal *HST15: Onasemnogene abeparvovec for treating spinal muscular atrophy*. The HST QALY weight is determined by undiscounted QALY gain, whereas the severity modifier is determined by QALY shortfall under current SoC. However, QALY gain is a function of both the QALY shortfall of current SoC and how much that shortfall is restored by the intervention. There is therefore even more overlap between the QALY modifier and the 1.5% discount rate criteria in HST, yet the committee chose to apply both in HST15.

Health inequalities

Health inequalities are addressed in section 2.2.24 of the NICE methods guide, a section dedicated to 'Other issues likely to affect the evaluation'. While NICE makes it clear that they will consider whether the technology could address inequality or unfairness in the distribution of health across society, there is no explicit description of how it will be used in committee decision-making from a quantitative perspective. This lack of transparency could be considered a weakness of existing deliberation processes. We have simply applied published methods of quantifying the impact of exa-cel on health inequalities and applied the associated, published, weightings to incremental costs and QALYs.

Disease severity has no impact on the calculation of the DCEA weights. The severity modifier is applied post-calculation of the DCEA weighting. Hence, the severity modifier does not impact the Quality Adjusted Life Expectancy (QALE) values that are used in the DCEA calculation. As discussed in B30, applying the severity modifier to the base-case incremental QALYs (i.e., pre-DCEA weighting) would overestimate the intervention's effect on population-level health inequality.

Furthermore, a severe disease on its own would not generate a DCEA weighting; the DCEA weighting is *only* generated if the disease is disproportionately experienced by people living in the most deprived population quintiles; this population-level criterion is completely unrelated to either the severity modifier or the 1.5% discount criteria.

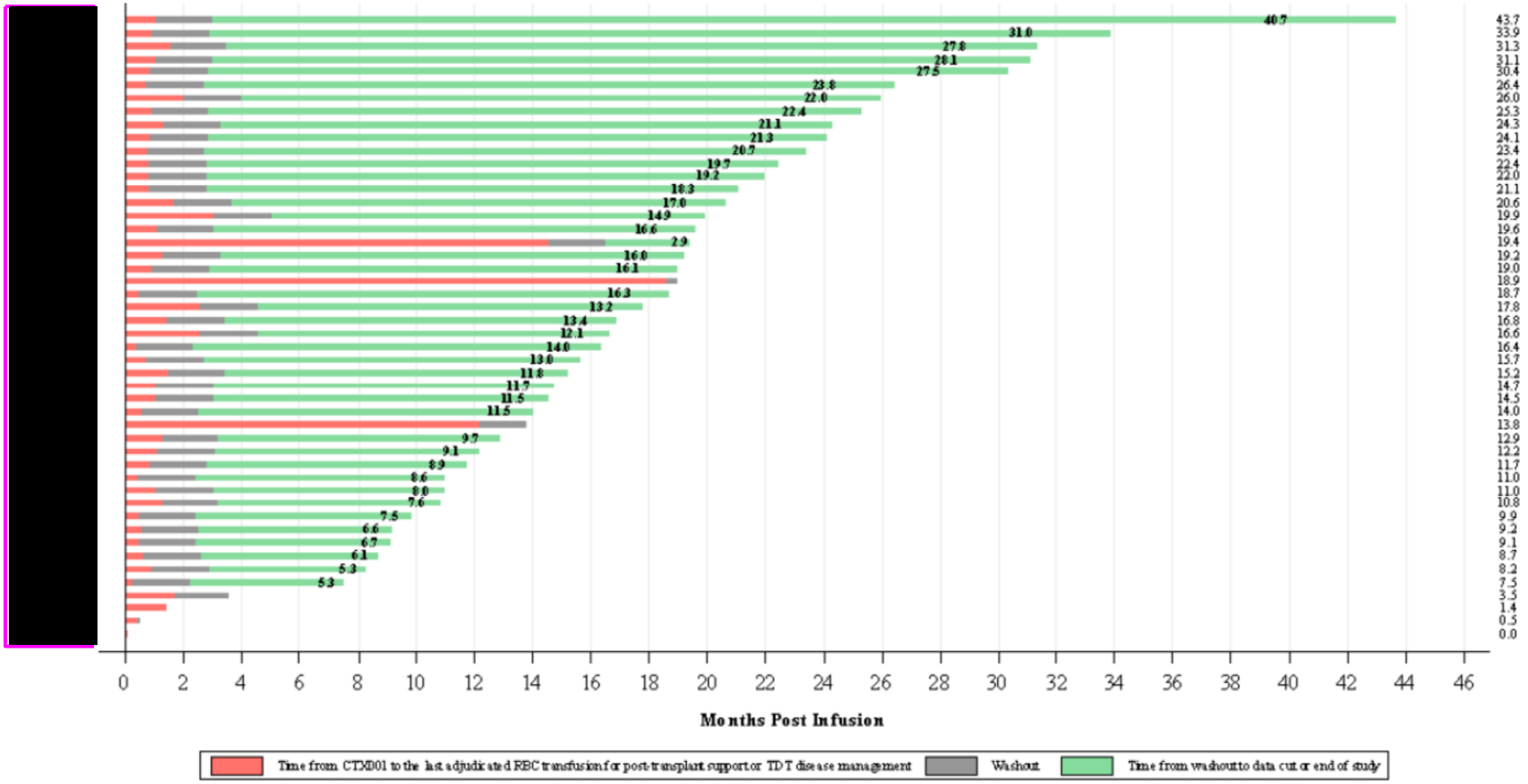
Section C: Textual clarification and additional points

C1. Priority Question: A different patient numbering system seems to have been used in Figure 13. For example, on p70 it is stated that Patient 002 did not achieve TI12. Although this patient number corresponds to Figure 14 (patient 002 receives numerous infusions after exa-cel), it does not correspond to Figure 13 (participant 2 is transfusion free). Please present Figure 13 with the trial patient numbers, so that an individual patient's results can be seen across the transfusion outcomes.

Company response

Please find the requested figure, Figure 6, below.

Figure 6: Duration of Period Free From Transfusions (Studies 111 and 131, FAS)



Key: CTX001: exagamglogene autotemcel; EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia
Notes: Only RBC transfusions that were adjudicated by the EAC as for post-transplant support or TDT disease management were included. The number on the right end is the duration of total follow-up. One subject received exa-cel infusion on the data cutoff date with no RBC transfusion data available. *Indicates subjects in the PES.
Source: Figure 11-1, CLIMB-131 CSR.
For clarity given the image resolution, the red bar indicates time to last adjudicated RBC transfusion for post-transplant support/TDT management, grey is the washout period, and green is transfusion-free period.

C2. What do the dashes indicate in Table 3 of submission document B?

Company response

In all reporting, patient numbers <5 were masked (i.e., reported as '-') to protect patient confidentiality, and secondary masking was applied where required to avoid back-calculation.

Search strategies

C3. The search strategies cannot be appraised as the documentation of the strategies is not an accurate representation of how these were input and run on each of the databases. There are a significant number of errors in the strategies – many which the platform (Ovid) would either flag as unable to run or would correct to a variation not listed in the documentation of the strategies. As examples, in the updated Embase strategy of Appendix D, line 11 on p. 56 would correct to searching for the numbers in the .mp. field. The same Embase strategy uses incorrect date limits and uses ':ti,ab' (used on the Wiley platform) instead of .ti,ab. (used on Ovid), these cannot be run on the Ovid platform. For all searches in Appendix D and Appendix G, please provide accurate copies of the exact searches run with correct details of limits applied, database indexing, segments used, dates searches were run, and correct number of hits per line, as there are also many mistakes in these aspects of the documentation as well.

Company response

The searches for Embase, MEDLINE, and Cochrane in Appendix D and Appendix G were conducted on different search platforms. For the initial clinical SLR in Appendix D, searches were carried out for the Embase, MEDLINE, and Cochrane databases using the Ovid platform. However, for the updated clinical SLR, due to a change of database subscription, two search strategies were developed for the Ovid and Embase databases, with the latter adapted according to the different syntax requirements for the Embase database. The Embase search strategy was performed in the Embase database (hosted by Elsevier), whilst the searches for MEDLINE and Cochrane were conducted using the Ovid platform. This is also applicable to the cost-effectiveness systematic literature review in Appendix G.

Due to the variation in syntax requirements between platforms, the Embase search strategies in Appendix D and Appendix G could not be performed on the Ovid platform. However, when performed in the Embase database, searches were performed without any error messages. Hence, the number of search hits represented in Appendix D and Appendix G are anticipated to be correct.

C4. Please provide the following search strategies which are missing: strategies of conference proceedings in Appendix D; strategies of conference proceedings and all sources listed under 'following databases' on p. 87 in Appendix G; strategies for the systematic literature review conducted for the indirect treatment comparison (ITC).

Company response

Search strategies of conference proceedings in Appendix D

In addition to the bibliographic databases, websites of the following three conferences were searched (the most recent two years as abstracts from prior meetings are indexed in EMBASE). Table 24 details the number of search hits for each conference database in the original clinical SLR.

Table 24: Clinical SLR conference abstract search strategy

Database	Hits
ASH	0
EBMT	2
EHA	7

Key: ASH: American Society of Hematology; EBMT: European Society for Blood and Marrow Transplantation; EHA: European Haematology Association.

For the updated clinical SLR, conference abstracts were hand searched from 1st May 2022 to 13th May 2023 to retrieve the latest clinical studies which have not yet been published in full-text articles or supplement results of previously published studies. The search terms and associated hits from conference proceedings are provided below in Table 25.

Table 25: Updated clinical SLR conference proceedings search strategy

Conference database	Search	Hits
ASH	Beta-thal	3
	β-thal	3
	Exa-cel	2
	Beti-cel	2
	Gene therapy	1

	CTX001	1
	Transfusion dependent beta thalassaemia	8
	Transfusion dependent thalassaemia	21
	CLIMB-111	1
	NCT03655678	1
EBMT	Beta-thal	21
	β-thal	6
	Exa-cel	0
	Beti-cel	0
	Gene therapy	18
	CTX001	0
	Transfusion dependent beta thalassaemia	0
	Transfusion dependent thalassaemia	0
	CLIMB-111	0
	NCT03655678	0
EHA	Beta-thal	41
	β-thal	6
	Exa-cel	0
	Beti-cel	0
	Gene therapy	99
	CTX001	0
	Transfusion dependent beta thalassaemia	0
	Transfusion dependent thalassaemia	0
	CLIMB-111	0
	NCT03655678	0

Key: ASH: American Society of Hematology; EBMT: European Society for Blood and Marrow Transplantation; EHA: European Haematology Association.

Search strategies of conference proceedings and all sources listed under 'following databases' on p. 87 in Appendix G

Similar to the search for conference proceedings outlined in Appendix D, conference abstracts published from January 2020 onwards were hand searched according to the search terms outlined in Table 26. Table 26 details the number of search hits for each search term in each manually searched conference proceeding.

Table 26: Economic SLR conference proceedings search strategy

Conference database	Search	Hits
ASH	Beta-thal	7
	β-thal	10
	Exa-cel	2
	Beti-cel	8
	Gene therapy	5

	CTX001	4
	Transfusion dependent beta thalassaemia	15
	Transfusion dependent thalassaemia	23
	CLIMB-111	2
	NCT03655678	2
EBMT	Beta-thal	25
	β-thal	25
	Exa-cel	0
	Beti-cel	20
	Gene therapy	83
	CTX001	0
	Transfusion dependent beta thalassaemia	0
	Transfusion dependent thalassaemia	1
	CLIMB-111	0
	NCT03655678	0
EHA	Beta-thal	102
	β-thal	94
	Exa-cel	0
	Beti-cel	31
	Gene therapy	245
	CTX001	43
	Transfusion dependent beta thalassaemia	0
	Transfusion dependent thalassaemia	5
	CLIMB-111	0
	NCT03655678	2

Key: ASH: American Society of Hematology; EBMT: European Society for Blood and Marrow Transplantation; EHA: European Haematology Association.

In addition, Table 27 details the grey literature databases which were manually searched using the search term 'beta-thalassaemia'. Altogether, this retrieved 18 search hits. In Figure 34 within Appendix G, the PRISMA displays these studies as 'records identified through other sources'.

Table 27: Economic SLR grey literature search strategy

Database	Search	Hits	Source
INAHTA	• 'beta-thalassaemia'	9	https://database.inahta.org/search?limit=&terms=beta-thalassaemia&client=user
CEA	• 'beta-thalassaemia'	5	https://cear.tuftsmedicalcenter.org/results?expressions=%5B%7B"term"%3A"keyword","value"%3A"beta-thalassaemia"%7D%5D&formType=basic&dataType=methods

ICER	• 'beta-thalassaemia'	2	https://icer.org/explore-our-research/assessments/
CADTH	• 'beta-thalassaemia'	0	https://searchfilters.cadth.ca/list?q=thalassaemia&p=1&ps=20
NICE	• 'beta-thalassaemia'	1	https://www.nice.org.uk/guidance/published?q=beta-thalassaemia&sp=on
SMC	• 'beta-thalassaemia'	1	https://www.scottishmedicines.org.uk/search/?keywords=beta-thalassaemia

Key: CADTH: Canadian Agency for Drugs and Technologies in Health; CEA: Cost-Effectiveness Analysis Registry; ICER: Institute for Clinical and Economic Review; INAHTA: International Network Association of Health Technology Assessment; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium.

Search strategies for the systematic literature review conducted for the ITC

The clinical SLR was conducted for the ITC feasibility. Database searching was conducted on 10th May 2022 for the following databases using the OvidSP platform:

- MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Medline® Daily, Medline and Versions®
- EMBASE®
- Cochrane Central Register of Controlled Trials

The search strategy was based on a combination of free text words, indexing terms (e.g., Excerpta Medica database [EMBASE] subject heading [EMTREE] or Medical Subject Headings [MESH] terms) and their relationship using Boolean terms (e.g., 'and', 'or', 'not'). A complete search strategy for the bibliographic databases searched can be found below in Table 28.

Table 28: Search strategy for initial clinical SLR (Ovid)

#	Search string	Results as of May 10, 2022
1	(beta thalass* or B-thalass* or beta-thalass* or B-thal).ti,ab. or exp beta thalassemia/ or exp beta thalassaemia/ or exp thalassemia/ or exp thalassaemia/ or (beta adj2 thalass*).mp.	65,412
2	(crispr* OR "Clustered Regularly Interspaced Short Palindromic Repeat*").ti,ab. or exp exagamglogene autotemcel/ or exp CRISPR-Cas Systems/ or exp Clustered Regularly Interspaced Short Palindromic Repeats/ or (CTX001 or "CTX 001" or CTX-001).mp.	81,731
3	exp Zynteglo/ or exp betibeglogene autotemcel/ or (Zynteglo or betibeglogene autotemcel or beticel or beti-cel or LentiGlobin).mp.	225

4	exp Luspatercept/ or (Luspatercept* or Reblozyl or ACE-536 or ACE536 or "ACE 536").mp.	710
5	Hydroxyurea/ or (hydroxycarbamide or hydroxyurea or Hydrea or Droxia or Siklos).mp.	45,382
6	exp Thalidomide/ or (thalidomide or Contergan or Thalomid).mp.	45,776
7	(Deferoxamine or Desferal or Deferasirox or Exjade or Jadenu or Deferiprone or Ferriprox).mp. or exp iron chelation/ or (Iron chelat* or FeAsc or ferrous-ascorbate complex).ti,ab.	46,601
8	(stem adj3 cell adj3 transplant*).ti,ab. or (hematopoietic adj3 transplant*).ti,ab or exp Stem Cell Transplantation/ or (((allogenic or allogeneic) adj (stem or transplantation)) or alloSCT or allo-SCT).ti,ab. or (haploidentical adj (transplant* or donor)).ti,ab.	335,443
9	exp thrombocyte transfusion/ or exp Erythrocyte transfusion/ or Blood Transfusion/ or exp Leukocyte transfusion/ or Platelet transfusion/ or Plasma exchange/ or ((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj3 (transfus* or infus* or therap*)).ti,ab.	381,422
10	exp placebo/ or exp medical care/ or (best medical care or supportive care or BSC).ti,ab.	1,526,254
11	or/2-10	2,392,428
12	1 and 11	21,085
13	exp Prospective Studies/ OR exp Random Allocation/ or exp Adaptive Clinical Trial or exp Randomized controlled trials as Topic/ or Randomized Controlled Trial/ or Clinical Trial/ or Controlled clinical trial/ or Multicenter study/ or Prospective study/ or Phase 1 clinical trial/ or Phase 2 clinical trial/ or Phase 3 clinical trial/ or Phase 4 clinical trial/ or exp randomization/ or (randomi?ed controlled trial$ or rct).tw. or (random$ adj2 allocat$).tw. or ((singl$ or doubl$ or tripl$) adj (blind$3 or mask$3)).ti,ab. or placebo$.ti,ab.	5,445,295
14	(animal$ not human$).mp. or (animal/ not (animal/ and human/)) or (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/)	16,193,710
15	(news or comment or editorial or note or case reports).pt. or (historical article/ or case report/ or editorial/)	8,491,923
16	13 not (14 or 15)	4,875,471
17	12 and 16	2,884
18	limit 18 to english language	2,833
19	MEDLINE = 722 Embase = 1,910 Cochrane = 201	FINAL NUMBER TO SCREEN = 2,270

Details of the hand searches and associated hits from conference proceedings is detailed previously in Table 24.

C5. The Excel file containing results of the targeted literature review (TLR) literature search mentioned on p. 132 of 'ID4015 exa-cel company submission

(doc B) 03072023CM [CON]' is not provided. Please provide this with any search strategies and explain the methodology for conducting the review.

Company response

In a review of previous economic models for TDT, it was acknowledged that the algorithms used to predict the incidence of chronic and acute morbidities of TDT were derived primarily from US patient cohorts and no formal literature review had been employed to identify algorithms from the UK (or Europe). Thus, a pragmatic literature review was conducted to identify publications that could provide alternative sources for risks of morbidity and mortality in the economic model.

The requested targeted literature review spreadsheet is submitted alongside our clarification response. This file provides details on search strategies and databases searched and relevant studies identified through abstract screening,

C6. For the HRQoL searches, which use studies from Appendix D, why were studies limited to study types such as prospective studies, clinical trials etc? There are no terms used for health-related quality of life. For the HRQoL searches, it would have been better to search on the population with terms for health-related quality of life. Please can the company clarify if any relevant studies were missed?

Company response

Thank you for highlighting this. In the opening narrative for Appendix H, we highlight that the same search strategy used in Appendix D was applied for the HRQoL SLR. This is in fact an error. The search strategy used for retrieving records from the published literature in Appendix H differs from that of Appendix D and is provided below in Table 29.

Table 29: Search strategy for HRQoL SLR (Ovid)

Search No.	Query	Hits
1	exp beta thalassemia/ or exp beta-Thalassemia/ or exp hemoglobin E-beta thalassemia/ or hemoglobin E-beta thalassemia.mp. or beta thalassemia.mp. or ((beta or intermedia* or minor* or major*) adj2 (thalass?emia* or hemothalass?emia*)).ab,ti. or "beta-thalass?emia*".ab,ti. or hemoglobin E-beta thalassemia.mp. or "e-beta thalass?emia*".ab,ti. or	46,083

	"hbe-b thalass?emia*".ab,ti. or "hbe-beta thalass?emia*".ab,ti. or (microcyt?emia* adj2 beta).ab,ti. or "h?emoglobin f".ab,ti. or ((erythroblastic or mediterranean or cooley*) adj1 an?emia*).ab,ti.	
2	((health adj1 utilit*) or (economic adj1 utilit*) or (utilit* adj1 (value* or function*)) or "standard gamble" or "time trade-off" or "time trade off" or "tto").ab,ti.	21,377
3	("quality of life*" or "life quality" or hrqol or "eq 5d*" or "eq-5d*" or eq5d* or eqol* or euroqol* or euroquol* or aqol or "quality of wellbeing" or "quality of well being" or "quality of well-being" or qwb* or 15d or "15-dimensional" or "15 dimensional" or "fifteen-dimensional" or "fifteen dimensional" or ("quality of life*" or "life quality" or hrqol or "eq 5d*" or "eq-5d*" or eq5d* or eqol* or euroqol* or euroquol* or aqol or "quality of wellbeing" or "quality of well being" or "quality of well-being" or qwb* or 15d or "15-dimensional" or "15 dimensional" or "fifteen-dimensional" or "fifteen dimensional")).ab,ti.	1,098,329
4	((ferrans adj2 powers) or "ferrans-powers" or "international classification of functioning disability and health" or (icf adj1 (classification* or code* or core)) or qli).ab,ti. or "short from 36".mp. or "short form 36".ab,ti. or sf36.ab,ti. or "sf 36".ab,ti. or "sf-36".ab,ti. or "36 item short form health survey".ab,ti. or "short form 12".ab,ti. or sf12.ab,ti. or "sf 12".ab,ti. or "sf-12".ab,ti. or "12 item short form health survey".ab,ti. or "short form 8".ab,ti. or sf8.ab,ti. or "sf 8".ab,ti. or "sf-8".ab,ti. or "8 item short form health survey".ab,ti. or "sf-6*".ab,ti. or sf6*.ab,ti. or "sf 6*".ab,ti. or "short form 6*".ab,ti. or "shortform 6*".ab,ti. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	149,635
5	("adjusted life year*" or "adjusted life-year*" or "quality-adjusted life-year*" or qaly* or qualy* or "healthy years equivalent*" or "disability adjusted life year*" or "disability adjusted life-year*" or "disability-adjusted life-year*" or daly* or "years lived with disabilit*" or "willingness to pay" or (utilit* adj1 score*) or (utilit* adj1 weight*) or "whoqol-100" or "who-qol 100" or "world health organi?ation qol" or "who qol").ab,ti.	88,964
6	"health utility index".mp. or exp utility value/ or utility value.mp. or exp Standard Gamble/ or standard gamble.mp. or exp time trade-off method/ or time trade-off method.mp. or exp "quality of life"/ or exp "European Quality of Life 5 Dimensions questionnaire"/ or european quality of life 5 dimensions questionnaire.mp. or exp "European Quality of Life 5 Dimensions 3 Level questionnaire"/ or european quality of life 5 dimensions 3 level questionnaire.mp. or exp "European Quality of Life 5 Dimensions 5 Level questionnaire"/ or european quality of life 5 dimensions 5 level questionnaire.mp. or exp "European Quality of Life 5 Dimensions Visual Analogue Scale"/ or european quality of life 5 dimensions visual analogue scale.mp. or assessment of quality of life.mp. or quality of well being scale.mp. or (ferrans and powers quality of life index).mp. or (international classification of functioning, disability and health).mp. or exp WHOQOL-100/ or whoqol-100.mp. or exp "Quality of Life Index"/ or quality of life index.mp. or exp Short Form 12/ or short form 12.mp. or short form 8.mp. or short form 6.mp. or short form 6d.mp. or exp quality adjusted life year/ or exp Quality-Adjusted Life Years/ or exp disability-adjusted life year/ or exp	988,951

	Disability-Adjusted Life Years/ or exp Willingness To Pay/ or willingness to pay.mp.	
7	2 or 3 or 4 or 5 or 6	1,440,480
8	1 and 7	1,365
9	limit 8 to human	1,258
10	(comment or letter or case report or editorial or case study or case report or case series or note or short survey or in vitro).pt.	5,516,466
11	9 not 10	1,199
12	limit 11 to (article or article in press or erratum or "review")	621
13	limit 11 to (conference abstract or conference paper or "conference review")	659
14	limit 13 to yr="2021 - 2023"	96
15	12 or 14	705
16	remove duplicates from 15	581

Furthermore, conference proceedings were hand searched from January 2020 onwards to retrieve the latest clinical studies which have not yet been published in journals as full-text articles or supplement results of previously published studies. The search strategy and associated search hits for the relevant conference proceedings can be found below in Table 30.

Table 30: HRQoL conference proceedings search strategy

Conference database	Search	Hits
ASH	Beta-thal	3
	β-thal	3
	Exa-cel	2
	Beti-cel	2
	Gene therapy	1
	CTX001	1
	Transfusion dependent beta thalassaemia	8
	Transfusion dependent thalassaemia	21
	CLIMB-111	1
	NCT03655678	1
EBMT	Beta-thal	21
	β-thal	6
	Exa-cel	0
	Beti-cel	0
	Gene therapy	18
	CTX001	0
	Transfusion dependent beta thalassaemia	0
	Transfusion dependent thalassaemia	0
	CLIMB-111	0
	NCT03655678	0

EHA	Beta-thal	41
	β-thal	6
	Exa-cel	0
	Beti-cel	0
	Gene therapy	99
	CTX001	0
	Transfusion dependent beta thalassaemia	0
	Transfusion dependent thalassaemia	0
	CLIMB-111	0
	NCT03655678	0

Key: ASH: American Society of Hematology; EBMT: European Society for Blood and Marrow Transplantation; EHA: European Haematology Association.

The remaining details on the methodology for the SLR can be found in Appendix H. Additional research was also used to supplement the SLR to ensure that all relevant records were captured.

C7. In the company submission, there are ambiguities with the PRISMA diagrams:

a. For the clinical searches in Appendix D, the update searches of MEDLINE list 10 results but the PRISMA lists 12.

b. For the searches for cost-effectiveness studies in Appendix G, why does the PRISMA on p. 94 show the total for 'records identified through database searching' from Medline and Embase only, when there are additional sources listed under 'following databases' on p. 87, which the company states were searched (though are not documented)?

c. The searches to find HRQoL studies are noted on p. 113 of Appendix H to be the same as those run in Appendix D. Why is the number for 'records identified through database searching' in the PRISMA on p. 116 different to the PRISMA for p. 60 of Appendix D?

Company response

Thank you for highlighting ambiguities between the search hits and the PRISMA diagrams. The corresponding responses to each query can be found below.

a. There was an error in the reporting of MEDLINE searches in the updated search strategy hits. This should report 12 hits rather than the 10 hits

presented in Appendix D. With this correction, the updated searches of MEDLINE and the PRISMA are aligned. The corrected search strategy is displayed below in Table 31.

Table 31: Ovid MEDLINE® search strategy for updated clinical SLR

#	Search string	Results
1	(beta thalass* or B-thalass* or beta-thalass* or B- thal).ti,ab. or exp beta thalassemia/ or exp beta thalassaemia/ or exp thalassemia/ or exp thalassaemia/ or (beta adj2 thalass*).mp.	1,022
2	(crispr* OR "Clustered Regularly Interspaced Short Palindromic Repeat*").ti,ab. or exp exagamglogene autotemcel/ or exp CRISPR-Cas Systems/ or exp Clustered Regularly Interspaced Short Palindromic Repeats/ or (CTX001 or "CTX 001" or CTX-001).mp.	9,313
3	exp Zynteglo/ or exp betibeglogene autotemcel/ or (Zynteglo or betibeglogene autotemcel or beticel or beti-cel or LentiGlobin).mp.	14
4	exp Luspatercept/ or (Luspatercept* or Reblozyl or ACE-536 or ACE536 or "ACE 536").mp.	46
5	Hydroxyurea/ or (hydroxycarbamide or hydroxyurea or Hydrea or Droxia or Siklos).mp.	530
6	exp Thalidomide/ or (thalidomide or Contergan or Thalomid).mp.	472
7	(Deferoxamine or Desferal or Deferasirox or Exjade or Jadenu or Deferiprone or Ferriprox).mp. or exp iron chelation/ or (Iron chelat* or FeAsc or ferrous-ascorbate complex).ti,ab.	914
8	(stem adj3 cell adj3 transplant*).ti,ab. or (hematopoietic adj3 transplant*).ti,ab or exp Stem Cell Transplantation/ or (((allogenic or allogeneic) adj (stem or transplantation)) or alloSCT or allo- SCT).ti,ab. or (haploidentical adj (transplant* or donor)).ti,ab.	8,239
9	exp thrombocyte transfusion/ or exp Erythrocyte transfusion/ or Blood Transfusion/ or exp Leukocyte transfusion/ or Platelet transfusion/ or Plasma exchange/ or ((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj3 (transfus* or infus* or therap*)).ti,ab.	6,547
10	exp placebo/ or exp medical care/ or (best medical care or supportive care or BSC).ti,ab.	2,355
11	or/2-10	27,844
12	1 and 11	317
13	exp Prospective Studies/ OR exp Random Allocation/ or exp Adaptive Clinical Trial or exp Randomized controlled trials as Topic/ or Randomized Controlled Trial/ or Clinical Trial/ or Controlled clinical trial/ or Multicenter study/ or Prospective study/ or Phase 1 clinical trial/ or Phase 2 clinical trial/ or Phase 3 clinical trial/ or Phase 4 clinical trial/ or exp randomization/ or (randomi?ed controlled trial$ or rct).tw. or (random$ adj2 allocat$).tw. or ((singl$ or doubl$ or tripl$) adj (blind$3 or mask$3)).ti,ab. or placebo$.ti,ab.	119,153

14	(animal* not human*).mp. or (animal/ not (animal/ and human/)) or (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) {Including Related Terms}	228,675
15	(news or comment or editorial or note or case reports).pt. or (historical article/ or case report/ or editorial/)	185
16	13 not (14 or 15)	22,279
17	12 and 16	12
18	Limit 17 to English English language	12

b. In the PRISMA on p. 94 of the CS, the total 'records identified through database searching' constituted search results from Embase and Medline. The conference databases outlined in Table 26 in the response to C4 are included in the coverage by the Embase database. The 'records identified through other sources' constitutes the 18 grey literature search hits, as outlined in Table 27 in the response to C4.

c. See response to C6. A different search strategy was implemented to identify HRQOL studies, hence the number of 'records identified through database searches' is different from the number of hits outlined in the PRISMA for Appendix D.

C8. **For the clinical searches in Appendix D, why was no evidence sought from HTA databases or individual clinical trials registries?**

Company response

HTA databases for NICE, HAS, and G-BA were reviewed for published, ongoing, or suspended treatments of TDT. The desktop research search did not identify any treatments beyond those already included in the SLR search strings based on clinical input and clinical guidelines. The results are in the ITC Feasibility Short Report, submitted as an appendix to our clarification response.

References

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Appendix

Table 32 presents adaptations made to the economic model to allow scenario analyses. This was only done in cases where the scenario could not be conducted easily using the blue override buttons.

Table 32: Summary of model adaptations made in response to clarification

Clarification question	Model update	Base case setting
B6	Adherence added to Cohort inputs rows 72 to 82. Disutility of subcut ICT in Utility inputst!H52 multiplied by the weighted average adherence of regimens including deferasirox.	100% adherent - now applied via blue override cells
B17	Row added to Cost inputs row 97 with a dropdown that adds £10,548 to transplant hospitalisation costs in row 95	Cost inputs!E97 set to "No"
B16	Corrected carer disutility calculation - carer disutilities are now bounded at a maximum age (26 years [user defined]) and added user defined override input to set death decrement to a value desired by user.	Carer disutilities were calculated until the end of the model time horizon
B23 and B24	Added scenarios for alternative QALE and General Population Shares, and added Love-Koh et al. 2020 Health opportunity costs as scenario	No scenario user list, base case used set values from Love-Koh. et al 2015 for General pop shares and QALEs, and assumed several linear, proportional opportunity costs gradient scenarios

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Day 120 Data Cut Off

August 2023

File name	Version	Contains confidential information	Date
ID4015_exa-cel_TDT_D120 [DPD]	1.0	Yes	11/08/2023

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Introduction to relevant clinical effectiveness evidence

CLIMB THAL-111 is the pivotal Phase 1/2/3 trial evaluating the efficacy and safety of exa-cel in the treatment of TDT patients aged 12 to 35 years. CLIMB-131 is designed to evaluate the long-term safety and efficacy of exa-cel in patients who received exa-cel in CLIMB THAL-111 and CLIMB SCD-121 (for patients with severe SCD) for a total of up to 15 years after exa-cel infusion. For the sake of brevity, the study methodology for CLIMB THAL-111 is reported in the relevant sections below, with details on CLIMB-131 provided when reporting clinical effectiveness and safety data.

In response to a request by regulatory authorities, an analysis of efficacy and safety data at Day 120 post-marketing authorisation application (MAA), not pre-specified in the statistical analysis plan, was performed (hereafter referred to as the D120 data cut-off, or D120). The database lock for this analysis was 16th April 2023, providing 51.1 months of follow up post exa-cel infusion, or 48.1 months of follow-up after the 60 day washout. D120 provides the longest duration of follow-up for patients treated with exa-cel, and as such the reporting of efficacy outcomes from CLIMB THAL-111 and CLIMB-131 focuses on the D120 data cut-off. As D120 was not pre-specified, the level of detail reported is less than for interim analysis 2 (IA2), dated 6th September 2022. The IA2 clinical study reports (CSRs) for CLIMB THAL-111 and CLIMB-131 have previously been provided as data on file (Vertex Pharmaceuticals Inc., 2022b).

Study Design

CLIMB THAL-111 is a Phase 1/2/3 single-arm, open-label, multi-site, single-dose study investigating the safety and efficacy of exa-cel in patients aged 12 to 35 years with TDT. In the study, transfusion dependence was defined as a history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the two years before signing the informed consent form (Vertex Pharmaceuticals Inc., 2023a).

At the time of D120 data cut-off, 59 patients were enrolled in the pivotal CLIMB THAL-111 clinical study, of which 54 had received exa-cel infusion. Of these 54 patients, 53 had completed the initial RBC transfusion washout period, defined as a 60-day period after the last RBC transfusion for post-transplant support or TDT disease management (Vertex Pharmaceuticals Inc., 2023a).

Upon the conclusion of CLIMB THAL-111 at Month 24, or upon the discontinuation of the study, all patients who received infusion with exa-cel were asked to participate in the long-term follow-up study, CLIMB-131. This study aims to evaluate the long-term efficacy and safety of exa-cel in patients who received exa-cel in a parent study (CLIMB THAL-111 or CLIMB SCD-121) for a total follow-up of 15 years after exa-cel infusion. Patients who roll over into the long-term follow-up study will have follow-up visits every three months for the first three years, every six months in years four and five, and annual visits thereafter for up to 15 years after infusion of exa-cel in CLIMB THAL-111 (Vertex Pharmaceuticals Inc., 2022a).

At the time of the most recent data cut-off, 23 patients who completed CLIMB THAL-111 rolled over to study CLIMB-131 (Vertex Pharmaceuticals Inc., 2023a).

Eligibility criteria

Please refer to section B.2.3.3 of the original submission and the CSR.

Settings and locations where the data were collected

Please refer to section B.2.3.4 of the original submission and the CSR.

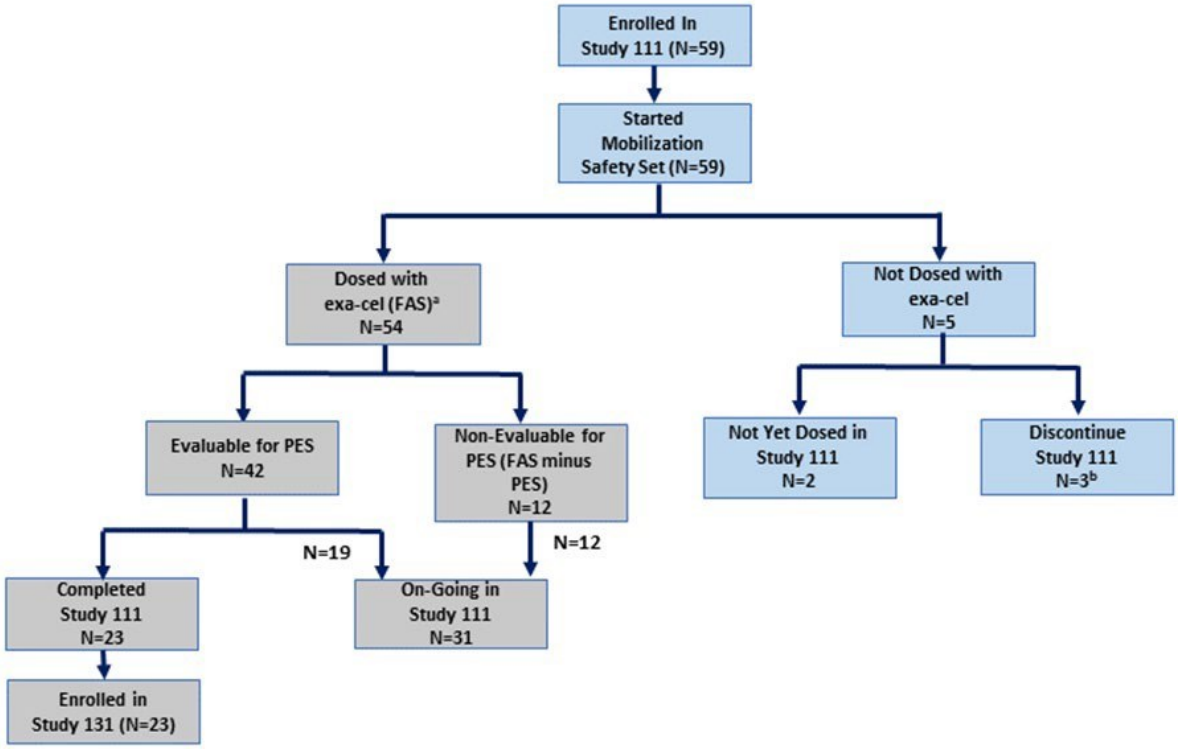
Trial drugs and concomitant medications

Please refer to section B.2.3.5 of the original submission.

Patient disposition

As of the D120 data cut-off, 54 patients had received exa-cel infusion and are included in the FAS. Forty-two patients were included in the PES. Twenty-three patients have completed the two-year follow-up after exa-cel in CLIMB THAL-111 and have rolled over into the long-term CLIMB-131 study. Three patients discontinued from the study after the start of mobilisation but before conditioning: one patient discontinued because they did not want to undergo a second apheresis procedure, one patient discontinued due to concerns with continued study participation, and one patient discontinued due to reasons that they did not disclose; no patient discontinued due to an AE. No patient has discontinued after starting busulfan conditioning or after exa-cel infusion in CLIMB THAL-111 or discontinued from CLIMB-131 (Vertex Pharmaceuticals Inc., 2023a).

Figure 1: Patient disposition for CLIMB THAL-111 and CLIMB-131 (Enrolled Set)



Key: exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; PES: Primary Efficacy Set; TDT: transfusion-dependent β-thalassemia
Notes: The study was planned to dose approximately 45 patients. To account for early discontinuations prior to exa-cel dosing, additional patients were enrolled. Ultimately, 59 patients were enrolled, and 54 patients had been dosed at the time of the data cut-off date (16th April 2023).
Source: Figure 1, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

Baseline demographics

Table 1 presents key baseline characteristics for the CLIMB THAL-111 FAS and PES. For the 54 patients in the FAS, the mean (range) age of patients was 21.3 years (range 12 to 35 years), with 19 patients ≥12 and <18 years of age. The mean age in CLIMB THAL-111 aligns closely with the mean age of UK patients enrolled in the BoI study (24.8 years [range: 1 to 88 years]) (Vertex Pharmaceuticals Inc., 2023d). The majority of patients were Asian (42.6%) or White (33.3%) (Vertex Pharmaceuticals Inc., 2022b, 2023b). The proportion of Asian patients enrolled onto CLIMB THAL-111 is lower than the proportion enrolled onto the UK BoI study (53.6%) (Vertex Pharmaceuticals Inc., 2023d).

Baseline mean (standard deviation [SD]) annualised units of TDT-related RBC transfusions per year for the prior two years before screening in CLIMB THAL-111 was 36.4 (11.7) units (Vertex Pharmaceuticals Inc., 2022, Vertex Pharmaceuticals Inc., 2023) a value similar to that reported by Shah *et al.,* (2021) in a UK TDT population (Shah et al., 2021), and the baseline mean (SD) annualised volume of TDT-related RBC transfusions was 197.6 (62.0) mL/kg per year (Vertex Pharmaceuticals Inc., 2022b, Vertex Pharmaceuticals Inc., 2023a).

In addition, the majority of patients (61.1%) in the FAS had β^0/β^0-like genotypes (Table 1), which reflects the broader eligibility criteria of exa-cel compared to previously appraised therapies (NICE, 2021). Clinical experts consulted by Vertex highlighted that the inclusion of patients with β^0/β^0-like genotypes was highly important, given that these patients are typically worst affected by TDT (Vertex Pharmaceuticals Inc., 2022c). The genotypes observed in CLIMB THAL-111 were considered to reflect the spectrum of genotypes of TDT seen in UK clinical practice.

Table 1: Baseline characteristics (CLIMB THAL-111; FAS & PES)

Baseline Characteristics	FAS (n=54)	PES (n=42)
Sex, n (%)		
Male	29 (53.7)	21 (50.0)
Female	25 (46.3)	21 (50.0)
Childbearing potential, n (%)		
Yes	25 (100.0)	21 (100.0)
Age at screening (years), n (%)		
n	54	42
Mean (SD)	21.3 (6.6)	21.6 (6.4)
Median	19.5	20.0
Min, Max	12, 35	12, 32
Age category at screening (years), n (%)		
≥12 and <18 years	19 (35.2)	13 (31.0)
≥18 and ≤35 years	35 (64.8)	29 (69.0)
Race, n (%)		
White	18 (33.3)	17 (40.5)
Black or African American	0	0
Asian	23 (42.6)	16 (38.1)
Not collected per local regulation	8 (14.8)	5 (11.9)
Other	2 (3.7)	1 (2.4)
Multiracial	3 (5.6)	3 (7.1)
Genotype, n (%)		
β^0/β^0-like	33 (61.1)	25 (59.5)
β^0/β^0	21 (38.9)	13 (31.0)
β^0/IVS-I-110	9 (16.7)	9 (21.4)
IVS-I-110/IVS-I-110	3 (5.6)	3 (7.1)
Non-β^0/β^0-like	21 (38.9)	17 (40.5)
β^+/β^+	4 (7.4)	4 (9.5)
β^+/β^0	12 (22.2)	9 (21.4)
β^E/β^0	5 (9.3)	4 (9.5)
Annualised volume of RBC transfusion (mL/kg)		
n	54	42
Mean (SD)	197.6 (62.0)	199.7 (57.2)
Median	205.7	201.0
Min, Max	48.3, 330.9	115.2, 330.9
Annualised units of RBC transfusion		
n	54	42
Mean (SD)	36.4 (11.7)	36.5 (10.5)
Median	35.3	35.0

Min, Max	11.0, 71.0	20.5, 71.0
Annualised number of RBC transfusion episodes[a]		
n	54	42
Mean (SD)	16.5 (5.2)	17.0 (5.0)
Median	16.5	16.5
Min, Max	5.0, 34.5	10.5, 34.5
Total Hb concentration (g/dL)		
n	53	42
Mean (SD)	10.4 (1.9)	10.6 (2.0)
Median	10.2	10.2
Min, Max	6.9, 14.2	6.9, 14.2
HbF concentration (g/dL)		
n	53	42
Mean (SD)	0.7 (0.9)	0.5 (0.6)
Median	0.3	0.3
Min, Max	0.0, 5.8	0.0, 2.2
HbF concentration (%)		
n	54	42
Mean (SD)	6.7 (11.1)	5.1 (5.8)
Median	3.4	3.1
Min, Max	0.0, 74.0	0.0, 21.3
F-cell level (%)		
n	54	42
Mean (SD)	14.2 (14.8)	13.0 (12.0)
Median	8.7	8.6
Min, Max	2.3, 83.9	2.9, 50.1
Serum ferritin level (pmol/L)[b]		
n	54	42
Mean (SD)	3,712.4 (2,832.3)	3,785.4 (2,908.2)
Median	3,115.5	3,157.0
Min, Max	584.2, 1,0837.3	584.2, 1,0837.3
Cardiac T2* (msec)[c]		
n	54	42
Mean (SD)	34.2 (9.0)	35.0 (8.9)
Median	34.4	34.8
Min, Max	12.4, 61.1	12.4, 61.1
Liver iron concentration (mg/g)[d]		
n	54	42
Mean (SD)	4.5 (3.0)	4.7 (3.2)
Median	3.5	3.8
Min, Max	1.2, 14.0	1.2, 14.0
Weight (kg)		
n	54	42
Mean (SD)	55.0 (13.9)	54.6 (14.3)
Median	52.0	52.0
Min, Max	30.0, 96.0	30.0, 96.0

Key: FAS: Full Analysis Set; F-cells: circulating erythrocytes expressing γ-globin (HbF); Hb: haemoglobin; HbF: fetal haemoglobin; ICF: informed consent form; LIC: liver iron concentration; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia.

Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. Baseline volume of RBC transfusions, units of RBC transfusions, and number of RBC transfusion episodes were based on the 2 years before signing of the ICF or the latest rescreening for patients who rescreened. RBC transfusions were excluded from the baseline calculation if they were not for TDT disease management. Annualised volume = total volume/number of years. Annualised units = total units/number of years. Annualised number of episodes = total number of episodes/number of years. One year = 365.25 days. Hb measurements in this table are from central laboratories. Percentages were calculated relative to the number of patients in the FAS or the PES, unless otherwise specified. Percentages for childbearing potential were calculated relative to the number of females in the FAS or the PES.

[a]An RBC transfusion episode was defined as all transfusions within 5 days, starting from the first transfusion in the episode.

[b]Serum ferritin level is the measurement of tissue iron content. Normal serum ferritin is ≤2,247 pmol/L according to UKTS 2016 guidelines (United Kingdom Thalassaemia Society, 2016).

[c]Cardiac T2* is the measurement of cardiac iron content. Normal cardiac T2* score is >20ms according to UKTS 2016 guidelines (United Kingdom Thalassaemia Society, 2016).
dLiver iron concentration was derived from Liver R2. Normal LIC score is <7mg/day according to UKTS 2016 guidelines (United Kingdom Thalassaemia Society, 2016).
Sources: Table 7 and Table 8, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

Primary and key secondary efficacy endpoints

The primary outcome of CLIMB THAL-111 was the proportion of patients who achieved TI12. TI12 is defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after the RBC transfusion washout period (60 days after the last RBC transfusion for post-transplant support or TDT disease management) (Vertex Pharmaceuticals Inc., 2022b).

Forty-two patients had at least 16 months of follow-up after exa-cel infusion and were evaluable for the primary endpoint (included in the PES). Following infusion with exa-cel, 92.9% of patients (39 of 42 patients, 95% CI: 80.5%, 98.5%) in the PES achieved TI12 (p<0.0001) (Vertex Pharmaceuticals Inc., 2023a).

Information on the three patients in the PES who had not achieved TI12 at the time of the D120 data cut-off is presented below (Vertex Pharmaceuticals Inc., 2022b, 2023a). All 3 have demonstrated clinical benefit with reductions in transfusion volumes and frequency, have subsequently stopped receiving transfusions (12.2- 21.6 months post exa-cel), and have been transfusion-free at the time of the D120 cut-off for 2.8-10.3 months.

- Patient [redacted], had an 83.4% annualised reduction from baseline in RBC transfusion volume). At the time of the data cut-off, the patient had stopped receiving transfusions (14.5 month after exa-cel infusion) and has been transfusion-free for 10.3 months starting 60 days after the last RBC transfusion.
- Patient [redacted] has been transfusion free for approximately 7 months starting 60 days after the last RBC transfusion; however, as with Patient [redacted], they did not meet the criteria for TI. This patient had a 98.5% reduction from baseline in annualised transfusion volume.
- Patient [redacted] has been transfusion-free for approximately 2.8 months starting 60 days after the last RBC transfusion. This patient had an 86.9% reduction from baseline in annualised transfusion volume.

Relevant secondary endpoints

As predicted, the results of the subgroup analyses confirm a substantial treatment benefit of exa-cel in all patients with TDT, regardless of age, genotype, and sex. It must be noted that subgroup analyses should be interpreted with caution given the small sample sizes involved.

Proportion of patients achieving TI6

Following infusion with exa-cel, 92.9% of patients (39 of 42 patients, 95% CI: 80.5%, 98.5%) in the PES achieved TI6 ($p<0.0001$) (Vertex Pharmaceuticals Inc., 2023a).

Time to last RBC transfusion

For patients in the FAS (n=53) who were past 60 days after the last RBC transfusion, including the three patients who did not achieve TI12, the mean (SD) time from exa-cel infusion to last RBC transfusion was 58.0 (110.2) days (Vertex Pharmaceuticals Inc., 2023a). The median (range) time to the last RBC transfusion for the 39 subjects in the PES who achieved TI12 was 28.0 (11 to 91) days after exa-cel infusion. This illustrates the rapid recovery of erythropoiesis after exa-cel infusion consistent with observed early increases in the HbF levels.

Duration of transfusion free period

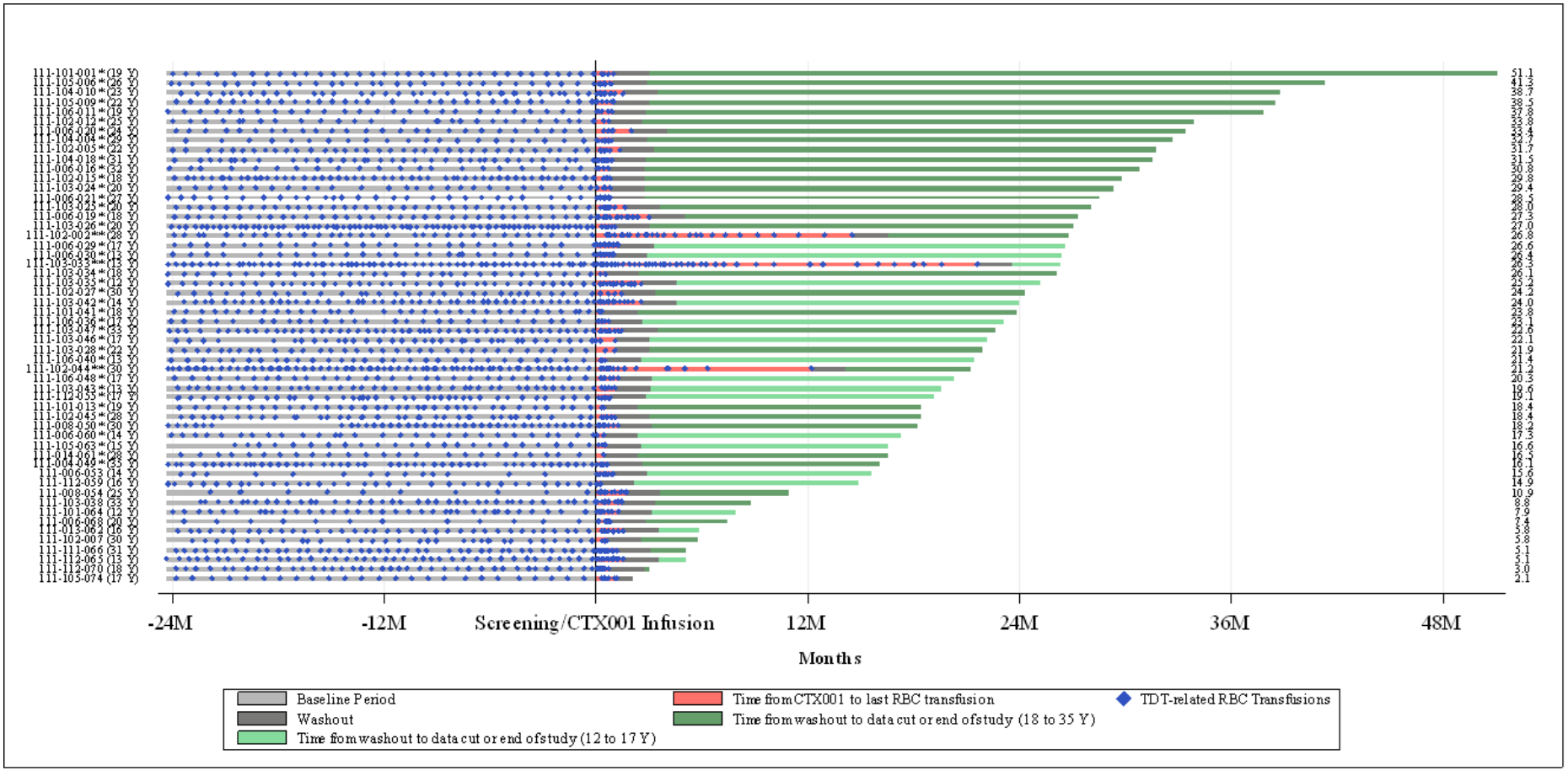
At the time of the D120 data cut-off, 100.0% of patients in the FAS who had completed the RBC transfusion washout period (n=53) were transfusion free, with duration free from transfusion ranging from 0.3 to 48.1 months. One patient within the FAS was within the initial RBC transfusion washout period and had <60 days of follow-up after the last transfusion (Vertex Pharmaceuticals Inc., 2023a).

All 39 subjects in the PES who met the primary endpoint remained transfusion independent for all subsequent follow-up; the mean (SD) duration of transfusion independence was 23.6 (7.8) months, ranging from 13.5 to 48.1 months.

Duration of period free from transfusion by individual patient in CLIMB THAL-111 and CLIMB-131 is presented below in Figure 3, demonstrating the substantial transfusion burden faced by patients at baseline, and the impact of exa-cel treatment in reducing this. Note that at baseline, patients in the FAS were receiving on average (mean) 16.5 annualised transfusion episodes, and 36.4 annualised units of blood.

Overall, these results indicate that once achieved, transfusion independence is durable and maintained. The durability of efficacy is anticipated given that the MOA of exa-cel is an irreversible and permanent edit in long term HSCs.

Figure 2: Duration of period free from transfusions (CLIMB THAL-111 and CLIMB-131, FAS)



Key: EAC: Endpoint Adjudication Committee; FAS: Full Analysis Set; PES: primary analysis set; RBC: red blood cells; TDT: transfusion-dependent β-thalassemia; TI: transfusion independence.
Note: Each row in the figure represents an individual patient. Only RBC transfusions adjudicated by the EAC for post-transplant support or TDT disease management were included. The number on the right end is the duration of TI including the washout period of 60 days.
* Indicates patients in the PES who achieved TI12.
** Indicates patients in the PES who did not achieve TI12.
Source: Figure 2, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

Total Hb and HbF concentration over time

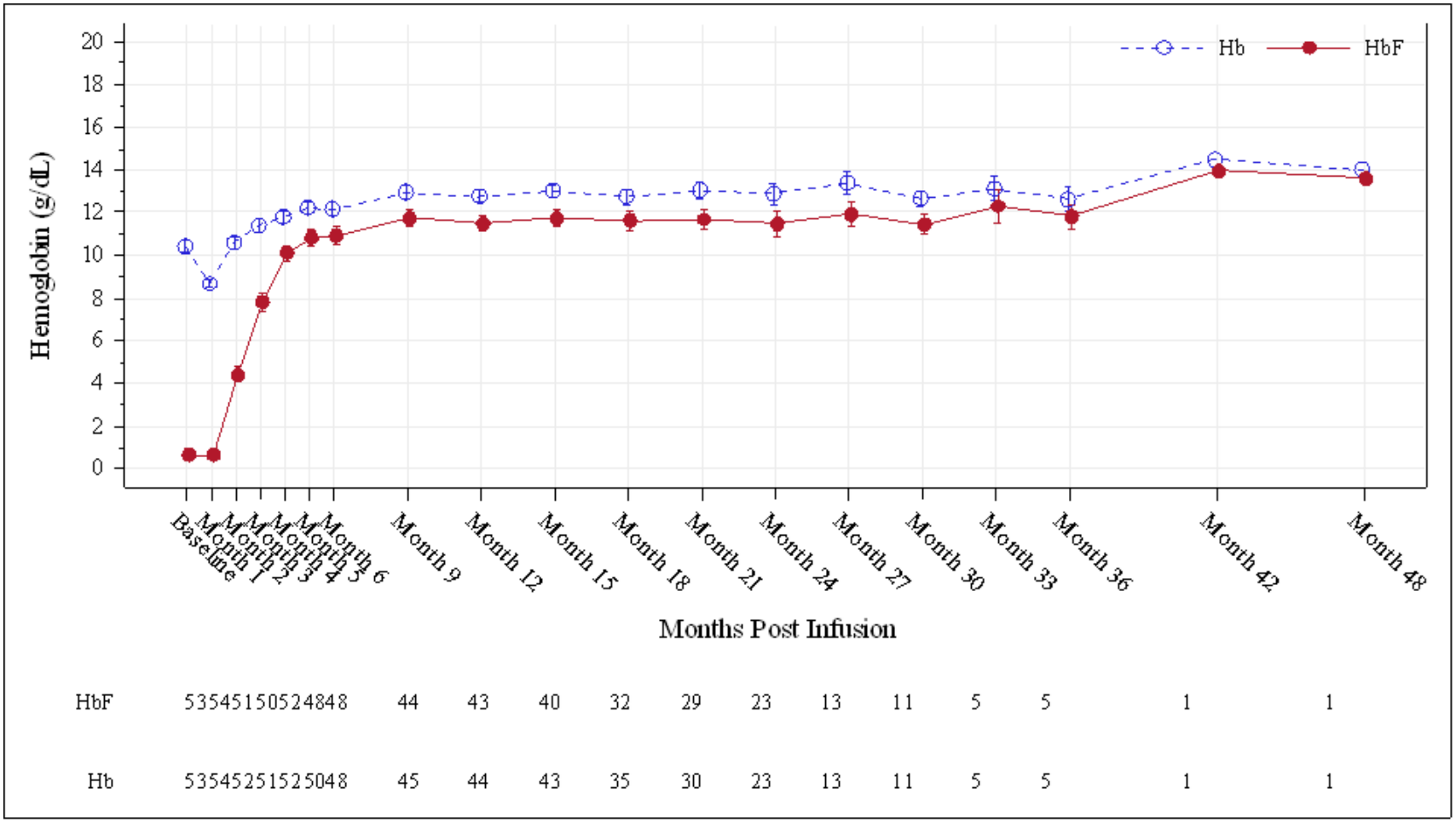
In CLIMB THAL-111, increases in total Hb and HbF occurred within three months of exa-cel infusion and were maintained over the duration of follow-up (Vertex Pharmaceuticals Inc., 2022a, 2023a).

Total Hb concentration increased substantially in TDT patients treated with exa-cel. Mean (SD) total Hb levels of 11.4 (2.3) g/dL were achieved by Month 3 after exa-cel infusion, with mean total Hb levels increasing to and maintained at mean ≥12.2 g/dL thereafter (Figure 3) (Vertex Pharmaceuticals Inc., 2022a, 2023a). Clinical advisors were encouraged by the data showing that steady-state Hb levels had increased (Vertex Pharmaceuticals Inc., 2022c).

At Month 3 after infusion with exa-cel, mean (SD) HbF levels of 7.8 (2.9) g/dL were observed, which represented a substantial increase from baseline (mean: 0.7 [0.9] g/dL). Mean HbF levels were thereafter maintained at mean ≥10.9 g/dL over the duration of follow-up (Figure 4) (Vertex Pharmaceuticals Inc., 2022a, 2023a). The observed increase in HbF levels is consistent with the mechanism of action of exa-cel, which mimics the activity of HPFH, a naturally occurring genetic variation identified in some β-thalassaemia patients that causes continued expression of HbF into adulthood (Frangoul et al., 2021; Musallam et al., 2012; Sharma et al., 2020).

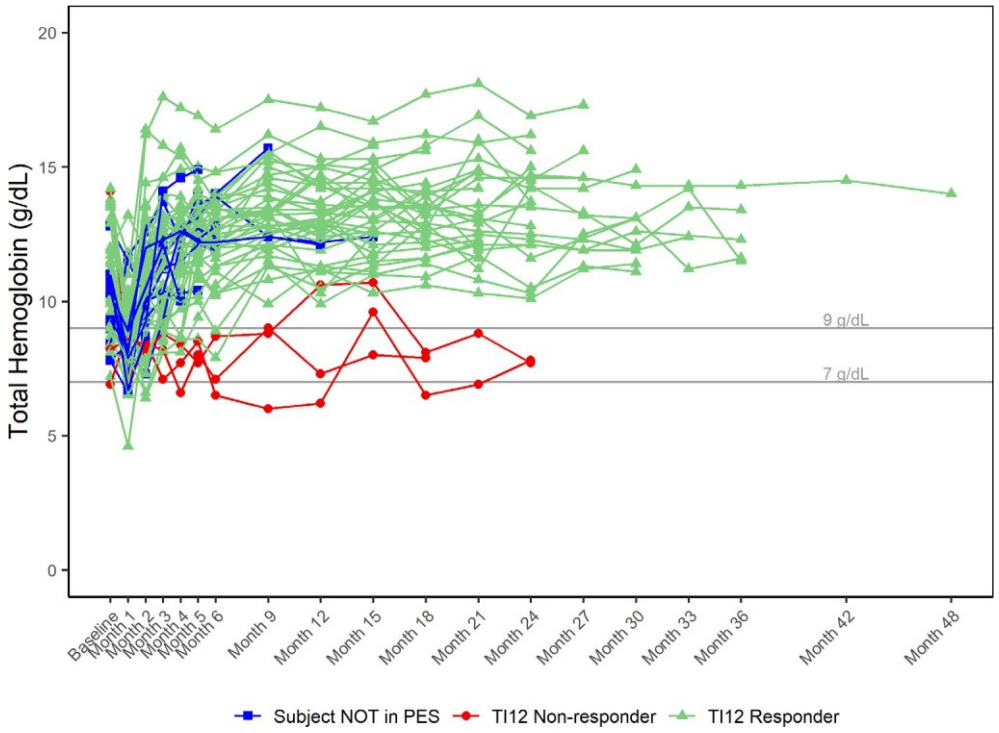
Patients with co-inheritance of β-thalassaemia and HPFH have raised HbF throughout their lives, and experience reduced or no β-thalassaemia-associated symptoms (Frangoul et al., 2021; Musallam et al., 2012; Sharma et al., 2020). The mean (SD) proportion of total Hb comprised by HbF was 67.4% (19.9%) at Month 3 after exa-cel infusion, substantially greater than the levels observed in patients with the HPFH phenotype, with the mean proportion increasing and maintained at ≥88.3% thereafter (Figure 5).

Figure 3: Summary of total Hb (g/dL) and HbF (g/dL) over time (CLIMB THAL-111 and CLIMB-131, FAS)



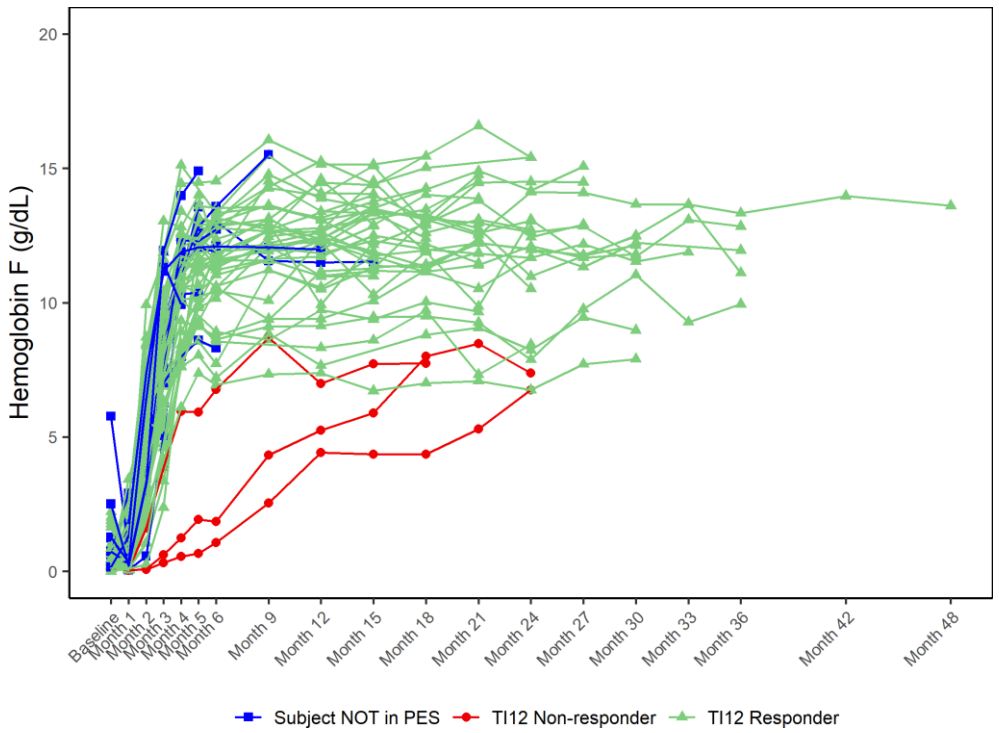
Key: FAS: Full Analysis Set; Hb: haemoglobin; HbF: fetal haemoglobin; SE: standard error.
Notes: Mean values are plotted in the line; mean + SE and mean – SE values are plotted as bars at each visit. The numbers of patients with total Hb and HbF values available at the corresponding visits are shown at the bottom. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. Analysis visit was used in the figure.
Source: Figure 3, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

Figure 4: Total Hb concentration (CLIMB THAL-111 and CLIMB-131, FAS)



Source: Exa-cel D120 efficacy update, data on file (Vertex Pharmaceuticals Inc., 2023a).

Figure 5: Total HbF concentration (CLIMB THAL-111 and CLIMB-131, FAS)



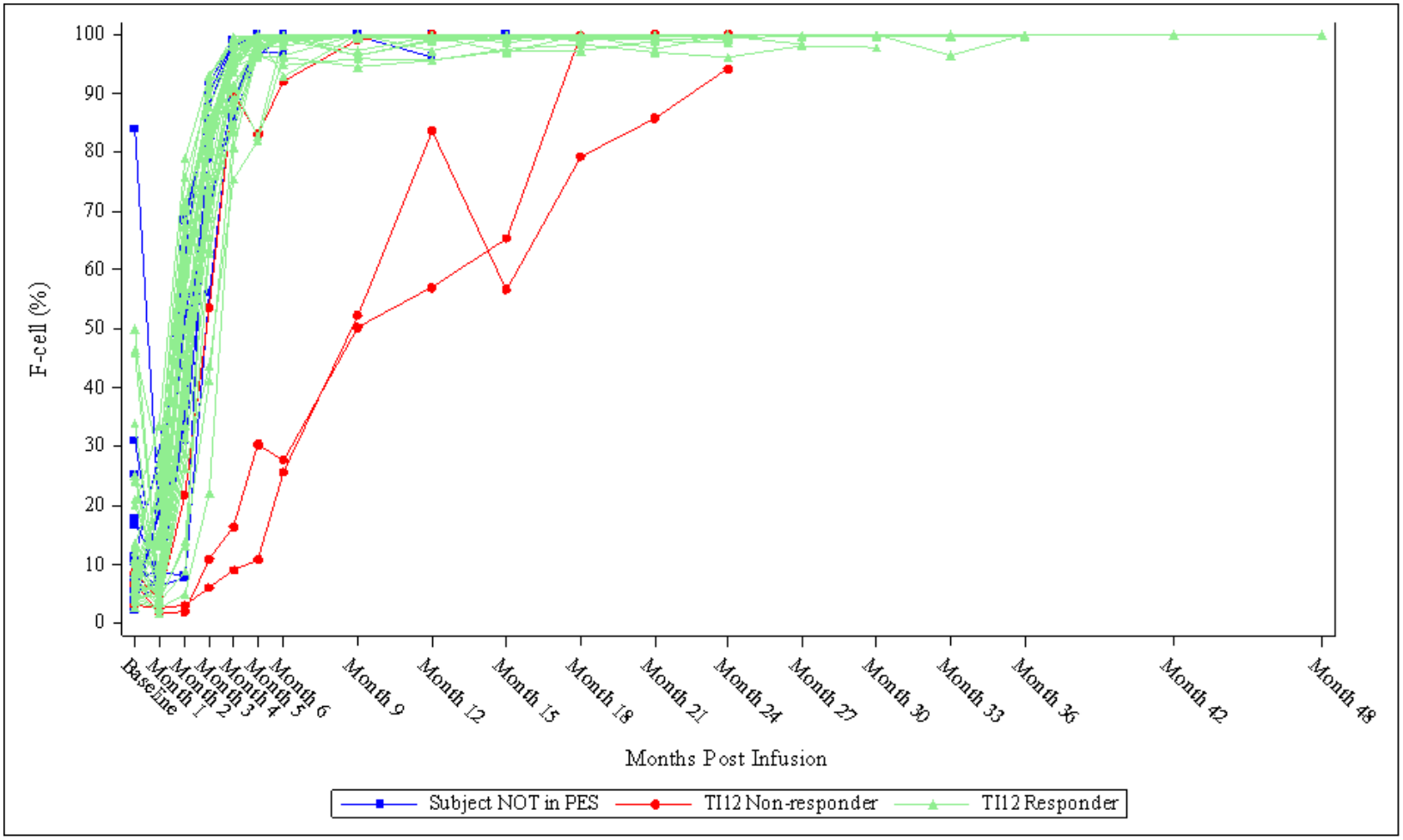
Source: Exa-cel D120 efficacy update, data on file (Vertex Pharmaceuticals Inc., 2023a).

Change in proportion of F-cells over time

Consistent with observed HbF increases, the mean proportion of circulating RBCs expressing HbF (termed F-cells) was maintained at mean ≥96.15% from Month 6 through the duration of follow-up in CLIMB-131 (Figure 6) (Vertex Pharmaceuticals Inc., 2023a). Elevated HbF can reduce the α-globin to β-globin chain imbalance by providing γ-globin chains that are able to bind to the unpaired α-globin (Musallam et al., 2013). These raised levels of HbF are a characteristic of β-thalassaemia patients with the HPFH phenotype who, as already highlighted, experience reduced or no β-thalassaemia-associated symptoms (Frangoul et al., 2021; Musallam et al., 2012; Sharma et al., 2020).

Of note, patients not included in the PES demonstrate a rapid and robust increase in the proportion of F-cells and demonstrate a very similar initial trajectory to those patients who are included in the PES (Figure 6) (Vertex Pharmaceuticals Inc., 2023a).

Figure 6: Individual F-cells (%) over time (CLIMB THAL-111 and CLIMB-131, FAS)



Key: FAS: Full Analysis Set; F-cells: erythrocytes expressing γ-globin (fetal haemoglobin); PES: Primary Efficacy Set; TDT: transfusion dependent β thalassemia; TI12: transfusion independent for at least 12 consecutive months.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization in Study 111. Analysis visit was used in the figure.
Source: Figure 7, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

Proportion of alleles with intended genetic modification

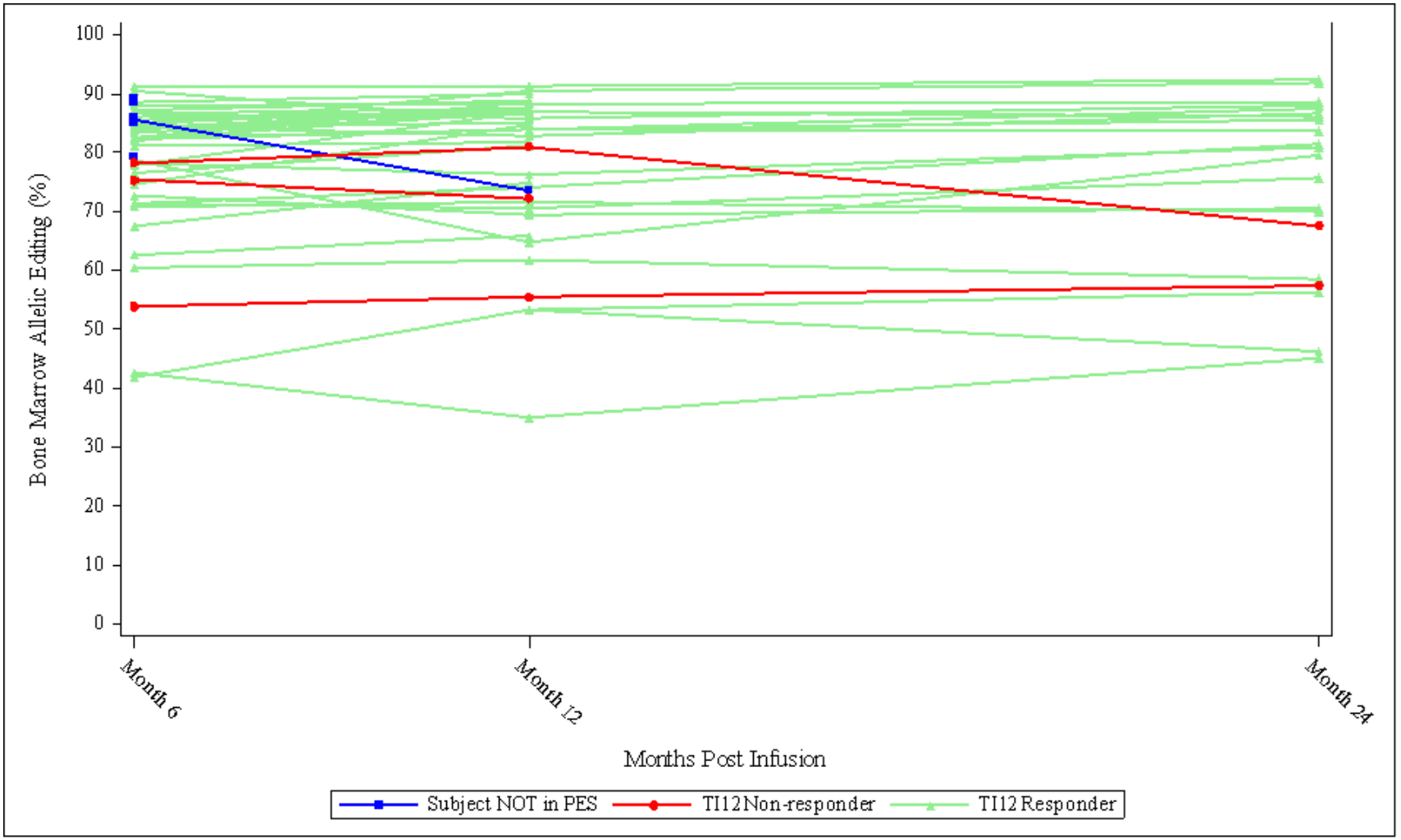
Allelic editing in bone marrow and peripheral blood remained stable for each patient for the duration of follow-up through Month 48 (Vertex Pharmaceuticals Inc., 2023a), indicating stable engraftment of edited long-term HSCs and supporting durability of effect (Vertex Pharmaceuticals Inc., 2022c).

At Month 6 (first timepoint of evaluation), the mean (SD) proportion of alleles with intended genetic modification in the $CD34^+$ cells of the bone marrow was 78.5% (11.4%), which was consistent with allelic editing of the drug product. The mean proportion of alleles with the intended genetic modification in the $CD34^+$ cells of the bone marrow remained stable at Month 12 (≥73.4%) onwards (Figure 7) (Vertex Pharmaceuticals Inc., 2023a).

Similarly, allelic editing in the peripheral blood was detectable within one month after exa-cel infusion. The mean (SD) proportion of alleles with the intended genetic modification in peripheral blood was 50.2% (20.4%) at Month 1 and the mean remained ≥62.2% from Month 2 onwards (Figure 8) (Vertex Pharmaceuticals Inc., 2023a).

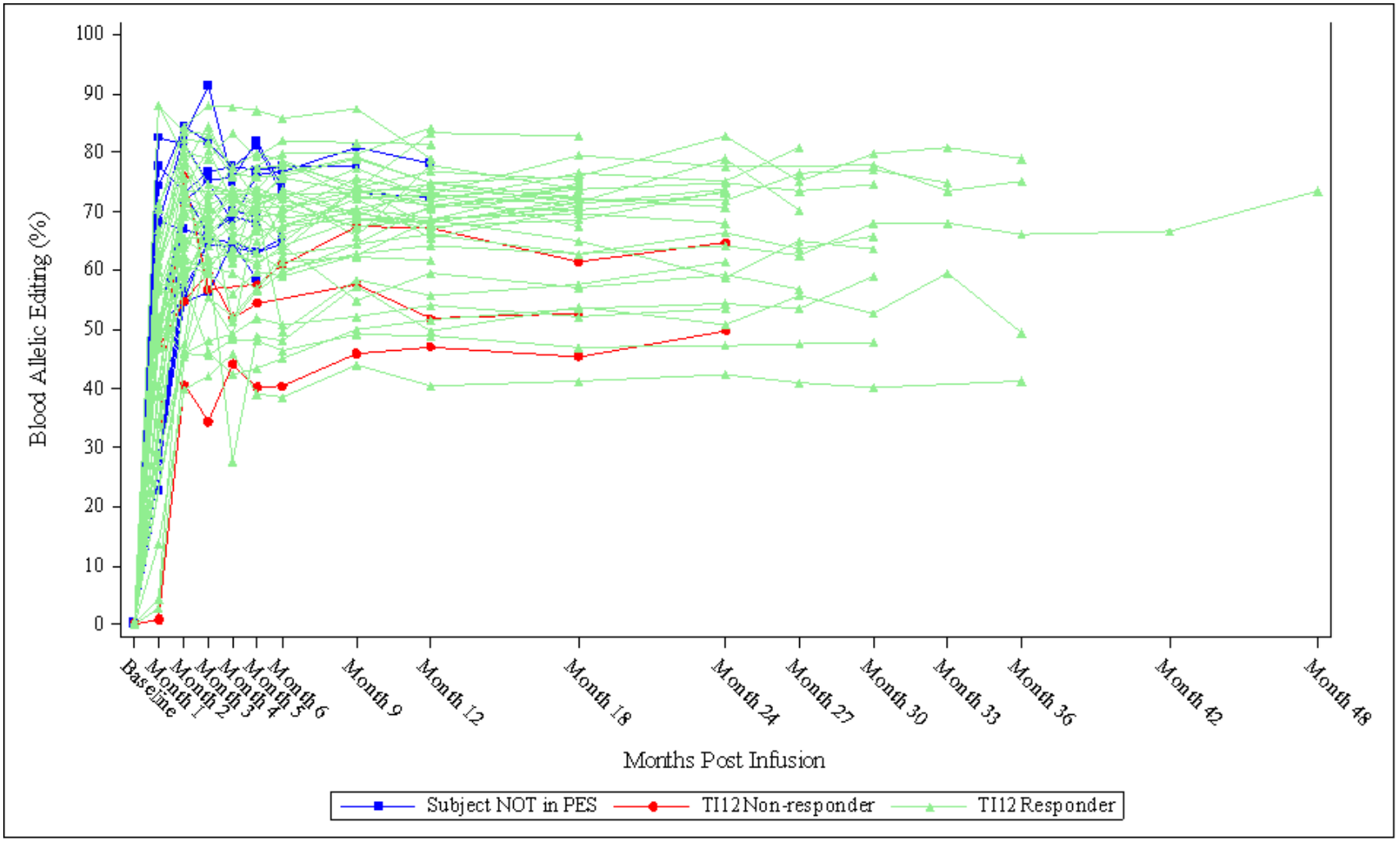
All patients, including the three patients in the PES who did not achieve TI12, had percent allelic editing that remained stable over time for the duration of follow-up. Even patients who had the lowest levels of peripheral blood or bone marrow editing at Months 12 and 24 achieved the primary endpoint of TI12 (Vertex Pharmaceuticals Inc., 2023a).

Figure 7: Proportion of edited alleles in CD34+ bone marrow (CLIMB THAL-111 and CLIMB-131, FAS)



Key: FAS: Full Analysis Set; PES: Primary Efficacy Set; TI12: transfusion independent for at least 12 consecutive months.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. Analysis visit was used in the figure.
Source: Figure 9, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

Figure 8: Proportion of edited alleles in peripheral blood cells (CLIMB THAL-111 and CLIMB-131, FAS)



Key: FAS: Full Analysis Set; PES: Primary Efficacy Set; TI12: transfusion independent for at least 12 consecutive months.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. Analysis visit was used in the figure.
Source: Figure 10, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

Parameters of iron overload

Reductions in iron overload are indicative of additional benefits of transfusion independence and a reduction in ineffective erythropoiesis imparted by treatment with exa-cel. Reductions in iron overload and ineffective erythropoiesis are known to occur slowly, over two to four years following successful allo-SCT, because the body's homeostatic processes for iron metabolism and removal may require many months, if not years to process (Angelucci et al., 1997; Chaudhury et al., 2017). These parameters were assessed in the patients included in the PES because they have the longest follow-up.

Serum ferritin

Consistent with their transfusion dependent disease, all patients in the PES (n=42) had significantly elevated SF with mean (SD) at baseline 3,785.4 (2,908.2) pmol/L. Following treatment with exa-cel, at Month 24, patients (n=23) had mean (SD) SF decreased to 2,220.9 (1,655.2) pmol/L, which were below baseline values (Vertex Pharmaceuticals Inc., 2022a, 2023a). These findings are consistent with that observed in patients with TDT after allo-SCT and are supportive of a beneficial treatment effect on iron accumulation (Chaudhury et al., 2017). It is expected that further reduction in iron overload leading to prevention of end-organ damage and overall improvement in survival will be observed with additional follow-up. This endpoint is assessed in the long-term extension study, CLIMB-131 (Vertex Pharmaceuticals Inc., 2022a).

Assessments of ineffective erythropoiesis in the bone marrow

Ineffective erythropoiesis is measured by myeloid: erythroid (M: E) ratio in the bone marrow. Patients with TDT generally have an M:E ratio of <0.1 due to ineffective erythropoiesis (Origa, 2000). With transfusion support, this <0.1 ratio increases reflecting the suppression of the erythroid series by the transfusions. Increases in the M:E ratio toward 1 in the setting of TI indicate improvement in ineffective erythropoiesis. A normal M:E ratio is 1.2 to 5 (Bain, 1996).

At baseline, patients with TDT (n=21), had a mean (SD) M:E ratio of 0.64 (0.47) consistent with being on chronic transfusion prior to exa cel treatment. After exa-cel infusion, mean (SD) M:E ratios increased over time to 0.83 (0.38) at Month 24 (n=23; including 21 patients who were TI and two patients who stopped RBC transfusions at 14.5 and 21.6 months after exa-cel infusion). This increased M:E ratio in the absence of transfusion, which is well above the <0.1 ratio for patients with TDT, indicates reduced ineffective erythropoiesis, and is supportive of the overall treatment effect of exa-cel (Vertex Pharmaceuticals Inc., 2023a).

Patient-reported outcomes

PRO scores indicated substantial improvement in general well-being, HRQoL, and overall health status, including improvements in fatigue scores, after exa-cel infusion. Consistent improvements were observed in the EuroQol Quality of Life Scale-5-dimensions-5 levels of severity (EQ-5D-5L) and EuroQol-Visual Analogue Score (EQ-VAS) scores despite the high scores reported at baseline that were similar to the general UK population (Vertex Pharmaceuticals Inc., 2023a). However, as discussed below, the EQ-5D-5L is not an effective tool for capturing the impact of TDT on HRQoL and is shown not to be responsive to change in this patient population.

EQ-5D-5L

At baseline, mean (SD) EQ-5D-5L utility index scores in CLIMB THAL-111 (0.89 (0.14) in the PES population) were reported to be greater than the average UK population score (Table 2) (Janssen et al., 2019; Vertex Pharmaceuticals Inc., 2023a). Despite the near normal baseline scores, positive changes in EQ-5D-5L utility scores were observed over time, with a mean (SD) change from baseline of 0.04 (0.22) points (MCID = 0.08 points) at Month 24, indicating improvement in overall health status after exa-cel infusion. This trend of improvement is expected to continue out to Month 24 onwards (Vertex Pharmaceuticals Inc., 2023a).

Table 2: Summary of EQ-5D-5L scores and change from baseline for patients ≥18 and ≤35 years of age (CLIMB THAL-111, PES)

Visit	PES	
	EQ-VAS	UK Health Utility Index Score
Baseline		
N	29	29
Mean (SD)	81.8 (17.1)	0.89 (0.14)
Median	90.0	0.94
Min, Max	40.0, 100.0	0.49, 1.00
Month 9		
N	28	28
Mean (SD)	88.5 (10.8)	0.91 (0.12)
Median	90.0	1.00
Min, Max	60.0, 100.0	0.62, 1.00
Month 12		
N	29	29
Mean (SD)	89.7 (11.3)	0.91 (0.14)
Median	95.0	1.00
Min, Max	60.0, 100.0	0.49, 1.00
Month 18		
N	25	25
Mean (SD)	87.8 (18.0)	0.91 (0.16)

Median	95.0	1.00
Min, Max	20.0, 100.0	0.28, 1.00
Month 24		
N	19	19
Mean (SD)	90.5 (11.1)	0.91 (0.13)
Median	95.0	1.00
Min, Max	60.0, 100.0	0.59, 1.00

Key: EQ-5D-5L: EuroQol Quality of Life Scale-5-dimensions-5 levels of severity; PES: Primary Efficacy Set; SD: standard deviation.

Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. EQ-5D-5L responses were mapped to the 3L value set using the Hernández-Alava algorithm.

Source: Table 43, D120 Interim Analyses {Vertex Pharmaceuticals Inc., 2023 #4}

Empirical evidence suggests that EQ-5D-5L lacks content validity and the derived health utility index score may not fully represent the burden of disease in TDT. Support for this comes from vignette studies in which the general public valued TDT health state vignettes using the time trade-off (TTO) method (Martin, 2022; Matza et al., 2020). The utility values from these valuations, even for the mildest TDT states were far lower (0.63-0.75) than those observed at baseline in the PES (0.89). Further issues may be the absence of a fatigue domain in the EQ-5D-5L, a symptom which is particularly relevant to TDT patients. A recent study demonstrated improved psychometric performance of the EQ-5D-5L in a chronic disease population when a fatigue domain was added (Spronk et al., 2022).

FACT-BMT

The Functional Assessment of Cancer Therapy - Bone Marrow Transplant (FACT-BMT) consists of the Functional Assessment of Cancer Therapy – General (FACT-G), which measures overall HRQoL (includes subscales for physical, social/family, emotional, and functional well-being) and treatment-specific concerns of bone marrow transplantation subscale (BMTS). For each total and subscale score, higher values indicate better quality of life (Vertex Pharmaceuticals Inc., 2023a).

Mean FACT-BMT total scores progressively improved from baseline to Month 24, with the mean (SD) change from baseline at Month 24 of 13.9 (21.4) points, indicating a robust improvement in general well-being and HRQoL after exa-cel infusion that was sustained through the duration of follow-up (Table 6) (Vertex Pharmaceuticals Inc., 2023a).

Similarly, the FACT-G and BMTS scores progressively increased from baseline, with the mean (SD) change from baseline for FACT-G of 8.3 (16.9) points and BMTS of 5.6 (5.6) points at Month 24 (Vertex Pharmaceuticals Inc., 2023a). Of note, the minimal clinically important difference is considered to be 3 to 7 points for FACT-G and 2 to 3 points for BMTS (Table 3). These minimal clinically important differences are not TDT-specific, however they are largely consistent across numerous conditions (King et al., 2010). FACT-G subscores indicated that improvements in the overall score at Month 24 were driven by the physical

and emotional well-being subscales, with mean (SD) change from baseline of 3.0 (6.1) points and 3.0 (2.4) points, respectively (Table 3) (Vertex Pharmaceuticals Inc., 2023a).

Table 3: Summary of FACT-BMT scores (CLIMB THAL-111 and CLIMB-131, PES)

Visit	FACT-BMT total score	FACT-G total score	BMTS	FACT-G subscores			
				PWB score	EWB score	FWB score	SWB score
Baseline							
n	29	29	29	29	29	29	29
Mean (SD)	112.5 (19.5)	84.6 (15.5)	27.9 (4.8)	22.4 (5.4)	18.7 (3.7)	21.1 (5.2)	22.3 (4.7)
Median	116.0	86.0	28.0	24.0	20.0	20.0	23.3
Min, Max	68.0, 142.0	53.0, 107.0	15.0, 35.0	9.0, 28.0	11.0, 24.0	11.0, 28.0	10.5, 28.0
Month 12							
n	29	29	29	29	29	29	29
Mean (SD)	119.9 (18.6)	88.5 (14.2)	31.4 (5.0)	25.1 (4.4)	20.9 (2.6)	20.8 (5.7)	21.6 (6.5)
Median	123.0	91.0	31.0	27.0	21.0	21.0	22.2
Min, Max	73.0, 148.0	48.0, 108.0	18.0, 40.0	10.0, 28.0	12.0, 24.0	6.0, 28.0	4.0, 28.0
Month 18							
n	23	23	23	23	23	23	23
Mean (SD)	120.1 (14.3)	89.5 (11.1)	30.6 (4.2)	25.2 (4.2)	20.5 (2.4)	21.0 (4.8)	22.8 (4.2)
Median	122.0	92.0	31.0	27.0	20.0	21.0	22.0
Min, Max	93.0, 143.0	65.0, 106.0	23.0, 39.0	13.0, 28.0	14.0, 24.0	10.0, 28.0	15.0, 28.0
Month 24							
n	19	19	19	19	19	19	19
Mean (SD)	124.4 (18.6)	91.6 (13.8)	32.8 (5.3)	25.3 (3.8)	21.5 (2.8)	22.1 (4.9)	22.7 (4.8)
Median	128.0	94.0	34.0	27.0	22.0	23.0	24.0
Min, Max	77.0, 145.0	60.0, 108.0	17.0, 39.0	15.0, 28.0	13.0, 24.0	13.0, 28.0	14.0, 28.0
Change at Month 24							
n	19	19	19	19	19	19	19
Mean (SD)	13.9 (21.4)	8.3 (16.9)	5.6 (5.6)	3.0 (6.1)	3.0 (3.4)	1.4 (5.8)	0.8 (4.5)
Median	10.0	4.5	5.0	2.0	2.0	0.0	1.0
Min, Max	-22.0, 73.0	-20.0, 53.0	-7.0, 20.0	-10.0, 17.0	-4.0, 12.0	-9.0, 15.0	-6.0, 9.0

Key: BMTS: bone marrow transplantation subscale; EWB: emotional well-being; FACT-BMT: Functional Assessment of Cancer Therapy-Bone Marrow Transplant; FAS: Full Analysis Set; FWB: functional well-being; PWB: physical well-being; SWB: social/family well-being.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation.
Source: Table 44, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

PedsQL

The Pediatric Quality of Life Inventory (PedsQL) is a brief, standardised, generic instrument that systematically assesses patients' and parents' perceptions of health-related quality of life in paediatric patients with chronic health conditions (Varni et al., 2002). The teen version of PedsQL (self-report and parent proxy versions), administered to patients ≥12 to <18 years of age, comprises of 23 items across four domains including Physical Health, Emotional Functioning, Social Functioning and School Functioning (Varni, 2023). PedsQL scores by domain are summarised below in Table 4.

The mean (SD) baseline total score for adolescent patients was 75.9 (9.6) points, below the population norm of 82.87 points. Total scores showed clinically meaningful improvements at Month 6, exceeding the minimal clinically important difference (MCID) of 4.36 points (Varni et al., 2003), with mean (SD) change from baseline at Month 24 of 12.3 (17.4) points, indicating robust improvements in general well-being and HRQoL.

Table 4: Summary of PedsQL scores and change from baseline for patients ≥12 to <18 years of age (CLIMB THAL-111, PES)

Visit	Total Score	Physical Functioning Score	Psychosocial Health Summary Score	Psychosocial Health Subscores		
				Emotional Functioning	Social Functioning	School Functioning
Baseline						
n	12	12	12	12	12	12
Mean (SD)	75.9 (9.6)	76.3 (11.7)	75.7 (10.5)	72.8 (11.4)	83.3 (14.8)	70.8 (14.0)
Median	77.2	78.1	75.0	72.5	87.5	75.0
Min, Max	60.9, 96.7	53.1, 100.0	55.0, 95.0	50.0, 90.0	55.0, 100.0	50.0, 95.0
Month 4						
n	13	13	13	13	13	13
Mean (SD)	84.4 (9.0)	82.9 (10.7)	85.2 (10.0)	85.4 (13.3)	92.7 (11.1)	77.2 (14.2)
Median	84.8	84.4	85.0	85.0	100.0	75.0
Min, Max	67.4, 97.8	59.4, 100.0	68.3, 100.0	60.0, 100.0	65.0, 100.0	45.0, 100.0
Change at Month 4						
n	12	12	12	12	12	12
Mean (SD)	7.4 (12.0)	5.2 (16.5)	8.7 (11.7)	11.4 (14.9)	8.8 (16.0)	5.7 (19.1)
Median	7.1	4.7	10.0	5.6	10.0	0.0
Min, max	-14.1, 27.2	-25.0, 31.3	-13.3, 26.7	-20.0, 30.0	-20.0, 35.0	-15.0, 50.0
Month 6						
n	13	13	13	13	13	13
Mean (SD)	87.5 (8.5)	87.0 (10.9)	87.7 (8.5)	84.6 (12.5)	95.0 (9.6)	83.5 (10.3)
Median	88.0	87.5	90.0	90.0	100.0	85.0
Min, Max	68.5, 100.0	65.6, 100.0	68.3, 100.0	65.0, 100.0	70.0, 100.0	70.0, 100.0
Change at Month 6						
n	12	12	12	12	12	12
Mean (SD)	10.8 (10.2)	9.6 (16.7)	11.4 (9.6)	10.5 (13.0)	11.3 (15.7)	12.5 (14.5)
Median	12.0	9.4	12.5	10.0	10.0	12.5
Min, max	-5.4, 29.3	-12.5, 34.4	-5.0, 26.7	-10.0, 31.3	-20.0, 35.0	-15.0, 40.0
Month 12						
n	12	12	12	12	12	12

Mean (SD)	87.9 (8.9)	91.4 (9.1)	86.0 (10.2)	80.4 (15.1)	96.7 (8.6)	80.8 (16.4)
Median	88.6	92.2	88.3	77.5	100.0	82.5
Min, Max	64.1, 100.0	71.9, 100.0	60.0, 100.0	55.0, 100.0	70.0, 100.0	50.0, 100.0
Change at Month 12						
n	11	11	11	11	11	11
Mean (SD)	12.0 (10.3)	15.1 (13.8)	10.4 (10.3)	6.5 (11.1)	13.6 (11.9)	11.4 (19.0)
Median	14.1	15.6	10.0	10.0	10.0	5.0
Min, max	-1.1, 29.3	-6.3, 37.5	-6.7, 26.7	-15.0, 25.0	0.0, 35.0	-15.0, 40.0
Month 18						
n	11	11	11	11	11	11
Mean (SD)	87.5 (9.7)	89.8 (10.3)	86.4 (9.7)	82.7 (11.9)	95.5 (8.2)	80.9 (15.3)
Median	88.0	90.6	86.7	80.0	100.0	80.0
Min, Max	67.4, 100.0	68.8, 100.0	66.7, 100.0	60.0, 100.0	75.0, 100.0	50.0, 100.0
Change at Month 18						
n	10	10	10	10	10	10
Mean (SD)	11.5 (12.4)	15.0 (16.6)	9.6 (11.5)	7.6 (11.2)	10.5 (16.1)	11.0 (20.1)
Median	12.5	18.8	8.3	10.0	10.0	5.0
Min, max	-7.6, 29.3	-12.5, 37.5	-6.7, 26.7	-15.0, 25.0	-10.0, 35.0	-15.0, 50.0
Month 24						
n	4	4	4	4	4	4
Mean (SD)	91.3 (10.6)	91.4 (17.2)	91.3 (8.0)	90.0 (12.2)	95.0 (10.0)	88.8 (8.5)
Median	94.6	100.0	91.7	92.5	100.0	87.5
Min, Max	76.1, 100.0	65.6, 100.0	81.7, 100.0	75.0, 100.0	80.0, 100.0	80.0, 100.0
Change at Month 24						
n	3	3	3	3	3	3
Mean (SD)	12.3 (17.4)	15.6 (22.5)	10.6 (15.1)	13.3 (16.1)	5.0 (25.0)	13.3 (12.6)
Median	13.0	21.9	8.3	20.0	5.0	15.0
Min, max	-5.4, 29.3	-9.4, 34.4	-3.3, 26.7	-5.0, 25.0	-20.0, 30.0	0.0, 25.0

Key: PedsQL: Paediatric Quality of Life Inventory; PES: Primary Efficacy Set.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation.
Source: Table 45, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

The safety and tolerability of exa-cel for the treatment of patients aged 12-35 years with TDT was evaluated in the SAS of CLIMB THAL-111. The analysis of safety was performed on the Safety Analysis Set (SAS), a subset of all enrolled patients who signed informed consent and met the eligibility criteria which included patients who started the mobilisation regimen. The discussion of adverse events (AEs) focuses on the period from exa-cel infusion to Month 24, with narrative added to the long-term study where applicable.

AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

Exposure to exa-cel

In the FAS, the median dose of exa-cel was 8.0 x 106 CD34+ cells/kg (range: 3.0 to 19.7 x 106 CD34+ cells/kg) (Vertex Pharmaceuticals Inc., 2023a). The median follow-up duration after exa-cel infusion was 22.8 months (range: 2.1 to 51.1) months, which corresponds to a total 100.5 patient-years (Table 5) (Vertex Pharmaceuticals Inc., 2023a).

Table 5: Follow-up Duration After Exa-cel Infusion through Study 131 (Long term Follow Up): FAS

	Total (n=54)
Exa-cel dose (10^6 x CD34+ cells/kg)	
n	54
Mean (SD)	22.3 (10.51)
Median	22.8
Min, Max	2.1, 51.1
Follow-up duration after exa-cel infusion by interval, n (%)	
≤3 months	2 (3.7)
>3 months to ≤6 months	4 (7.4)
>6 months to ≤12 months	4 (7.4)
>12 months to ≤24 months	20 (37.0)
>24 months	24 (44.4)

Key: FAS: Full Analysis Set; SD: standard deviation.
Notes: Follow-up duration after exa-cel infusion (months) = (data cutoff date or end of study date – exa-cel infusion date +1)/30.
Source: Table 22, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

Summary of adverse events

An overview of AEs is presented for the interval from exa-cel infusion to Month 24 in Table 6.

Table 6: Overview of AEs after exa-cel infusion to Month 24 (CLIMB THAL-111 and CLIMB-131, FAS)

Visit	Exa-cel to Month 24 (n=54)
Patients who received exa-cel infusion, n	54
Patients who received busulfan, n	54
Patients with any AEs, n	54 (100.0)
Patients with any AEs related or possibly related to exa-cel, n	14 (25.9)
Patients with any AEs related or possibly related to busulfan	53 (98.1)
Grade 3 or above AEs	48 (88.9)
SAEs	19 (35.2)
SAEs related or possibly related to exa-cel	2 (3.7)
SAEs related or possibly related to busulfan	9 (16.7)
AEs leading to study discontinuation	0
AEs leading to death	0

Key: AE: adverse event; exa-cel: exagamglogene autotemcel; SAE: serious adverse event.
Notes: MedDRA version 26.0. Percentages were calculated as n/N1*100 within each interval, unless otherwise specified. Percentages of patients with AEs/SAEs related or possibly related to exa-cel/busulfan were calculated relative to the number of patients with exa-cel infusion/busulfan dosing within each interval, as n/N2*100 or n/N3*100. Percentages of patients with AEs by strongest relationship to exa-cel/busulfan were calculated relative to the number of patients with exa-cel infusion/busulfan dosing within each interval, as n/N2*100 or n/N3*100. When summarizing number and percentage of patients for each study interval, a patient with multiple events within a category and study interval was counted only once in that category and study interval. An AE with relationship missing to busulfan/exa-cel was counted as related to busulfan/exa-cel in this table. Table shows exa-cel to M24 study interval: day of exa-cel infusion to Month 24 visit or end of study visit.
Source: Table 24, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

A summary of frequent AEs after exa-cel infusion by preferred term occurring in ≥25% of patients can be found below in Table 7.

Table 7: AEs occurring in ≥25% of patients after exa-cel infusion (CLIMB THAL-111, FAS)

Preferred Term[a]	Exa-cel to Month 24 (n=54)
Patients with any AEs	**54 (100.0)**
Febrile neutropenia	33 (61.1)
Headache	30 (55.6)
Stomatitis	28 (51.9)
Thrombocytopenia	25 (46.3)
Anaemia	24 (44.4)
Mucosal inflammation	23 (42.6)
Nausea	23 (42.6)
Vomiting	22 (40.7)
Hypokalaemia	21 (38.9)
Platelet count decreased	21 (38.9)
Abdominal pain	20 (37.0)
Epistaxis	20 (37.0)
Arthralgia	19 (35.2)
Constipation	18 (33.3)
Neutrophil count decreased	16 (29.6)
Diarrhoea	15 (27.8)
Pruritus	15 (27.8)
Pyrexia	15 (27.8)
COVID-19	14 (25.9)
Decreased appetite	14 (25.9)

Key: AE: adverse event; exa-cel: exagamglogene autotemcel.
Notes: AEs were coded using MedDRA Version 26.0. Percentages were calculated as n/N1×100. When summarising number and percentage of patients for each study interval, a patient with multiple events within a category and study interval was counted only once in that category and study interval. The table is sorted in descending order of frequency of the exa-cel to Month 24 column by preferred term.
[a]All PTs are described in busulfan product information by matching PT or similar medical concept (Pierre Fabre Medicament).
Source: Table 25, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

The most common AEs (occurring in more than two patients) considered related or possibly related to exa-cel were headache and laboratory-related events (CD4 lymphocytes decreased, neutrophil count decreased, lymphopenia, platelet count

decreased, thrombocytopenia, and white blood cell count decreased). Most AEs considered related or possibly related to exa-cel were also considered related or possibly related to busulfan. Only five patients (9.3%) had at least one AE that was considered related or possibly related to exa-cel only (Vertex Pharmaceuticals Inc., 2023a).

No AEs of new malignancies and new or worsening haematologic disorders have occurred any time after exa-cel infusion, including after Month 24 in CLIMB-131 (Vertex Pharmaceuticals Inc., 2023a).

Summary of serious adverse events

The incidence and nature of serious adverse events (SAEs) from exa-cel administration to Month 24 were generally consistent with myeloablative busulfan conditioning (Pierre Fabre Medicament). In total, two patients (3.7%) with TDT had an SAE considered related, or possibly related, to exa-cel.

Among the patients who completed busulfan conditioning and received exa-cel, 19 patients (35.2%) with TDT had at least one SAE. The majority of SAEs occurred within the first six months after exa-cel infusion. SAEs that occurred in ≥2 patients are presented below in Table 8.

Table 8: SAEs occurring in ≥2 patients after exa-cel infusion (CLIMB THAL-111, FAS)

Preferred Term[a]	Exa-cel to Month 24 (n=54)
Patients with any SAEs	19 (35.2)
Venoocclusive liver disease	5 (9.3)
Pneumonia	3 (5.6)
COVID-19	2 (3.7)
Hypoxia	2 (3.7)
Thrombocytopenia	2 (3.7)
Upper respiratory tract infection	2 (3.7)

Key: exa-cel: exagamglogene autotemcel; SAE: serious adverse event.
Notes: AEs were coded using MedDRA Version 26.0. Percentages were calculated as n/N1×100. When summarising number and percentage of patients for each study interval, a patient with multiple events within a category and study interval was counted only once in that category and study interval. The table is sorted in descending order of frequency of the exa-cel to Month 24 column by preferred term.
[a]All PTs are described in busulfan product information by matching PT or similar medical concept (Pierre Fabre Medicament).

Source: Table 25, D120 Interim Analyses (Vertex Pharmaceuticals Inc., 2023a).

Two patients had SAEs considered related or possibly related to exa-cel (Vertex Pharmaceuticals Inc., 2023a):

- One [redacted] patient with TDT had SAEs of headache, haemophagocytic lymphohistiocytosis, and acute respiratory distress syndrome that were considered related or possibly related to exa-cel only and an SAE of idiopathic pneumonia syndrome that was considered related to busulfan and possibly related to exa cel. All events started within 32 days after completion of busulfan conditioning and subsequent exa-cel infusion and all resolved.
- One [redacted] patient with TDT had SAEs of delayed engraftment (verbatim: delayed neutrophil engraftment; onset: Study Day 43) and thrombocytopenia (onset: Study Day 97); both events were considered related or possibly related to busulfan and exa cel. The patient engrafted neutrophils on Study Day 56 without the use of backup cells and achieved platelet engraftment on Study Day 199; no serious infections were reported before or after the patient engrafted neutrophils. The patient did not have any other SAEs, including no serious bleeding events. Both events resolved.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Addendum to D120 clinical summary

September 2023

File name	Version	Contains confidential information	Date
ID4015_exa-cel_TDT_Updated model parameters [CON Redacted]	1.0	Yes	13/09/2023

CEA Model input changes between IA2 and D120 versions

Details of all updated model parameters are provided in the table below. Updates to D120 were based on availability of updated CSR data and/or *post-hoc* analyses at the time of post-clarification. All trial-related inputs not updated in the model were thus due to unavailability of data at the time of analysis and/or pending updated *post-hoc* analyses.

Parameter	Description of change	Previous value (IA2)	Updated value (D120)	Justification
CEA model input changes				
Age (years)	Updated mean baseline cohort age to D120	21.4	[redacted]	D120 data available
Weight ration	Updated weight ratio of TDT/general public to D120	0.76	[redacted]	D120 data available
Females (%)	Updated % of females in modelled cohort	52.1%	[redacted]	D120 data available
Proportion <18 years old	Updated % of cohort < 18 years old	33.3%	[redacted]	D120 data available
Annual transfusions per patient	Updated annual frequency of RBCTs per patient	[redacted]	[redacted]	D120 data available
Annualised unit of RBC transfusions	Updated annualised units of RBCTs per patient	[redacted]	[redacted]	D120 data available
Treatment withdrawal	Updated to reflect latest clinical and efficacy data (D120)	[redacted]	[redacted]	D120 data available
Initial engraftment success rate	Same as above	[redacted]	[redacted]	D120 data available
Proportion achieve TI	Same as above	[redacted]	[redacted]	D120 data available
Proportion achieve TR	Same as above	[redacted]	[redacted]	D120 data available

DCEA input updates to company base case at clarification in both IA2 and D120 model versions

Based on the EAG feedback we received during clarification questions, we updated the DCEA health opportunity cost shares, general population-level IMD proportions, and IMD-group QALEs values as below to align with the contemporary reference cited in priority question B23. DCEA-weighted economic outcome values have been updated accordingly. Consequently, both of our base case results tables refer to the updated DCEA modified base cases presented at clarification.

Parameter	Description of change	Previous value (IA2)	Updated value (D120)	Justification
DCEA input changes				
General Population Proportions (IMD groups)	Incorporate EAG scenario	Love-Koh 2020	Love-Koh 2023	Changed based on EAG clarification request
Quality-Adjusted Life Expectancy	Incorporate EAG scenario	Love-Koh 2015	Love-Koh 2023	Changed based on EAG clarification request
Health Opportunity Cost Shares	Incorporate EAG scenario	Assumption	Love-Koh 2020	Changed based on EAG clarification request

Comparison of IA2 and D120 economic results

The following tables incorporate our updated DCEA inputs implemented at clarification (which we now consider our base case DCEA analysis) and present results both using the IA2 and D120 data cut, where available.

Table 1: Base-case results (IA2, DCEA input changes, 1.5% discount rate)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER with 1.7 severity modifier
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted incremental results				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2: Base-case results (D120, DCEA input changes, 1.5% discount rate)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER with 1.7 severity modifier
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted incremental results				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3: Scenario analysis results (IA2, DCEA input changes, 3.5% discount rate)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER with 1.2 severity modifier
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted incremental results				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Scenario analysis results (D120, DCEA input changes, 3.5% discount rate)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER with 1.2 severity modifier
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted incremental results				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Patient Organisation Submission

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. [Please note that declarations of interests relevant to this topic are compulsory].

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	**Anthony Nolan**
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Anthony Nolan** is a charity founded in 1974 as the world's first stem cell register. We connect remarkable individuals willing to donate their stem cells to strangers in need of a lifesaving transplant, and provide outstanding support to patients receiving stem cell transplant and related therapies. We also conduct and enable ground-breaking research into improving outcomes from stem cell transplant and newer cell and gene therapies. Anthony Nolan's main source of income is the provision of stem cells for transplant to NHS providers, collected from volunteer donors. Voluntary income (and fundraising events through Anthony Nolan Trading Ltd (ANTL) comes from a wide variety of generous supporters, including individual giving, legacies, community and events fundraising, corporate support, and charitable trusts. This helps to fund our ground-breaking scientific research, and growth and diversity of the stem cell donor register.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	None

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	Anthony Nolan's Patient Services and medical officers have shared their professional experiences of supporting transfusion-dependent beta-thalassaemia (TDT) patients through the stem cell transplant pathway.

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?	**Living with TDT** • The impact of transfusion-dependent beta-thalassaemia (TDT) is significant for both patients and their families. The symptoms begin early in childhood and persist throughout a patients' life. • Patients with chronic anaemia, a key symptom of beta-thalassaemia, require lifelong regular blood transfusions, normally given every 2-5 weeks in order to maintain haemoglobin levels. This forces TDT patients to plan and revolve their lives around transfusion dates, knowing that they will need blood transfusion support in the near future. • Each transfusion can take 3-4 hours (for 2-3 units) which unless administered very early in the day, or later in the evening (which is unlikely), results in the patient's day being dominated around the transfusion, especially factoring in travel time to the hospital and return journey. • A number of complications can result from regular blood transfusions: o Iron overload and excessive absorption of iron in the gastrointestinal tract. Symptoms can include nausea, vomiting, diarrhoea and stomach pain. Over time, iron can accumulate in the organs, and cause fatal damage to the liver or brain. Toxic cellular effects occur as well. o Alloimmunisation in blood transfusions may result in an immediate or delayed haemolytic transfusion reaction that presents with several symptoms, including fever, chills, backaches or headaches, shortness of breath, and increased heart rate. o Transfusion-induced graft versus host disease (TI-GVHD) is a very serious but rare inflammatory response to patients being transfused with viable lymphocytes in donor red cell units. TI-GVHD usually occurs within 1-4 weeks of transfusion and is characterised by fever, rash, liver dysfunction, diarrhoea and pancytopenia due to bone marrow failure. TI-GVHD has a higher prevalence amongst haploidentical red cell donors, and is why unrelated donors are most favoured for blood transfusions.

- Patient's initial height, growth and stature may be within typical expectations. But after 8 years of age, patients' stature may begin to fall behind relative to their peers – particularly since many patients do not experience a typical growth spurt.
- The impact on major organs can be significant with patients' spleen, liver, and heart become enlarged. Bones can also become thin, brittle, and deformed.
    - Cardiac complications can be a result of iron overload complications, as well as unrelated conditions such as pulmonary hypertension and arrhythmia such as Atrial Fibrillation.
- Patients with TDT are considered immunocompromised, putting them at higher risk of infections with sepsis being a leading cause of mortality in TDT.
- TDT places an enormous strain on a patient's body, with an average life expectancy of 17 years and most patients will sadly die by 30 years of age. Most deaths are caused by the cardiac complications of iron overload.

Mental health and wellbeing impact

- Experiences of depression are common for TDT patients, however there is a lack of research in this area.
- Patients naturally want to live life in ways typical for their peers, but due to pain and fatigue this is not always possible. Seeing their peers and family members hitting milestones such as sports days and going to university can create a sense of loss.
- Education is regularly disrupted in order to attend clinic and transfusion appointments, making it difficult for children and young people to feel included in their school community. This can result in school bullying and abusive behaviour which has a detrimental impact on a patients' wellbeing.
- Many TDT patients are employed, however, substantial groups work part-time or not at all. Repeated absences for appointments and pain management are regularly cited as limiting factors.

Effect on daily life

- Patients learn how to manage their pain levels and understanding when to take rest breaks to recover.
- Managing activities and commitments around clinic and transfusion appointments is neccessary, as well as staying on top of any chelation therapy to tackle iron overload. Maintaining strong adherence to any regimen and courses of tablets is critically important and understandably difficult for children and young people.

	• Personal hydration is important and remembering to stay hydrated during the day, and recognising changes in your body and the air temperature is a constant struggle. • Damage caused to patients' organs such as their heart can mean physical exertion is more difficult, making travelling or commuting an arduous task. This means they may need more support from others when attending hospital or going to work. **Carers and family support** • The impact of TDT during childhood means that parents, guardians and wider family naturally become more involved in a patient's care plan. Attending hospital appointments together is a common part of life, meaning parents and family have to be absent from their work and other commitments too. • If a patient has developed orthopaedic or other musculoskeletal issues such as brittle bones, they may require the use of a wheelchair or other mobility devices. Families' support will likely be required in helping with mobility and travel. • Prompting by carers around medication is very important, especially until a child or young people can be relied upon to self-prompt and manage their medication routine.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**Blood transfusions and red cell exchanges** • The procedures themselves are very time consuming, and continue to carry with them significant side effects for some patients that require surveillance and emergency management. • Not all patients can easily find a vein, resulting in multiple painful attempts to gain intravenous access. • Whilst TDT patients are a priority, patients do experience anxiety around supply knowing that regular donors are required and that donated products have to be screened for any impurities. **Chelation therapies** • Constant blood tests to monitor iron levels are themselves painful and a nuisance. This is truer for invasive biopsies of a patients' liver for example. • The most common reason for inadequate control for chelation therapy is poor adherence prescribed dosages and timings, especially true for younger patients. • Desferrioxamine is administered subcutaneously through a battery-operated portable pump and is considered the most effective and safest method of preventing or treating iron overload, but it is very demanding since it requires the patients' compliance for 8 to 12 hours **daily**. • Deferiprone is administered orally and is much more widely accepted by patients, however, it still carries the risk of agranulocytosis, neutropenia, arthropathy and gastro-intestinal inflammation. • Deferasirox is also orally administered but still carries the risk of gastro-intestinal inflammation and potentially drug induced hepatitis. **Allo- hematopoietic stem cell transplantation** • Around 250 people a year are born with thalassaemia in the UK. • There were 12 stem cell transplants in the UK to treat thalassaemia in 2021 (latest data available). • Finding a fully-matched donor is not guaranteed for any patient searching for a match, and some patients may need to rely on alternative stem cell sources such as cord blood or a haploidentical donor. Stem cell transplant is not generally recommended for adult TDT patients. • Post-transplant side effects such as severe immunosuppression and Graft vs Host disease can result in life-long impacts for patients. • Allo-HSCT 5-year survival is approximately 50% (for all HSCT inidications), and carries with it significant risk factors that require ongoing management.

	Management of TDT-related complications • Patients rely on good access to various specialist teams to manage liver and spleen output, cardiovascular resilience, orthopaedics and dental services. • Service quality and route to access can vary across the country, and ultimately add to the contact time required with health services, further impacting patients' quality of life.
8. Is there an unmet need for patients with this condition?	Transfusion-dependent beta-thalassaemia (TDT) continues to have a significant and detrimental impact on patients' physical and mental wellbeing, as well as negatively impacting their social opportunities. The current standard of care has failed to extend their average life expectancy beyond the higher threshold of 30 years old – this measure in of itself is a signal that a gross unmet need exists and further treatments are needed for patients and their families to consider. Day-to-day living is currently affected through the side effects of TDT such as an increase in pain levels, fatigue and musculoskeletal changes – all reducing a patients physical ability to engage socially and economically. Current management regimens are time consuming, carry with them their own side effects that require further management. It is difficult for a TDT patient to ignore their condition as it remains an all-consuming factor in their daily lives and opportunities.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	• Patients are attracted to the option of having a single, one-off treatment option, which if successful would significantly change the impact on their daily lives of this condition. • The prospect of a reduced number of blood transfusions and thus a reduced chelation regimen would be greatly appreciated by patients. • The safety profile of CTX001 is generally consistent with myeloablation and autologous hematopoietic stem cell transplant, which has much lower risks compared to allo-transplantation. This demonstrates that those considering allo-HSCT could view this gene therapy as an alternative treatment.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	• The number of SAEs was not insignificant but this is thought to be due to the use of busulfan rather than the gene therapy itself; conditioning agents are also necessary for allogeneic stem cell transplant and as noted earlier standard treatments for TDT also pose significant side effects and toxicity risks to patients.

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.	• Traits for thalassemia are more common in people from Mediterranean countries, like Greece and Turkey, and in people from Asia, Africa, and the Middle East. • Patients experiencing severe side effects of TDT will more likely have ethnic backgrounds from these groups.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	• Patients from minority ethnic backgrounds should have more treatment options made available to them. • Transfusion-dependent beta-thalassaemia (TDT) can itself be a disabling and life-threatening condition and risks severely impacting a patients' social and economic equality. Improving upon this reality should be a priority.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Transfusion-dependent beta-thalassaemia (TDT) significantly impacts the lives of patients; physically, mentally and socially with much reduced life expectancies for severe cases. • Regular blood transfusions disrupt patients' education, employment opportunities, and require additional chelation therapies which carry their own side effects. • Allo-stem cell transplantation can be one option but patients' ethnic background can affect their ability find a matching donor, and all post-transplant patients have to monitor additional risk factors. • This gene therapy offers a potential alternative to allo-transplantation and other lifelong management regimens, with the prospect of significantly reduced healthcare plans and an improved quality of life.

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Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

NHS organisation submission (ICBs and NHS England)

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.

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- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Haemoglobinopathy Clinical Reference Group, NHS England
3. Job title or position	[redacted] and [redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? Yes An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? Yes Other (please specify): Specialist in managing haemoglobinopathy diagnoses
5a. Brief description of the organisation (including who funds it).	The clinical reference group (CRG) is a group of clinicians, commissioners, public health experts, patients and carers who provide advice to NHS England based on their specific knowledge and expertise. CRGs provide advice on various areas such as service specification development, commissioning policies, innovation and quality of services. This CRG specifically advises the NHS on matters regarding haemoglobinopathy and rare anaemias
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?	We have National standards of care for thalassaemia: Standards for the clinical care of children and adults with thalassaemia in the UK There are also a variety of national guidelines hosted at the British Society for Haematology website: 1. Red blood cell specifications for patients with haemoglobinopathies 2. Significant haemoglobinopathies a guideline for screening and diagnosis 3. Investigation and management of acute transfusion reactions Guidelines for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias
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.)	Care for thalassaemia was divided into 4 networks with lead centres named Haemoglobinopathy Coordinating Centres in 2019 across England. The Hospitals managing patients were also divided into Specialist centres and local centres based on a combination of facilities, staffing and patient number. These established networks of clinical care ensure patients have equitable care in their regions and access to specialist care and advice. Core to this system was the development of the National Haemoglobinopathy Panel which is a national multidisciplinary meeting which advises on complex patient management and acts as a central fulcrum of patient care.
8. What impact would the technology have on the current pathway of care?	Autologous gene therapy using exagamglogene autotemcel has the potential to offer a universal cure to patients with TDT who would qualify for curative options but lack a matched sibling donor. It additionally overcomes a number of other limitations including graft versus host disease, a post-allogeneic transplant complication which may be organ or life limiting.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	This technology is not in current clinical use.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Exagamglogene autotemcel will be a single treatment and is expected to obviate or significantly reduce the need for blood transfusion and hence requirement for iron chelation therapy. Treatment with this technology is expected to reduce health care utilisation significantly.
10a. How does healthcare resource use differ between the technology and current care? Would additional costs be required for fertility preservation (due to potential for pre-treatment/'conditioning' drugs to impact fertility)?	Exagamglogene autotemcel will be a single treatment and is expected to reduce both transfusions, and need for iron chelation, treatment with this technology is expected to reduce health care utilisation for the lifespan of the patient
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Exagamglogene autotemcel will be administered in specialist hospitals with appropriate accreditation who are capable of and experienced in delivering cellular therapies.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Although cellular therapies, including gene therapy, are commonly used in the NHS, gene therapy for this specific indication (haemoglobinopathies) is not currently available. The facilities to deliver the care exist and the processes for collecting stem cells are also currently in existence and common use within the NHS. There will be a moderate amount of training required to ensure the collection, preparation and administration of this specific product follows the principles for other Advanced Therapy Medicinal Products (ATMPs) and the units delivering exagamglogene autotemcel may require additional staff for this additional new treatment. There will be the need for using plerixafor for mobilisation, which is not covered by the current NHS England commissioning policy for plerixafor..

<table>
<tr><td></td><td>At present there is uncertainty about how many patients may progress to treatment. Existing transplant bed capacity and staffing capacity may limit the number of patients who are able to access treatment each year.
Given the complexity of the patient pathway, the considerable number of steps involved and the resource required, clinical feedback suggests that the CAR-T tariff will most accurately reflect the service costs that are to be expected with this treatment.

<table>
<tr><th>Year</th><th>Predicted patient numbers</th><th>Service costs using CAR-T tariff</th></tr>
<tr><td>2024</td><td>0</td><td>£0</td></tr>
<tr><td>2025</td><td>8</td><td>£628,135</td></tr>
<tr><td>2026</td><td>21</td><td>£1,590,932</td></tr>
<tr><td>2027</td><td>33</td><td>£2,394,124</td></tr>
<tr><td>2028</td><td>21</td><td>£1,590,923</td></tr>
<tr><td>2029</td><td>6</td><td>£401,596</td></tr>
<tr><td>2030</td><td>2</td><td>£133,865</td></tr>
<tr><td>Total</td><td>91</td><td>£6,739,583</td></tr>
</table>
</td></tr>
<tr><td>10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?</td><td>No this is a one-off treatment for which patients will need to fulfil criteria as set and agreed, be consented and proceed through to a potential cure.</td></tr>
<tr><td>11. What is the outcome of any evaluations or audits of the use of the technology?</td><td></td></tr>
</table>

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes. The majority of British patients with thalassaemia tend to be of South Asian heritage. South Asians, particularly those from Pakistani or Bangladeshi ethnic groups are over three times as likely as White British people to live in the most income-deprived 10% of neighbourhoods. Due to chronic underfunding, lack of medical research investment, there has been very little by way of drug development for thalassaemia especially TDT. The approval of gene therapy in England will encourage diffusion of this technology to lower income countries and eventually lead to the reduction in manufacturing costs.
12b. Consider whether these issues are different from issues with current care and why.	No

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Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Professional organisation submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted], [redacted]
2. Name of organisation	The Royal College of Pathologists and General Haematology Guidelines Task Force for British Society of Haematology
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **Yes** Other (please specify):
5a. Brief description of the organisation (including who funds it).	British Society for Haematology, to provide training/trainee support, education and leadership in the field of haematology. BSH is funded by membership subscriptions.
5b. 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.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

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.)	To cure the condition
7. 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.)	Transfusion independence
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The only cure currently available is a sibling bone marrow transplantation. There is only a 1 in 4 chance of a sibling, with both the same parents, being a suitable donor. Moreover, they cannot have inherited the same beta thalassaemia condition for themselves (also a 1 in 4 chance of this happening). Therefore the number of patients with an eligible donor available is very limited, and well under 10%. This treatment will address a vital unmet need in providing the opportunity for a curative treatment for their life long and life-limiting condition.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Transfusion dependent thalassaemia requires regular transfusion therapy, usually 3 weekly, usually started within the first year of life and continues lifelong. To counter the accumulation of iron in the body, which can be life-threatening when severe amounts are present, patients are required to take iron chelation therapy, either in tablet form, or by subcutaneous or intravenous infusion. These medications and the iron overload itself can have significant side effects and health consequences. They require yearly screening for endocrine complications

	such as diabetes, and thyroid function. They need careful monitoring of growth rates. They require annual audiology and ophthalmology reviews. If a sibling bone marrow is available, the recommendation is that they are put forward for an allogenic bone marrow transplant within the first 5 years of life.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, Standards for the Clinical Care of Children and Adults with thalassaemia in the UK, version 3, 2016
9b. 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.)	Pathway is generally well defined and there are clearly defined Thalassaemia Haemoglobinopathy Coordinating Centres designated by NHS England to help manage and standardise care and ensure equitable access to new treatments and provide and expert forum for discussion of complex cases.
9c. What impact would the technology have on the current pathway of care?	If this technology was available, all patients would be offered this treatment at the earliest age that it would be available. If successfully treated, they would no longer require regular transfusions, and once they have cleared any residual iron burden from their body, would no longer be required to take iron chelation therapy. They would therefore not require the additional yearly follow up measures of endocrine, growth, audiology, ophthalmology reviews. Successful curative treatment to normalise their haemoglobins would allow subsequent removal of excess iron rapidly by sae and cheap venesection.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It would be similar to the pathway for sibling allogenic bone marrow transplantation except that rather than only being applicable to a small minority (<10%) of eligible patients due to lack of suitable donors, all those choosing and eligible for this treatment will have an available donor source.
10a. How does healthcare resource use differ between the technology and current care? Would additional costs be	As above, patients would no longer require 3 weekly blood tests and blood transfusions. Once they have cleared any residual iron burden from their body, they would no longer be required to take expensive and intrusive iron chelation therapy. They would therefore not require the additional regular subspeciality follow up measures of endocrine, growth, audiology, cardiology, and ophthalmology reviews.

required for fertility preservation (due to potential for pre-treatment/'conditioning' drugs to impact fertility)?	The technology does require a full myeloablative conditioning regimen, so there is a potential impact on fertility and patients would require fertility preservation services.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care where age-appropriate bone marrow transplantation services are already in place – i.e. regional centre only.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This would be similar to the set up of Car-T therapy services in the haemato-oncology.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Definitely. Patients who currently have no chance of a cure, which is the majority of the patients, will now have this available to them. They will avoid the morbidity and early deaths associated with long-standing anaemia and iron loading.
11a. Do you expect the technology to increase length of life more than current care?	Yes, life expectancy is still limited, even with excellent transfusion and iron chelation management. With this treatment, they would potentially have no limitation to their life expectancy on account of the thalassaemia condition.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. The burden of requiring regular transfusions cannot be underestimated. Attending for at least half a day every 3 weeks, sometimes required to come 1 – 2 days in advance for the pre-transfusiong blood testing, plus all the other health-related appointments and scans required add up to a significant impact on their quality of life. Moreover, patients report they often feel tired and unable to function optimally in the week prior to their next transfusion. They are also still significantly anaemic on a daily basis (despite the transfusion). With this treatment, they would have normal haemoglobin levels, thus they would have no chronic and fluctuating fatigue symptoms and the burden of hospital appointments and impact on their life would be significantly reduced.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This would only be effective for patients with transfusion dependent thalassaemia

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 process of receiving the treatment will be more intensive in the short term. They will be required to be an inpatient for a period of a few weeks, then have close monitoring for a few months afterwards. After that though, the anticipation is that they will have far less need for use of healthcare facilities. Overall, this will be easier for the patients. For the healthcare professional, additional expertise around the transplant process will be needed and services to provide this are required, hence the need for this to be offered in centres already performing bone marrow transplantation (autologous or allogenic) for other reasons.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I am not aware of any
15. Do you consider that the use of the technology	No

will result in any substantial health-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?	This is a new technology that will revolutionise the way patients with transfusion dependent thalassaemia are managed. There is no other treatment available that works in the same way, or offers the same chance of total cure, outside of the small population of patients who have suitable sibling donors for allogenic bone marrow transplantation.
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	<10% of patients have a suitable sibling donor. The remainder of patients are reliant on regular blood transfusions and iron chelation therapy which is difficult to tolerate and comes with its own health complications. These patients have had no real progress in their management for at least a decade and this technology would address their unmet need.
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?	The gene therapy technology includes a myeloablative conditioning regimen. This may have an effect on fertility and in some very rare cases be associated with a secondary malignancy such as Leukaemia that

	may onset 2-7 years subsequently. This would be dependent on the exact types of chemotherapy used though.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Transfusion independence. And yes, this is the primary outcome of the trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not used
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that we are aware of
19. Are you aware of any relevant evidence that might not be found by a	No

systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	This technology has not been used outside the context of a clinical trial yet.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Almost all those with transfusion dependent beta thalassaemia are non-white and there is a significant history of under resourcing and de-prioritising their care, as well as stigmatisation and prejudice. This needs to be redressed
21b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions

22 How is transfusion-dependence defined in current clinical practice?	Transfusion dependence occurs when an average of more than 2 units of blood transfused every 28 days is required over a period of at least 3 month, outside of physiological challenges such as puberty and pregnancy where a period of transfusion may be required, but then following this period, the patient returns to being transfusion independent.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• The majority of patients with thalassaemia do not have a curative treatment currently available • These patients experience significant reduction in quality of life, and an overall reduced life expectancy with current best available care • This treatment would provide a curative option to all patients and significantly improve quality of life • There is a risk of myeloablative chemotherapy that needs to be considered • These patients have suffered from chronic under-funding and de-prioritisation of the care on racial grounds and it is important to offer new therapies to adequately address this

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Professional organisation submission

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About you

1. Your name	[redacted]
2. Name of organisation	United Kingdom Forum on Haemoglobin Disorders (UKFHD)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify): Specialist in managing haemoglobinopathy diagnoses
5a. Brief description of the organisation (including who funds it).	The UKFHD is a charitable organisation whose membership consists of multidisciplinary clinicians including doctors, nurses, allied health professionals such as clinical psychologists alongside patient organisation representatives, together, we strive for equal access of optimal care for all individuals living with an inherited haemoglobin disorder. We apply for funding grants and unrestricted educational grants, we additionally receive annual membership fees from all our registered members.
5b. 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.**	The UKFHD receives no direct funding from Vertex for our routine running costs, however we have applied to a number of commercial companies including Vertex, successfully for unrestricted educational grants to support an educational event (study day).
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

Professional organisation submission

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

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.)	Exagamglogene autotemcel is a potentially curative treatment for transfusion dependent beta thalassaemia (TDT). TDT patients are initiated on regular transfusions, which they remain on life long. The indication for commencing a child on transfusions include evidence of severe anaemia causing failure to thrive (measured by failure to grow and gain weight in children) or evidence extramedullary haematopoiesis where organs such as the liver or spleen enlarge or expansion of the bone marrow causing facial or other skeletal deformities. In patients with genetic mutations in keeping with “thalassaemia major” this will occur within the first few years of life, whereas patients with the severe “thalassaemia intermedia” genetic mutations may develop transfusion dependence later in life. TDT is associated with a high burden of comorbidities due to the impact of chronic lifelong anaemia and iron overload. TDT patients are also at increased risk of from blood borne infections, thrombosis (blood clots) and a high level of anxiety and depression. In children aged 18 or less, stem cell transplant from a matched sibling donor is the only curative option. This is not currently an option for adults with TDT. Even so access to this therapy is most limited by donor availability, <25% of eligible patients have a matched sibling donor.
7. 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.)	Absence or significant reduction in the need for blood transfusion Improved haematological parameters (haemoglobin levels) within 12 months of completing the treatment No requirement for iron chelation therapy once de-ironed (chelated to normal levels) post treatment. Low or no patients with no off-target effects of this technology including, development of therapy related myelodysplasia or leukaemia No mortality Improved health related quality of life measures

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	YES. We welcome this appraisal as there is very significant unmet need for patients living with transfusion dependant thalassaemia syndromes. TDT is defined primarily by the clinical presentation it describes a group of patients with mutations that results in inadequate production of red cells such that they are dependent on regular transfusion for survival. Patients attend hospital between two to four weekly for transfusion and will usually feel well in the first week or so after receiving the blood. However, the reoccurrence of anaemia prior to the next transfusion means that they then develop progressive tiredness and bone pain as they approach the next transfusion. In patient who have not had their spleen surgically removed (non-splenectomised) patients, the haemoglobin will fall at around 15g per week equivalent to the loss of 1.5 pints of blood in a week. This has significant impact on patient's wellbeing and functional performance. TDT patients are also more likely to develop alloantibodies to transfused red cells as they often require transfusion after the age of 2 years are therefore more likely to mount an immune response which results in the formation of these antibodies. This then impacts on blood availability for the patient for the rest of their life. Repeated transfusion leads to accumulation of iron in the heart, liver and other organs, which unless treated with iron-removing agents (which are toxic, unpalatable and often difficult to adhere to) may lead to patients suffering sudden death or severe disability. Newer drugs such as Luspatercept which reduce the volume of blood TDT patients require, is not currently funded in England leaving patients with only transfusion therapy for this condition. It is important to note that although patients will survive and function on regular blood transfusion and iron chelation there is a considerable burden of disease on patients, as well as a high degree of morbidity and mortality in the patient cohort. Crude 10-year mortality rate for patients with TDT in England was recently reported as more than five times higher than the age/sex adjusted general population There is a dire need for curative approaches to treatment of TDT in England to combat the high burden of morbidity and mortality currently associated with the condition.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	The mainstay of treatment for TDT is regular, lifelong blood transfusion and iron chelation. Children aged 18 or less with a matched sibling donor can access stem cell transplant. • Lifelong regular blood transfusion is initiated in patients with thalassaemia if there is evidence of severe anaemia causing failure to thrive (measured by failure to grow and gain weight in children), or evidence extramedullary haematopoiesis where organs such as the liver or spleen enlarge or expansion of the bone marrow causing facial or other skeletal deformities. In patients with genetic mutations in keeping with thalassaemia major this will occur within the first few years of life, whereas patients with the severe thalassaemia intermedia genetic mutations may develop transfusion dependence later in life. • However, treatment with blood transfusion is not without complications. Patients especially those who commence transfusion later in life may develop allo antibodies to transfused red cells, which can make it more difficult to find compatible blood units for them. This also increases their risks of serious transfusion reactions. Additionally, regular blood transfusion leads to accumulation of iron in the heart, liver and other organs, which unless treated with iron-removing agents (which are toxic, unpalatable and often difficult to adhere to) patients can suffer sudden death or severe disability. • Novel therapies: Nil in the UK at present ○ Luspatercept is a novel drug therapy which has been shown to reduce the transfusion burden and is currently available to TDT patients in Europe but not the UK at the present time, despite patients from the UK having actively participated in the clinical trials of this new agent. • The only currently available curative treatment is allogeneic stem cell transplant from a fully matched sibling donor, but it is only available for children and teenagers. Once classed an adult this option becomes unavailable to patients. Additionally it is a therapy that is limited by donor availability, less than 25% of patients are likely to have suitable stem cell donors, thus severely restricting this curative option for patients

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	We have National standards of care for thalassaemia: Standards for the clinical care of children and adults with thalassaemia in the UK There are also a variety of national guidelines hosted at the British Society for Haematology website: 1. Red blood cell specifications for patients with haemoglobinopathies 2. Significant haemoglobinopathies a guideline for screening and diagnosis 3. Investigation and management of acute transfusion reactions 4. Guidelines for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias
9b. 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.)	Care for thalassaemia was divided into 4 networks with lead centres named Haemoglobinopathy Coordinating Centres in 2019 across England. The Hospitals managing patients were also divided into Specialist centres and local centres based on a combination of facilities, staffing and patient number. These established networks of clinical care ensure patients have equitable care in their regions and access to specialist care and advice. Core to this system was the development of the National Haemoglobinopathy Panel which is a national multidisciplinary meeting which advises on complex patient management and acts as a central fulcrum of patient care.
9c. What impact would the technology have on the current pathway of care?	Autologous gene therapy using exagamglogene autotemcel has the potential to offer a universal cure to patients with TDT who would qualify for curative options but lack a matched sibling donor. It additionally overcomes a number of other limitations Including graft versus host disease a post-transplant complication which may be organ or life limiting.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This technology is not in current clinical use. Exagamglogene autotemcel will be a single treatment and is expected to obviate or significantly reduce the need for blood transfusion and hence requirement for iron chelation therapy. Treatment with this technology is expected to reduce health care utilisation significantly. The only other available curative intent is matched sibling donor stem cell transplant (SCT) and the criteria for this treatment overlaps with this technology with no significant difference.
10a. How does healthcare resource use differ	Exagamglogene autotemcel will be a single treatment and is expected to reduce both transfusion, and need for iron chelation, treatment with this technology is expected to reduce health care utilisation

between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Exagamglogene autotemcel will be administered in specialist hospitals with appropriate accreditation who are capable of and experienced in delivering cellular therapies.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Although cellular therapies, including gene therapy are commonly used in the NHS, gene therapy for this specific indication (haemoglobinopathies) is not currently available. The facilities to deliver the care exist and the processes for collecting stem cells are also currently in existence and common use within the NHS. There will be a moderate amount of training required to ensure the collection, preparation and administration of this specific product follows the principles for other Advanced Therapy Medicinal Products (ATMPs) and the units delivering exagamglogene autotemcel may require additional staff for this additional new treatment.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Based on the evidence to date patients undergoing the treatment are expected to have: 1. Markedly reduced need or no requirement for transfusion 2. Reduction then absence of a requirement for chelation therapy
11a. Do you expect the technology to increase length of life more than current care?	Long term data on use of this technology is not currently available. Based on current evidence this is likely to be the outcome for patients.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. Early data from the studies using this technology already show cumulative improvement in patient reported experience and outcome measures Patient reported outcome surveys in the UK, as well as the rest of the world consistently report high burden in patients and caregiver, influenced by disease-management time, fatigue, pain and an impaired quality of life.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	TDT patients with a high burden of comorbidities and poor performance scores may cope less well with the Busulphan chemotherapy conditioning regimen, which is relatively intensive chemotherapy treatment. A good performance status score is generally required for such procedures.

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.)	This technology is a form of advanced cellular therapy hence there only a few sites and centres will be accredited and capable of delivering it. All the steps of delivering this technology are undertaken within NHS sites daily: collection of stem cells, conditioning chemotherapy, inpatient management through engraftment and then treatment/transplant follow up. The only step which will be undertaken off an NHS site will be producing the cellular product, in an accredited facility. Discussions pre-treatment with patients, care givers and parents, will cover the risk of infertility from the conditioning regimen, especially when the patient is of a young age and may not wholly grasp the implications. Most especially so if they are too young to undergo fertility preserving treatments. However there is recently emerging data suggesting although important, the risk of infertility has not been found to be a barrier to patients or parents pursuing this treatment option.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No this is a one-off treatment for which patients will be need to fulfil criteria as set and agreed. Be consented and proceed through to a potential cure.

15. 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?	Yes. The main findings on TDT patient reported experience surveys focusing on quality of life, have consistently shown the significant burden of the diagnosis, with a large amount of time spent in health institutions receiving care, a high burden of fatigue, pain and reduced quality of life. This technology based on the early phase trials results would be expected to lead to significant improvements as the need for regular transfusions will either stop entirely or reduce very markedly.
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?	Yes. This technology, exagamglogene autotemcel offers a curative option at the level of the stem cell, but does not require an allogeneic donor, hence will be more accessible for patients who do not have suitable matched sibling donors. This technology promises to increase the option of cure to many more TDT individuals. Currently less than 25% of TDT patients who are eligible to receive matched sibling donor stem cell transplants will be able to proceed as most will lack a donor. Additionally, this technology will avoid the unacceptable adverse effects of graft rejection and graft versus host disease that are seen in allogeneic stem cell transplants. As this is an autologous product there will be no requirement for prolonged immunosuppression after treatment.
16a. Is the technology a 'step-change' in the management of the condition?	Yes the only curative option available to patients currently is the matched sibling donor. Less than 25% of TDT patients will have a matched sibling donor available to donate to them. Exagamglogene autotemcel which autologous, hence uses stem cells taken from the patient, is highly innovative and offers the option of cure to a wider population of patients with severe sickle cell disease. There are no other comparative curative options available for sickle cell disease apart from a matched sibling donor SCT.

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, currently of the adults with TDT have no option of curative treatment in the UK and even the children who do will have small chance of a matched sibling donor. The only option open to most is to remain on a lifelong transfusion program and continue to take iron chelation therapy. This technology offers TDT patients a chance at disease free survival, improved quality of life and reduced health utilisation.
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?	1. Stem cell harvest from patients with GCSF pre treatment, although overall this is expected to be well tolerated it may trigger side effects including bone pain in some patients. 2. The conditioning regimen with a chemotherapy agent called busulphan is likely to be associated with a number of side effects including nausea, neutropaenia which may be complicated by infection leading to febrile neutropaenia and risk of neutropaenic sepsis. Nausea, stomatitis and temporary hair loss are also expected side effects for which patients will need to be consented. These will all be expected to resolve after completing the inpatient stay part of the treatment. 3. Isolation; admission for delivery of the treatment is associated with a period of isolation up to a month long which can be mentally difficult for patients to manage. 4. Fertility, the conditioning chemotherapy is likely to result in infertility and patients will need to discuss fertility preservation options. Most of these (other than infertility) are temporary effects which would be expected to resolve once the admission for treatment is completed. Once a patient's blood counts recover post the treatment, and based on trial data this will be within a few months of receiving the treatment, the expectation is a steady improvement in overall health and well being with an absence of blood transfusions for the majority.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes patients with TDT all have regular reviews with their clinical teams and most will be on treatments additional to chelation and blood transfusion depending on which additional comorbidities they develop. Paediatric patient with siblings will usually have had testing completed and where there is a suitable consenting related donor they will progress to SCT. This option will hopefully become available to adult TDT patients in the near future. However the majority of patients will not have a suitable donor and hence will require interventions like this for any hope of a cure.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Reduced or absent need for blood transfusions Significantly reduced healthcare utilisation for thalassaemia related indications Improved fatigue Improved haemoglobin levels Reduced or absent need for any chelation therapies Improved patient reported outcome and experience measures
18c. If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None to date
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Long term outcome data (>10years) is lacking in this field at present as relatively new treatment
21. How do data on real-world experience compare with the trial data?	The patients treated on the clinical trials for this technology, exist in the clinic and have need for curative options so the data should compare well. However, it is likely a there will be a cohort of patients especially those with poor performance status or a high burden of comorbidity for whom the unmet needs will remain a significant issue as they will not be suitable candidates for this intervention.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	YES. The majority of British patients with thalassaemia tend to be of are of South Asian heritage. South Asians, particularly those from Pakistani or Bangladeshi ethnic groups are over three times as likely as White British people to live in the most income-deprived 10% of neighbourhoods. Due to chronic underfunding, lack of medical research investment, there has been very little by way of drug development for thalassaemia especially TDT. Stem cell transplant from a fully matched sibling donor is the only curative option currently available for adult patients with SCD in the UK. However, only the most severely affected patients are approved for this intervention and less than 25% of TDT patients are likely to have suitable bone marrow donors, thus severely restricting this curative option for patients. The approval of gene therapy in England will encourage diffusion of this technology to lower income countries and eventually lead to the reduction in manufacturing costs.
22b. Consider whether these issues are different from issues with current care and why.	NO

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• There a high degree of unmet need for treatment options in TDT • The only currently available curative therapy option is available to <25% of TDT patients • Current quality of life measures confirms a low quality of life with a high degree of daily pain in patients • There is a desperate need for this treatment option which offer hope a cure and the NHS has opportunity to be a world leading organisation for Sickle cell disease.

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 select YES if you would like to receive information about other NICE topics - YES

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

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Patient Organisation Submission

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. [Please note that declarations of interests relevant to this topic are compulsory].

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, organization 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 company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
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?	Lived experiences were gathered by means of members meetings, focus groups and online quantitative and qualitative questionnaires and interviews. Families also shared their life experiences by means of written testimonies (2021-23).

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with thalassaemia can present unique challenges and experiences for individuals and their families. While the severity of the condition can vary, it generally requires ongoing medical management and regular blood transfusions which affect all aspects of an individual and their family's life. One of the primary aspects of living with thalassaemia is the need for lifelong medical care. This includes frequent blood tests to monitor haemoglobin levels, iron overload, chelation toxicity, as well as regular transfusions to replenish healthy red blood cells. These transfusions are typically required every 2-4 weeks, depending on the severity of the condition. With transfusions, some individuals with thalassaemia can face transfusions reactions (due to alloimmunisation or allergies to materials/ equipment), venous access issues- (requiring multiple cannulations, the need for indwelling central lines) etc. This can be extremely distressing for patients. The continuous need for medical interventions can be physically and emotionally demanding, requiring individuals to be proactive in managing their health. Both patients and carers experience disruption of life activities having to attend regular hospital appoints. On average a patient with transfusion dependent thalassaemia with **no incidence of secondary conditions or periods of unwellness or emergencies** may spend at least 64 days in hospital for planned 3 weekly transfusions and iron monitoring whilst they spend 365 days receiving iron chelation medication administered up to four times a day. This not only affects overall attendance at educational and employment institutions for both patients and their parents and carers with consequences but we have been made aware that adult patients and carers have been asked to take their holiday leave to attend their life-saving transfusions and other hospital appointments. Managing the demands of the condition has been compared to meeting having a full-time job. Iron overload is a common concern for individuals with thalassaemia due to the frequent transfusions. Excessive iron can accumulate in various organs, leading to complications such as heart disease, diabetes, growth, liver problems to name a few. To manage this, individuals may need to undergo extensive iron chelation therapy, which involves taking medication to remove excess iron from the body. Adhering to a strict chelation regimen can be challenging for all individuals regardless of ages living with thalassaemia and they can face battles with this on a daily basis due to a variety of medication side effects, financial constraints (as patients are required to pay for their prescription) etc. The financial burden can be overwhelming for some families. One father shared his concern and expressed a need for support with regards to the financial burden of caring for a child with thalassaemia, as well as the emotional and physical toll it can have on the family. **"It's quite a lot for a parent to go through, but there is no support, not at all. Because now I'm self-employed, I can't even work like a fulltime job, why? Because if I'm on a fulltime job and I have appointments, my employer, he's going to say like, "Well, find another job. I can't give you like five, six times a month off so that you could do your**

	appointments," you know what I mean, because schedule is schedule. So, self-employed is like low income, because we are family, you know what I mean. So, sometimes you work. Sometimes you sit in the house. Most of the time, you are in appointments. So, there is no support for thalassaemia patients. You know, thalassaemia patients should be considered as disabled – not disabled, I mean, that way. I mean, they should be given support, as they do support disabled people." Living with thalassaemia can also impact an individual's daily life and wellbeing. Fatigue, tachycardia, breathlessness, chronic pain, cognition issues and weakness are common symptoms of anaemia, which can affect energy levels and the ability to engage in daily activities. Additionally, individuals may experience bone deformities (due to delayed diagnosis as thalassaemia is not formally part of the newborn screening programme in the UK), improper transfusion regime, delayed growth, and fertility issues, which can have a significant impact on their self-esteem and quality of life. In 2021, the society conducted an online questionnaire amongst members investigating the incidence of secondary conditions and the impact on their quality of life. Of 106 responses, 97% of patients reported having acquired more than one secondary condition, 63% of patients reported having 5 or more secondary conditions and 32% of patients reported having more than 10 or more secondary conditions. Chronic bone and joint pain which was previously underreported in publications and undertreated were experienced by 83.3% of patients and reported in children as young as 3. Worryingly, the survey also highlighted the significant disparity between life expectancy and the early onset of secondary conditions acquired amongst individuals from various ethnic groups. When asked about quality of life, 86.4% of respondents reported having a moderate to severe impact on their overall quality of life. Responders also reported thalassaemia having a significant emotional and social impact on patients and their families. 78.2% of patients reported feelings of anxiety, depression, and fear due to their condition and reported experiencing stigma and discrimination during several aspects of their lifetime. Support from health care professionals and the patient support system can only manage some of these of aspects. Psychological and social care remains a rare service offered to individuals living with thalassaemia and their families. In a recent project the society collaborated with the NHS Sickle Cell and thalassaemia screening programme to evaluate the feedback and experience of parents with recently diagnosed infants and children with thalassaemia. A qualitative report titled "It's in our Genes" available on our website, details some of the concerns, worries, feelings and experiences of parents. In 100% of the parents interviewed, the diagnosis needed to be followed up by parents after health care professionals did not report the results and there were instances of the diagnosis being missed and not reported, leading the severely unwell infants with irreversible damage.

	For parents who participated in the focus groups, a thalassaemia diagnosis aroused strong emotional response. Some of feelings expressed by parents were of shock, guilt, anxiety, grief, feeling lack of control and worried about the future. It was evident throughout this exercise that the degree to which this was felt was strongly influenced by the way in which a thalassaemia diagnosis was given. The findings of this exercise also underlined the disparities between parents who received care a high prevalent area such as parts of the UK with larger minority populations when compared to those in low prevalent areas. In high prevalent areas, it was apparent health care professionals were more likely to be aware, knowledgeable and had access to more resources on thalassaemia. Not only did this lead to earlier diagnosis, and better access to treatment and improved health outcomes,. In contrast, individuals living low prevalent areas, had fewer resources and less awareness of the condition which correlated to delays in diagnosis, inadequate treatment, poor health outcomes and a lack of support for patients and their families. Additionally, in some low prevalent areas, healthcare professionals did not have as much knowledge and experience with managing thalassaemia when compared to other blood conditions and as such patient's care is below national standards. These findings are consistent to those found during the 2020 Peer Review for Children and Adults living with Haemoglobin Disorders. This disparity in care is somewhat unique to thalassaemia, when compared to other genetic conditions in the UK and can often lead to significant challenges for patients and their families, including difficulties in accessing appropriate treatment, feeling isolated, and dealing with a lack of support.

7. What do patients or carers think of current treatments and care available on the NHS?	Whilst patients and their families were appreciative of the care they received from the NHS, they wished more would be done to improve their health outcomes and quality of life. Blood transfusions and iron chelation are the only treatment options available to the majority of the thalassaemia population and patients do not feel these options are sufficient. 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 which disrupted their lives. Families also commented on the disparity of care throughout the UK- where in many regions of the country, care is below national standards. 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 consider other treatments that could improve their health and overall quality of life. Lastly, patients also raised issues with regards to the lack of awareness and education about thalassaemia amongst health care professionals and in particular raised worrying concerns about the safety of care in accident and emergency departments and in patient wards throughout the condition (despite prevalence).
8. Is there an unmet need for patients with this condition?	Yes, there remains an unmet need for patients with thalassaemia. As thalassaemia is classed as a rare disease in the UK affecting fewer than 2000 patients from ethnic minority backgrounds, patients have faced significant inequalities with regards to treatment options and services. One of the primary unmet needs in thalassaemia treatment is the development of more effective and accessible curative therapies. Currently, the mainstay of treatment for severe forms of thalassaemia is regular blood transfusions, which can lead to iron overload in the body. Iron chelation therapy is then required to manage this excess iron, which can be burdensome for patients due to the need for continuous and lifelong treatment. Although hematopoietic stem cell transplantation (HSCT) can potentially provide a cure for thalassaemia, it is limited by several factors. This treatment is currently commissioned for only children living with thalassaemia and HSCT requires a suitable donor, which can be challenging to find with less than 10% of patients being suitable, especially for patients from ethnic minorities. Additionally, the procedure carries risks and complications such as rejection, graft versus host disease, making it unsuitable for all patients. Another unmet need in thalassaemia treatment is the improvement of iron chelation therapies. Currently available iron chelators have limitations, such as poor compliance due to frequent dosing and side effects like gastrointestinal disturbances, pain, kidney failure etc. there is currently no alternative to blood transfusions and iron chelation medication for patients with thalassaemia in the UK. Patients deserve to have a choice in accessing potential curative therapies which would allow them to be transfusion independent which could not only improve their overall quality of life but also life expectancy.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Despite the challenges, individuals with thalassaemia can lead fulfilling lives. Advances in medical research and treatment options, such as bone marrow transplants and gene therapies, offer hope for improved outcomes. Many individuals with thalassaemia are able to pursue education, careers, and personal goals, with the support of their healthcare team and loved ones. Patients and Carers thought the advantages of this technology were: • Transfusion independence or reduction in transfusions • Spending less time in hospital • Taking less time off education/ work • Receiving less iron due to transfused red cells- resulting in lower iron burden • The possibility of needing less iron chelation medication • Increasing quality of life • Lower overall cost to the NHS (blood transfusion appointments, medication) • Less demand on blood stocks • Patient choice in accessing a potential cure

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As gene editing is relatively new, and its long-term effects are not fully understood. Patients and carers were concerned about unforeseen consequences or potential risks associated with genetic interventions, including unintended genetic mutations or off-target effects etc.

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?	In the UK, there are smaller number of patients living with thalassaemia when compared to other genetic conditions. As a consequence of this, our community has been at a disadvantage with regards to awareness of the condition, patient care and drug innovation. As thalassaemia predominately affects individuals coming from ethnic minority backgrounds, our population have also suffered and suffers from racial discrimination which not only causes health disparities but also affects health outcomes. In our 2021 study, there was also a considerable disparity in the development of secondary conditions, life expectancy and quality of life between different ethnic communities. For instance, it has been observed that British Asians with thalassaemia may experience lower life expectancy and earlier onset of secondary conditions compared to other populations.

Other issues

13. Are there any other issues that you would like the committee to consider?	Gene therapy holds immense promise in providing a revolutionary curative option for patients who have been historically and are currently underserved in terms of healthcare access and treatment options. This ground-breaking approach has the potential to bridge the gap in health equity by offering new hope and improved outcomes for individuals living with thalassaemia. Individuals with thalassaemia currently face limited treatment options, often relying on symptom management and palliative care. This can not only lead to immense suffering for the entire family but also significant disparities in health outcomes.
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Patients deserve to have access to a curative option • The only treatment options for thalassaemia is blood transfusion and iron chelation therapy • Thalassaemia Care is not consistent throughout the UK with treatment being subpar in many regions of england • We are still losing young patients due to severe iron overload • There are tremendous disparities in care and services offered to patients with thalassaemia – this negatively affects health outcomes

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External Assessment Group Report
Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Nyanar Jasmine Deng, Research Fellow, CRD, University of York Mark Corbett, Research Fellow, CRD, University of York Eleonora Uphoff, Research Fellow, CRD, University of York Joseph Lord, Research Fellow, CRD, University of York Helen Fulbright, Information Specialist, CRD, University of York Susan Griffin, Professor of Health Economics, CHE, University of York Claire Rothery, Professor of Health Economics, CHE, University of York Robert Hodgson, Senior Research Fellow, CRD, University of York
Correspondence to	Robert Hodgson, Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD
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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Mark Corbett critically appraised the clinical effectiveness evidence, contributed to the critique of the decision problem, and took overall responsibility for the clinical effectiveness sections. Eleonora Uphoff wrote the critique of the decision problem and contributed to the critical appraisal of the clinical effectiveness evidence. Helen Fulbright wrote the search strategy sections. Nyanar Jasmine Deng, Joseph Lord, Susan Griffin, Claire Rothery and Robert Hodgson wrote the critical appraisal of the cost-effectiveness analysis submitted by the company and implemented the additional economic analyses presented by the EAG. Robert Hodgson took overall responsibility for the cost-effectiveness sections and took overall responsibility for the report.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all depersonalised data (DPD) are highlighted in pink and underlined.

Copyright statement

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List of abbreviations

ACD	Appraisal Consultation Document
AE	Adverse event
BoI	Burden of Illness
CEA	Cost effectiveness analysis
CMR	Cardiovascular magnetic resonance
CS	Company submission
CSR	Clinical study report
DCEA	Distributional cost effectiveness analysis
DSA	Deterministic sensitivity analysis
EAG	Evidence Assessment Group
EDE	Equally-distributed equivalent
ERG	Evidence Review Group
eMIT	Electronic market information tool
Exa-cel	Exagamglogene autotemcel
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GvHD	Graft-versus-host disease
Hb	Haemoglobin
HbA	Adult haemoglobin
HbF	Foetal haemoglobin
HLA	Human leukocyte antigen
HRQoL	Health related quality of life
HRU	Healthcare resource utilisation
HSC	Haematopoietic stem cells
HSCT	Haematopoietic stem cell transplant
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICT	Iron chelation therapy
IMD	Index of Multiple Deprivation
IPD	Individual Participant Data meta-analysis
ITC	Indirect Treatment Comparison
ITT	Intention to treat
LIC	Liver iron content
LSOA	Lower layer Super Output Area
MAIC	Matching adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency

MRI	Magnetic resonance imaging
NHB	Net health benefit
NHR	National Haemoglobinopathy Registry
NICE	National Institute for Health and Care Excellence
NICE DSU	NICE Decision Support Unit
ONS	Office for National Statistics
PAS	Patient access scheme
PES	Primary Efficacy Set
PfC	Point for clarification
PICOS	Population, intervention, comparator, outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALE	Quality adjusted life expectancy
QALY	Quality adjusted life-year
RBC	Red blood cell
SAE	Serious adverse event
SCT	Stem cell therapy
SF	Serum ferritin level
SII	Slope index of inequality
SLR	Systematic literature review
SMR	Standardised mortality ratio
SoC	Standard of care
TD	Transfusion dependent
TDT	Transfusion dependent β-thalassaemia
TI	Transfusion independence
TI 6	Transfusion independence for at least 6 consecutive months
TI 12	Transfusion independence for at least 12 consecutive months
TR	Transfusion reduced
TTO	Time trade-off
UKTS	United Kingdom Thalassaemia Society
US ICER	US Institute for Clinical and Economic Review
WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of Key Issues

ID4015	Summary of issue	Report sections
Key issues with a significant impact on decision making		
1	Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile	3.2.2, 3.2.3, 4.2.6.2
2	Definition of transfusion independence	3.2.1, 4.2.6.1
3	Uncertain relationship between transfusion status and final outcomes	3.5, 4.2.2
4	Modelling approach and how mortality risks are attributed to modelled patients	4.2.2
5	Omission of withdrawals from exa-cel treatment in the economic analysis	4.2.2
6	Frequency of red blood cell transfusions	4.2.4
7	Non-reference discount rate	4.2.5
8	Mortality in transfusion dependent patients and associated with complications	4.2.2, 4.2.6.5
9	HRQoL in transfusion dependent patients	4.2.7.1, 4.2.7.2
10	Additive vs multiplicative age adjustment of utilities	4.2.7.4
11	EMIT costs	4.2.8
12	Reweighting of QALY benefits and costs through the use of a non-reference case distributional cost-effectiveness analysis	8
13	Approach to distributional cost-effectiveness analysis	8
14	Input parameter used in the distributional cost-effectiveness analysis	8
15	Discounting, Severity modifier and DCEA,	8.1.1
Issues with less significance for decision-making*		
16	Source of baseline iron levels	4.2.3
17	Population weight used to inform cost of iron chelation agents	4.2.3
18	Baseline osteoporosis and diabetes complication rates	4.2.3
19	Risk of initial graft failure	4.2.6.2
20	Iron normalisation period	4.2.6.3
21	Ongoing risks of complications	4.2.6.4
22	Uncertainty in complication and infertility utility decrements	4.2.7.3
23	Underestimation of health state costs in exa-cel arm	4.2.8

* See body of the report for a description of these issues

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The EAG prefers to use a simplified model structure which remove iron overload related complications.

- The EAG prefers to account for costs and outcomes of patients who withdraw from exa-cel prior to transfusion.
- The EAG prefers to use a UK Chart Review (Shah et al.) to inform the frequency of blood transfusions in transfusion dependent patients.
- The EAG prefers to use a 3.5% discount rate.
- The EAG prefers to use the TI12 definition of transfusion independence (the primary outcome in the CLIMB THAL-111) to inform the proportion of transfusion independent patients.
- The EAG prefers to assume a 5-year iron normalisation period.
- The EAG prefers to apply a standardised mortality rate of 2.5 to transfusion dependent patients.
- The EAG prefers to use a HRQoL decrement of [redacted] to inform utilities in transfusion dependent patients.
- The EAG prefers to use a multiplicative approach to age adjustment.
- The EAG prefers to use eMIT costs to inform drug question costs.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing overall survival;
- Avoiding the need for red blood cell transfusions and iron chelation therapy, thereby improving health related quality of life (HRQoL)
- Preventing iron load related complications, thereby improving HRQoL and increasing survival.

Overall, the technology is modelled to affect costs by:

- Higher acquisition costs;
- Greater immediate administration costs;
- Avoidance of disease related and complication related healthcare costs.

The modelling assumptions that have the greatest effect on the ICER are:

- The modelling approach adopted and whether complications are explicitly modelled;

- Permanence of the treatment effect in patients who achieve transfusion independence following treatment with exa-cel;
- Mortality in patients who are transfusion-dependent;
- HRQoL in patients who are transfusion-dependent;
- The discount rate applied;
- Whether QALY benefits are reweighted in a distributional cost-effectiveness analysis.

1.3 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile

Report section	3.2.2, 3.2.3, 4.2.6.2
Description of issue and why the EAG has identified it as important	Efficacy: The company assumes that, once achieved, transfusion independence remains permanent (i.e. a 0% rate of thalassemia recurrence). Given both the limited follow-up available for the CLIMB THAL-111 cohort and evidence of occasional very late relapses in β-thalassaemia major patients with allogeneic SCTs, the EAG considers the assumption of a 0% recurrence rate to be highly uncertain and potentially optimistic. Safety: Whilst the EAG considers that exa-cel's mechanism of action is likely to reduce the risk of insertional mutagenesis and transcriptional deregulation when compared with viral vector-based gene therapies, it does not consider that there is sufficient evidence to warrant the mutagenic risk as having been eliminated (which is the company's assertion).
What alternative approach has the EAG suggested?	The EAG does not propose an alternative approach. Uncertainty in long-term effects should be accounted for in decision-making.
What is the expected effect on the cost-effectiveness estimates?	The EAG explores two alternative rates of relapse of 2.19% based on values reported by Santarone et al 2022 and 10% based on values from the betibeglogene US ICER report. The respective ICERs are [redacted] and [redacted]This compares with a company base case ICER of[redacted] ICERs are exclusive of severity weighting
What additional evidence or analyses might help to resolve this key issue?	Efficacy: The EAG's alternative rate of thalassemia recurrence is based on evidence derived from a long-term retrospective study. If clinicians are aware of data from other long-term studies this would be useful, since this area of research was not systematically reviewed within this appraisal. Further follow-up of transfusion independence via managed access is unlikely to resolve the uncertainty about the permanence of transfusion independence, given the issue primarily relates to very late relapses (i.e. relapses which would occur after managed access follow up has ended). Safety: Further follow of safety outcomes is ongoing in the CLIMB - 131 long-term follow up study.

Issue 2 Definition of transfusion independence

Report section	3.2.1, 4.2.6.1
Description of issue and why the EAG has identified it as important	The primary outcome in CLIMB THAL-111 was defined as maintaining a weighted average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months any time after exa-cel infusion ('TI12'). The EAG is concerned that this definition contrasts markedly with the definition used in the economic model, where transfusion independence (TI) was defined as patients who are transfusion-free starting 60 days after the last blood transfusion for post-transplant support or disease management. The company's use of this much easier to achieve post-hoc outcome has resulted in improved TI efficacy estimates when compared to the pre-defined TI outcomes reported in CLIMB THAL-111.
What alternative approach has the EAG suggested?	The EAG suggests using pre-defined TI definitions from the CLIMB THAL-111 trial, such as TI12.
What is the expected effect on the cost-effectiveness estimates?	Using the TI12 definition of TI to inform the economic analysis increases the ICER from [redacted] to [redacted] ICERs are exclusive of severity weighting.
What additional evidence or analyses might help to resolve this key issue?	Not applicable

Issue 3 Uncertain relationship between transfusion status and final outcomes

Report section	3.5, 4.2.2
Description of issue and why the EAG has identified it as important	The EAG acknowledges the direct benefits of patients achieving TI, although notes that this outcome represents only limited parts of the modelled benefits of exa-cel; the impact of TI on outcomes such as survival and the onset of complications remains somewhat uncertain. There is also limited direct evidence to support an association between transfusion status and health-related quality of life. This issue also has an important bearing on the type of model used, particularly in light of significant limitations associated with the company's modelling approach, see Issue 4. The current model relies on multiple complex chains of evidence and as a result is both opaque and subject to significant uncertainty. A simpler model structure, while more abstract has important advantages and may be preferred given the limitations of the evidence base and difficulties in evidencing surrogate relationships between interim and final outcomes.
What alternative approach has the EAG suggested?	Not applicable
What is the expected effect on the cost-effectiveness estimates?	It is not possible to establish the likely direction of bias. Decision making should seek to account for uncertainties in surrogate relationship used in the economic analysis.
What additional evidence or analyses might help to resolve this key issue?	Aligning with recommendation in the NICE methods guide, evidence should be provided demonstrating the plausibility and reliability of surrogate relationships used to infer HRQoL and survival benefits.

1.4 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 4 Modelling approach and how mortality risks are attributed to modelled patients

Report section	4.2.2
Description of issue and why the EAG has identified it as important	The economic model uses a Markov modelling approach which does not track the outcomes of individual patients. This imposes several structural assumptions which impact significantly on model outcomes. Firstly, this approach means that a single mortality rate is applied for the entire cohort. This is problematic as it does not attribute the elevated mortality risks associated with complications to the correct patients. This leads to a systematic over-accumulation of patients with complications, which, in turn leads to a progressive overestimation of mortality in the whole cohort. Secondly, the model assumes a static distribution of iron levels throughout the model time horizon, i.e. the same proportion of alive patients have low cardiac iron levels in cycle one as they do at the end of the model time horizon. This lacks face validity and fails to capture the expectation that patients with higher iron levels will have lower life expectancy than those with low iron levels.
What alternative approach has the EAG suggested?	The EAG considers the current model unsuitable for decision-making. There are several alternative approaches possible that could "correct" the issues identified with the model structure. These include redesigning the model as a patient simulation or simplifying the current conceptual model to reduce the number of complications modelled. None of these options represents a perfect model, and all have limitations. In choosing the most appropriate model structure it is necessary to balance complexity and the limitations of the current evidence base with the limited ability of simpler models to capture the full benefits associated with exa-cel.
What is the expected effect on the cost-effectiveness estimates?	The EAG has developed a simplified version of the company's model in which complications are removed from the model. This model is internally consistent but likely underestimates the full benefits of exa-cel.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence cannot address this issue.

Issue 5 Omission of withdrawals from exa-cel treatment in the economic analysis

Report section	4.2.2
Description of issue and why the EAG has identified it as important	The company stated that it typically takes 5-6 months from the cell cycle collection (apheresis) to patients being infused with exa-cel. This represents a significant period of time which is not explicitly accounted for in the economic analysis; the model commences at the point of infusion. This approach does not fully account for the possibility of withdrawals prior to infusion which may result not only in the costs associated with mobilisation but also those associated with manufacturing of exa-cel. The outcomes of these patients will also be inferior to those who proceed with exa-cel therapy which is not accounted for in the model.
What alternative approach has the EAG suggested?	The EAG notes that it is common to utilise a decision tree framework in the modelling of gene-therapies to capture the alternative outcomes of patients who are unable or unwilling to proceed to infusion. The EAG considers that a similar approach should be employed.
What is the expected effect on the cost-effectiveness estimates?	The EAG has adjusted model outcomes in the exa-cel arm of the model to account for the proportion of withdrawals. This was implemented using the proportion of withdrawals observed in the CLIMB THAL-111 trial. This increases the ICER from [redacted] to [redacted] ICERs are exclusive of severity weighting.
What additional evidence or analyses might help to resolve this key issue?	The EAG is unclear who bears these costs associated with the manufacturing of exa-cel when patients withdraw or otherwise become ineligible for treatment after gene editing has been performed but prior toinfusion. Clarification on the commercial arrangement by either the company or NHSE would be helpful.

Issue 6 Frequency of red blood cell transfusions

Report section	4.2.4
Description of issue and why the EAG has identified it as important	The company base-case uses the CLIMB THAL-111 trial to inform the frequency of RBC transfusions and assumes TDT patients received 16.4 transfusions per year. The EAG notes that this frequency of RBC infusions is substantially higher than observed in the Shah et al. (UK Chart Review) where patients received an average of 13.7 transfusions per year. The EAG considers the modelled number of transfusions to be uncertain and potentially higher than would be expected in UK patients eligible for treatment with exa-cel.
What alternative approach has the EAG suggested?	The EAG prefers to use the Shah Chart Review to inform the frequency of RBC blood transfusions.
What is the expected effect on the cost-effectiveness estimates?	Using the Shah Chart Review to inform the frequency of RBC blood transfusions reduces the frequency of transfusions and therefore costs associated with SoC. In a scenario analysis, the ICER increases from [redacted] to [redacted]. ICERs are exclusive of severity weighting.
What additional evidence or analyses might help to resolve this key issue?	Contemporary UK data on RBC transfusions in TDT patients that would be eligible to receive exa-cel. Further clinical input on the frequency of RBC transfusions in UK TDT patients.

Issue 7 Non-reference discount rate

Report section	**4.2.5**
Description of issue and why the EAG has identified it as important	The company base-case uses a non-reference discount rate of 1.5% on the grounds that the criteria outlined in the NICE methods guide are met. This is important as the majority of costs associated with exa-cel are accrued upfront, while benefits are accrued over a long period of time. The EAG had significant concerns regarding the company's position that patients would otherwise die or have a severely impaired life. There is limited evidence available reporting the life expectancy of patients treated optimally with current management strategies. The EAG highlights that literature cited in support of this assumption, is based on cohorts of patients who represent historical iron chelation practice, are older than those eligible to receive exa-cel and represents a restricted cohort of TDT patients which include patients otherwise ineligible for exa-cel. A number of evidence sources, including the pivotal CLIMB THAL-111 trial, supported the notion that the impact of TDT and current management on health related quality of life (HRQoL) was not as severe as argued by the company. The EAG is cautious in accepting the permanence of exa-cel engraftment in all patients, noting both the limited follow up available for the CLIMB THAL-111 cohort (median follow-up duration after exa-cel infusion was 16.7 months). Durable clinical efficacy has been demonstrated up to 24 months in a small number of patients (n=8); with a maximum follow-up of 42 months, there are no data beyond this point. There is also uncertainty with regards to surrogate markers of treatment efficacy and what these imply for long-term HRQoL and survival. The substantial upfront costs of exa-cel commits the NHS to substantial irrecoverable costs in the event of a non-permanent treatment effect.
What alternative approach has the EAG suggested?	The standard reference case discount rate of 3.5% should be applied.
What is the expected effect on the cost-effectiveness estimates?	In a scenario where the NICE reference case discount rate of 3.5% is applied to costs and benefits. The ICER increases from [redacted] to [redacted]. ICERs are exclusive of severity weighting.
What additional evidence or analyses might help to resolve this key issue?	Further follow up of patients will help establish the durability of the treatment effect. The EAG notes the availability of an updated data cut of the CLIMB THAL-111 trial which may partially resolve this issue. Ongoing data collection in the CLIMB-131 trial will also be useful in resolving this uncertainty.

Issue 8 Mortality in transfusion dependant patients and associated with complications

Report section	4.2.2, 4.2.6.5
Description of issue and why the EAG has identified it as important	To capture disease related mortality not attributable to cardiac or diabetes complications a standardised mortality ratio (SMR) of 3.45 was applied to patients who are transfusion dependent. This rate was informed by two published studies. A burden of illness study (BoI) sponsored by the company and a retrospective cohort study sponsored by the manufacturer of betibeglogene (an alternative gene therapy for the treatment of TDT). The EAG is concerned that the company has cherry picked evidence. The selected studies are outdated because they include older patients who would not be eligible to receive exa-cel. Therapeutic advances in the treatment of TDT including greater clinician experience, improved monitoring and iron chelation practices mean that these studies are not reflective of current SoC. Such advances are likely to have resulted in improved survival outcomes for TDT patients and as such these studies are likely to significantly overestimate disease related mortality. In addition to the SMR described above the economic analysis applies an additional mortality rate of 13% per annum to patients with cardiac complications. The EAG is concerned that the modelled rate of cardiac mortality is excessively high and does not reflect current NHS practice. The study used to justify this mortality rate is from the late 1990's and predates important advances in both oral chelation therapies and T2* cardiovascular magnetic resonance (CMR). These improvements in controlling iron loading and monitoring of cardiac symptoms have led to substantially improved outcomes for patients developing cardiac complications and imply a mortality rate far below that applied in the economic analysis.
What alternative approach has the EAG suggested?	The EAG considers alternative SMRs informed by the preferred committee assumptions in the appraisal of betibeglogene. The EAG has been unable to identify an alternative source of cardiac mortality rates. The EAG base-case, however does not directly model complication rates reflecting concerns outlined in Issue 4.
What is the expected effect on the cost-effectiveness estimates?	Alternative SMRs of 2 and 2.5 were applied. This respectively results in ICERs of [redacted] and [redacted]This compares to the company base case of [redacted] per QALY gained. ICERs are exclusive of severity weighting. Note the limited impact of these alternative assumptions is due to the misspecification of modelled mortality rates, see Issue 4.
What additional evidence or analyses might help to resolve this key issue?	Further contemporary data on mortality in patients treated with current SoC would be informative but is unlikely to be available due to the lag in the availability of such data. Similarly, contemporary data in TDT patients with cardiac complications would be informative.

Issue 9 HRQoL in transfusion independent patients

Report section	4.2.7.1, 4.2.7.2
Description of issue and why the EAG has identified it as important	While the company collected data on HRQoL in the CLIMB THAL-111 trial and identified several sources of published utility values, these were not used in the economic model. The company instead used values generated by a vignette study. This approach was justified on the basis that EQ-5D is unsuitable to capture the HRQoL burden of TDT due issues of adaptation, ceiling effects and the lack of a 'fatigue' domain. The EAG considers that the approach adopted by the company is inconsistent with the NICE reference case and that the company have not made a compelling case to reject the use of EQ-5D. The EAG notes a number of issues with the vignette study including the use of value-laden statements which may lead to bias in the resulting value set.
What alternative approach has the EAG suggested?	The EAG considers that EQ-5D available from the CLIMB THAL-111 trial should be appropriately analysed and used to inform the model. Despite requests from the EAG at points for clarification (PFC 12b, PfC 13), no scenario analysis has been implemented using the EQ-5D utility values from the trial. As a result, it is unclear how use of the trial base valued set impacts the cost-effectiveness results.
What is the expected effect on the cost-effectiveness estimates?	A range of scenarios for utility decrements of [redacted] 0.1, 0.15 considering the impact of transfusion dependence on HRQoL were implemented by the EAG. This respectively results in ICERs of [redacted] per QALY gained. This compares to the company base case of [redacted] per QALY gained. ICERs are exclusive of severity weighting.
What additional evidence or analyses might help to resolve this key issue?	Appropriate EQ-5D data is available from the CLIMB THAL-111 and should be used to inform the modelled value set.

Issue 10 Additive vs multiplicative age adjustment of utilities

Report section	4.2.7.4
Description of issue and why the EAG has identified it as important	The company base case implements age adjustment of utilities applied in the model to account for the impact of ageing on HRQoL. This is implemented using an additive approach which assumes a constant absolute utility decrement which is independent of health state utility values. The EAG prefers to use a multiplicative approach to modelling age-related decrements and notes that this has been generally the preferred method of implementing age adjustment in NICE technology appraisals. It is also stated as the preferred method of age adjustment in the NICE methods guide.
What alternative approach has the EAG suggested?	Multiplicative age adjustment.
What is the expected effect on the cost-effectiveness estimates?	Applying a multiplicative approach to age adjustment has only a limited direct impact on the ICER resulting in an increase from [redacted] to [redacted] per QALY gained. ICERs are exclusive of severity weighting. Use of the multiplicative methods, however, also has implications for the severity modifier criteria and results in multiplier of 1 in the company's preferred base case. Consequently, this issue has the potential to have significant impact on decision making.
What additional evidence or analyses might help to resolve this key issue?	Not applicable.

Issue 11 eMIT costs

Report section	4.2.8
Description of issue and why the EAG has identified it as important	The company model uses NHS drug tariff costs rather than electronic information tool (eMIT) costs to represent the acquisition cost associated with ICT regimes. The company argue that it is inappropriate to use eMIT costs for retail pharmacy drugs, as eMIT reports hospital-sector prices, which the company states have a different cost to the NHS than retail pharmacy costs. Following discussions with NICE, the EAG were directed to use the eMIT costs for all drug acquisition costs.
What alternative approach has the EAG suggested?	Use eMIT to inform all drug acquisition costs.
What is the expected effect on the cost-effectiveness estimates?	Applying eMIT costs increases the ICER from [redacted] to [redacted] per QALY gained. ICERs are exclusive of severity weighting.
What additional evidence or analyses might help to resolve this key issue?	Not applicable.

1.5 Other key issues: summary of the EAG's view

Issue 12 Reweighting of benefits and costs through use of non-reference case DCEA

Report section	8
Description of issue and why the EAG has identified it as important	The company apply distributional cost-effectiveness analysis (DCEA) methodology and present results in terms of reweighted QALY benefits and financial costs. They use weights based on the relative area level socioeconomic deprivation and quality adjusted life expectancy of people affected by both the technology, and by displaced NHS activities. They use an Atkinson social welfare function to determine the weights according to elicited preferences to reduce relative health inequality between rich and poor groups. The approach was justified on the basis that TDT is more prevalent in Pakistani and South Asian ethnic groups, and that TDT patients are more likely to live in more deprived areas. The EAG consider that the approach adopted by the company only characterises concern for health inequality by area level deprivation and does not reflect equity concerns related to ethnicity, and that it is inappropriate to use the Index of Multiple Deprivation as a proxy for ethnicity. The EAG note that equity concerns related to area level deprivation are not reflected in the final scope. Furthermore, the EAG considers that a DCEA approach is inconsistent with the NICE reference case, and that the company have not made a compelling case for the use of this methodology for this particular appraisal given that NICE has not adopted it more widely. The EAG considers that DCEA methodology only applies to health benefits and health opportunity costs, and that it is inappropriate to apply weights to financial costs. Therefore the EAG considers that the equity weighted ICERs presented by the company cannot be interpreted as they include financial costs rather than health opportunity costs.
What alternative approach has the EAG suggested?	The EAG considers that reweighting of QALY benefits and health opportunity costs to reflect concerns about health inequality should be consistently applied between evaluations. Given that NICE chose not to include DCEA methodology in the methods manual, the EAG considers that it should not be applied to this appraisal. The EAG considers that if DCEA methodology is to be applied, NICE should first develop suitable reference case guidance. The EAG considers that if there are concerns about health inequalities by ethnicity, that DCEA methods be used to estimate the distribution of QALY benefits and health opportunity costs by ethnicity and not by area level deprivation.
What is the expected effect on the cost-effectiveness estimates?	The cost-effectiveness results are presented with and without the reweighting by area level deprivation in order to assess the impact.
What additional evidence or analyses might help to resolve this key issue?	Potential issues relating to health inequalities by area level deprivation should be raised and consulted upon in the scoping process. The use of DCEA as a quantitative decision modifier requires a clear position statement from NICE and further NICE methods manual update with accompanying guidance as to how DCEA should be applied in the context of a NICE health technology evaluation. An additional DCEA that examines the distribution of QALY benefits and health opportunity costs by ethnicity could address the equity considerations raised in the scoping process.

Issue 13 Approach to distributional cost-effectiveness analysis

Report section	8
Description of issue and why the EAG has identified it as important	The company perform aggregate DCEA, wherein they adjust the summary cost-effectiveness results according to how the patient population expected to uptake the intervention is distributed among the area level deprivation subgroups in the UK general population. The company justify the use of aggregate DCEA by stating an assumption that the inputs to the cost-effectiveness analysis, including the treatment benefits, do not vary across subgroups. The company assume 100% uptake in all subgroups. The company present the results of the aggregate DCEA using an equity-weighted ICER. The EAG consider that the justification given for the aggregate approach to DCEA may conflict with arguments presented by the company in respect to ethnicity concerns. For example, if lower availability of ethnically matched transfusions were important for treatment outcomes, this would support the use of a full DCEA that adjusts relevant inputs to the cost-effectiveness analysis. The EAG received clinical advice that factors related to inequalities, such as distrust of the health care system, may also affect uptake of new technologies. The EAG note that the equity-weighted ICER presented by the company is not part of DCEA methodology.
What alternative approach has the EAG suggested?	The EAG consider that in the absence of evidence as to how input values vary by subgroup, an aggregate DCEA approach will produce similar results to a full DCEA. The EAG recommend sensitivity analysis to understand how differences in uptake affect DCEA results. The EAG considers that the appropriate way to present DCEA results is to use the 'health equity impact plane', and to determine first if there is dominance. In the absence of dominance, the EAG considers that equally distributed equivalent net health benefit is the most appropriate metric when using an Atkinson social welfare function. The use of net health benefit accords with recommendations in the NICE manual 4.2.16.
What is the expected effect on the cost-effectiveness estimates?	Lowering uptake to the same degree across all groups will have little impact on the results. In some scenarios, exa-cel is in the 'lose-lose' quadrant of the health equity impact plane and is dominated by SoC as it is has an ICER above the NICE cost-effectiveness threshold range of £20,000-£30,000 per QALY and it increases the slope index of inequality.
What additional evidence or analyses might help to resolve this key issue?	Further work to understand whether the costs, benefits and uptake of SoC or exa-cel vary across subgroups would inform a choice between full or aggregate DCEA methodology. A clear position statement from NICE on the preferred approach to convert financial costs into health opportunity costs would assist in presenting the results of a DCEA.

Issue 14 Input parameters used in the distributional cost-effectiveness analysis

Report section	8
Description of issue and why the EAG has identified it as important	The company did not report the methods used to identify sources for DCEA inputs, and have not justified their selection of sources. The EAG is concerned that some sources were missed, some sources are outdated, and that the company may have cherry-picked the sources. The company used unadjusted results from the Health Survey for England for the distribution of the general population by area level deprivation without applying the survey weights that correct for non-response. The EAG note that the company did not apply published estimates of the distribution of health opportunity cost by area level deprivation. The EAG is aware of more recent studies on quality-adjusted life expectancy by area-level deprivation, and on elicited preferences for reducing health inequality between rich and poor groups. The EAG consider that the distribution of the general population by area level deprivation is best informed by population data from the ONS. The EAG considers that the identification and selection of input parameters to the DCEA should be subject to the same rigour as the selection of inputs parameters to the cost-effectiveness analysis.
What alternative approach has the EAG suggested?	The EAG identified alternative sources for DCEA inputs, some of which were applied by the company in response to clarification. The EAG corrected some errors in how the company apply published estimates of the distribution of health opportunity cost by area level deprivation.
What is the expected effect on the cost-effectiveness estimates?	The use of the EAG preferred sources for DCEA inputs has a large impact on the DCEA results, decreasing incremental NHB from [redacted] to an incremental EDE NHB [redacted].
What additional evidence or analyses might help to resolve this key issue?	Establishing search criteria for DCEA inputs and performing a suitable literature review would identify the relevant alternative sources and permit sensitivity analysis to the selection of alternative input values.

Issue 15 Discounting and Severity modifier and distributional cost-effectiveness analysis

Report section	8.1.1
Description of issue and why the EAG has identified it as important	The company have applied a non-reference case discount rate of 1.5%, a decision modifier in terms of the severity modifier, and have conducted a DCEA. All three of these departures from the reference case have the impact of inflating the estimated incremental QALY gain associated with the technology. In addition, the non-reference case discount rate and the DCEA adjusts the incremental costs associated with the technology. The NICE methods manual does not address the combination of the non-reference case discount rate and decision modifiers. There is likely to be an association between meeting the criteria for the non-reference case discount of 1.5% (when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health), and a larger proportionate or absolute QALY shortfall. Indeed, while criteria for non-reference case discount of 1.5% are open to interpretation the EAG consider that the non-reference discount rate is primarily intended for severe conditions. Similarly, the NICE methods manual does not directly address the issue of whether it is appropriate to combine a severity modifier with a DCEA. The QALY shortfall calculations undertaken by the company, however, includes not only the difference in QALE attributable to the disease alone, but also differences in QALEs from other factors that are correlated with presence of the disease, including socioeconomic deprivation. The impact of social deprivation is therefore influencing the shortfall calculations used to inform the application of the NICE severity weights.
What alternative approach has the EAG suggested?	If the severity modifier is to be applied in combination with a DCEA that accounts for health inequalities between IMD quintiles, it would be appropriate to calculate the QALY shortfall between QALE in the target patient population and QALE in an age, sex and IMD matched general population. This would avoid any double counting or double weighting of differences in QALE associated with IMD.
What is the expected effect on the cost-effectiveness estimates?	Appropriate calculation of QALY shortfall accounting for IMD would likely reduce the QALY short fall with implications for the relevance of NICE severity weights.
What additional evidence or analyses might help to resolve this key issue?	Further input from the NICE technical team on the simultaneous application of the of 1.5% discount rate, severity modifier and DCEA may be informative. The EAG, however, in section 1.2 that there is no precedent for such a situation. The committee must decide to what degree each modifier accounts for disease severity and other relevant decision modifiers. It must then consider whether it is appropriate to apply each modifier simultaneously.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 summarises the EAG's preferred assumptions and resulting ICER. Table 3 and Table 4 reflect the EAG corrections and preferred assumptions to the DCEA and resulting NHBs. Modelling errors identified and corrected by the EAG are described in Sections Model validation and face validity check 5.2. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6 and Section 8. All ICERs are deterministic and are exclusive of severity weighting.

Table 2: Summary of EAG's preferred assumptions and resulting ICER

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY
Company base-case	5.1.1.1	[redacted]
1. Alternative assumptions mortality associated with complications	4.2.2	[redacted]
2. Costs and outcomes from exa-cel withdrawal	4.2.2	[redacted]
5. Frequency of blood transfusions based on Shah	4.2.4	[redacted]
6. Using a 3.5% discount rate	4.2.5	[redacted]
7. Aligning transfusion independence to the T12 primary outcome in CLIMB THAL-111	4.2.6	[redacted]
9. Assuming 5 years to iron normalisation	4.2.6	[redacted]
11. Assuming an SMR of 2.5 for TD patients	4.2.6.5	[redacted]
12. HRQoL decrement of [redacted] relative to the general population	4.2.7	[redacted]
15. Use of eMIT costs	4.2.8	[redacted]
17. Multiplicative approach to age-adjustment	4.2.7.4	[redacted]

Table 3 EAG DCEA exploratory analysis at £20,000

	NHB at £20,000	
Scenarios	**Base case**	**EDE**
Company base-case (1.5% discount rate)	[redacted]	[redacted]
Company base-case scenario (3.5% discount rate)	[redacted]	[redacted]
EAG preferred base-case (3.5% discount rate)	[redacted]	[redacted]
EAG preferred DCEA on EAG base-case	[redacted]	[redacted]

Table 4 EAG DCEA exploratory analysis at £30,000

	NHB at £30,000	
Scenarios	**Base case**	**EDE**
Company base-case (1.5% discount rate)	[redacted]	[redacted]
Company base-case scenario (3.5% discount rate)	[redacted]	[redacted]
EAG preferred base-case (3.5% discount rate)	[redacted]	[redacted]
EAG preferred DCEA on EAG base-case	[redacted]	[redacted]

EXTERNAL ASSESSMENT GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report presents the Evidence Assessment Group's (EAG's) critique of the company submission (CS) and executable economic model submitted by Vertex Pharmaceuticals to the National Institute for Health and Care Excellence (NICE). The CS reports on the clinical effectiveness and cost-effectiveness of exagamglogene autotemcel (exa-cel) within its marketing authorisation for treating transfusion-dependent β-thalassaemia (TDT).

In this section the EAG critiques the company's proposed positioning of exa-cel in the treatment pathway and its definition of the decision problem when compared with the NICE scope.

2.2 Background

2.2.1 Description of the technology being appraised

The company describe exagamglogene autotemcel (exa-cel), including the mechanism of action and the treatment process, in Section B 1.2 of the CS.

In most people, foetal haemoglobin (HbF) production reduces and then stops during the first year of life, after which adult haemoglobin (HbA) is present in red blood cells (RBCs) and carries oxygen to tissues and organs around the body. Exa-cel is a gene therapy using non-viral CRISPR/Cas9 gene-editing technology in which the BCL11A gene is edited *ex-vivo* to reactivate the production of HbF.

The company explained at the clarification stage that the process from cell collection to administration of exa-cel takes around 5 to 6 months. Some patients may require more than one round of apheresis, which must be spaced several weeks apart. [redacted] Once manufactured, exa-cel is stored and transported in a frozen state and thawed at the local site shortly before administration. Successful treatment is indicated by trilineage engraftment; the growth of stem cells and production of healthy RBCs. Subsequently, the increase in haemoglobin should reduce or negate the need for RBC transfusions. Iron chelation therapy (or phlebotomy) will continue until iron levels are restored to normal. Although exa-cel has the potential to be curative, patients may have developed reversible and/ or irreversible complications from transfusion-dependent β-thalassaemia prior to treatment with exa-cel, and these patients require ongoing care as they continue to live with chronic conditions.

The company expect regulatory approval for exa-cel by the MHRA in October 2023, following their submission on 29th December 2022.

2.2.2 Description of transfusion-dependent β-thalassaemia

Beta-thalassaemia patients carry a genetic mutation in the β-globin gene, which results in the reduced or absent production of adult haemoglobin (HbA). Clinical severity depends on genotype with the β^0/β^0 genotype representing the most severe disease, in which no HbA is produced.

Severe anaemia requires lifelong regular blood transfusions; the company describe a usual schedule of transfusions to be every two to five weeks. The EAG's clinical advisor indicated that a transfusion is normally given every three or four weeks for TDT, but there is variation between patients depending on the severity of the condition, and between treatment centres depending on the staff and facilities available. The submission defined TDT as patients with ≥ 8 RBC transfusions per year.

The company estimate that there are 920 patients aged 12 years and older with TDT in the UK. Patients born in the UK today are usually diagnosed early, mostly through screening programmes in pregnancy or after birth, and transfusions and iron chelation therapy will start before age three [1].

2.2.2.1 Burden of disease

The EAG's clinical advisor explained that, depending on severity of disease, past disease management, and exposure to infectious diseases, patients in their early twenties may already be developing chronic diseases as a complication of their condition and treatment. Older patients may not have received optimal treatment historically and may suffer more from the consequences of anaemia and iron overload. The company describe results from a UK study of patients with TDT more than 25% of patients suffer from hypopituitarism and over 25% live with osteoporosis. Over 25% of patients suffer from diabetes, another 25% of patients show signs of prediabetes or insulin resistance, and other physical and mental health problems are common (CS Table 3, p. 27). The company is concerned that the true burden of disease may be not be adequately reflected using quality of life measures, as the lifelong nature of the condition means patients are accustomed to living with TDT.

The EAG's clinical advisor stressed that there is much variation in the way patients experience the impact of symptoms of β-thalassaemia, treatments, and side effects. Quality of life is likely to fluctuate in the short term (for example, worse pain and fatigue before a transfusion), and over a lifetime. The clinical advisor pointed out that most patients would perceive their lives and quality of life to be impaired compared to peers, and that they are frequently reminded in contact with others that healthy children or adults of a similar age do not experience the same limitations.

2.2.3 Position of exa-cel in the clinical pathway

The clinical pathway for patients aged 12 years or older with TDT is described in section B.1.3.3.1 of the CS and the proposed position of exa-cel in the clinical pathway is shown in Figure 9 of the CS (p. 42).

For most patients, there are three main elements to their treatment, alongside continuous monitoring of their condition and symptoms: regular blood transfusions, iron chelation therapy, and treatment of complications. The EAG's clinical advisor explained that the type, frequency, and dose of treatments are adjusted over time to try and balance haemoglobin (Hb) and iron levels, quality of life, complications, and adverse events (AEs).

Allogeneic stem cell transplantation (allo-SCT) offers a chance to be cured. Allo-SCT requires the patient to be young (usually < 9 years old) and fit, with a suitable donor (preferably a matched sibling donor), and it carries the risk of serious adverse events (SAEs), such as graft-versus-host disease (GvHD), which can be life threatening.

The company position exa-cel as a potentially curative treatment option for TDT patients aged 12 years or over, who are fit enough to receive a transplant, but for whom there is no suitable HLA-matched related donor.

Out of an estimated 920 patients aged 12 or over with TDT in the UK, the company estimate that around 350 patients may be eligible for exa-cel. The EAG's clinical advisor explained that the number of patients opting to receive exa-cel is likely to be lower, as patients and their families weigh up the benefits and risks of exa-cel.

2.3 Critique of company's definition of decision problem

The EAG's critique of the company's definition of the decision problem and adherence to the final NICE scope is summarised in Table 1. Key points of critique are described below.

2.3.1 Population

The company state that exa-cel is to be indicated for the treatment of transfusion-dependent β-thalassaemia in patients 12 years of age and for whom a human leukocyte antigen (HLA)-matched related haematopoietic stem cell (HSC) donor is not available. The specified population was adjusted to match the proposed indication.

Figure 9 of the CS (p. 42) illustrates that only patients for whom allo-SCT is appropriate but who do not have an available donor are eligible. In the pivotal CLIMB THAL-111 trial, patients were eligible if they fit eligibility criteria for allo-SCT as per investigator's judgement (CS data on file, CLIMB

THAL-111 protocol, p. 40). The EAG's clinical advisor confirmed that this fits with similar requirements for fitness and physical ability to withstand the adverse events associated with chemotherapy ahead of either allo-SCT or exa-cel.

The CLIMB THAL-111 trial excluded patients over 35 years old (CS data on file, CLIMB THAL-111 protocol, p.40). Although no upper age limit is specified in the expected licence, the company anticipated that the age range of patients treated with exa-cel in clinical practice would be broadly similar to that of CLIMB THAL-111 (this is discussed further in Section 3.2.1.2).

A patient's eligibility for exa-cel may change over time. Firstly, the EAG's clinical advisor explained that, in rare cases, a donor may become available either through the birth of a new sibling, or a changed decision about donorship or treatment preference. Secondly, better adherence to treatment and iron chelation therapy in patients unfit for exa-cel may mean that patients can improve their health and subsequently meet the fitness criteria. Thirdly, the EAG's clinical advisor explained that the safety of allo-SCT continues to improve slowly with advances in treatment and medical technology. In the future, allo-SCT may therefore become a suitable treatment option for more older children and young adults.

2.3.2 Outcomes

Two outcomes stated in the NICE final scope, 'reduction in the use of iron chelating agents' and 'new or worsening haematologic disorders' were not included in the company's submission.

The company stated that the outcome 'reduction in the use of iron chelating agents' was not stated *a priori* as an endpoint in the CLIMB THAL-111 trial. However, the trial record (NCT03655678) does list 'proportion of subjects receiving iron chelation therapy' as an outcome, measured one month post infusion through to month 24 visit (and up to 15 years post infusion in CLIMB-131). As the company describe in the CS (p 24-25, 30-31, 40), iron chelating therapy is likely to have a detrimental effect on patients' burden of disease and quality of life. In their submission, the UK Forum on Haemoglobin Disorders (UKFHD) listed 'a reduced or absent need for any chelation therapies' as an important outcome. This was confirmed by the EAG's clinical advisor, who also highlighted the cost implication of iron chelation for the NHS. Outcome data for 'use of iron chelating therapy' is reported in the CS (p. 85-86). The EAG is of the opinion that this outcome should have been included in the decision problem.

The company state that the outcome 'new or worsening haematologic disorders' was not an endpoint in the CLIMB THAL-111 trial. It was however included as one of five primary outcomes in the CLIMB-131 follow-up trial, to be measured up to 15 years post-infusion. The trial registration specified that this outcome includes immune-mediated cytopenias, aplastic anaemia, and primary

immunodeficiency (NCT04208529). The Clinical Study Report (CSR) of CLIMB-131 reported that 42 out of 59 participants in the safety set experienced adverse events relating to this outcome after transfusion, with the most common events being related to busulfan and including febrile neutropenia, thrombocytopenia, and anaemia. The EAG is unsure why the outcome 'new or worsening haematologic disorders' was not included in the decision problem, given that data were available. Data taken from the CLIMB-131 CSR are summarised in Section 3.2.3.

2.3.3 Economic analysis

The critique of the company's economic analysis can be found in Section 4.2.

2.3.4 Special considerations including issues relating to equity or equality

The EAG's critique of the DCEA considering socioeconomic and ethnic inequalities presented by the company can be found in Section 8.

Table 5 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Transfusion-dependent β-thalassaemia (TDT) where there is no human leukocyte antigen (HLA)-matched related donor.	Patients with TDT 12 years of age or older for whom an HLA-matched related haematopoietic stem cell donor is not available	This population better aligns with the proposed Medicines and Healthcare products Regulatory Agency marketing authorisation.	The EAG agrees with the company rationale. As explained in the CS, only patients who are eligible for allogeneic SCT, but who have no suitable donor are eligible for exa-cel.
Intervention	Exagamglogene autotemcel (exa-cel)	Exa-cel	N/A	N/A
Comparator(s)	Established clinical management of β -thalassaemia without exagamglogene autotemcel including: Blood transfusions and iron chelating agents Best supportive care	Best supportive care (including blood transfusions and chelating agents)	N/A	N/A
Outcomes	The outcome measures to be considered include: Reduction in transfusions Change to haematological parameters (haemoglobin levels) Reduction in the use of iron chelating agents Proportion with and time to engraftment New or worsening haematologic disorders Mortality	The outcome measures to be considered include: Reduction in transfusions Changes to haematological parameters (haemoglobin levels) Proportion with and time to engraftment Mortality Adverse effects of treatment Health-related quality of life	The outcome 'reduction in the use of iron chelating agents' was not stated *a priori* as an endpoint in the pivotal CLIMB THAL-111 trial. The outcome 'new or worsening haematologic disorders' was not an endpoint in the pivotal CLIMB THAL-111 trial.	Outcome 'reduction in the use of iron chelating agents' was reported in the CS and outcome 'new or worsening haematologic disorders' was a primary outcome in CLIMB-131 and reported in the CSR.

	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. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a National Health Service and Personal Social Services perspective.	Exa-cel qualifies for the non-reference discount rate and the severity modifier	[abbreviated from CS] Exa-cel meets the criteria for a non-reference case discount rate of 1.5% as laid out in the NICE methods guide.	The company's economic analysis does comply with the NICE reference case. The company apply a non-reference case discount rate of 1.5%. Utilities used in the base case analysis were generated using a non-reference case methodology. See Table 11 for details. QALYs are reweighted using a distributional cost-effectiveness analysis.
Subgroups	If the evidence allows, the following subgroups will be considered: People with beta thalassaemia major People with beta thalassaemia intermedia	None	[abbreviated from CS] There is a continuum of clinical severity with no absolute cut-off between the two phenotypes and transfusion independence can vary over time. In the CLIMB THAL-111 trial only patients with TDT were included. The sub-groups of β-thalassaemia major and β-thalassaemia	The EAG agrees with the company's focus on TDT, which is in line with the Thalassaemia International Federation guidelines.

			intermedia were not used in the trial.	
Special considerations including issues related to equity or equality	NR	People with thalassaemia are largely from non-white backgrounds, including South Asian, Southeast Asian and Middle Eastern heritage. Therefore, they are subject to a number of challenges related to their condition which manifest as health inequalities. NICE should take account of issues relating to health inequalities faced by patients with TDT.	Principle 9 of NICE's charter aims to reduce health inequalities. Thus, NICE considers inequality or unfairness in the distribution of health to be an important factor in decision-making [2]. As part of this submission, Vertex has conducted a DCEA as a framework for incorporating health inequality concerns into the economic evaluation of exa-cel.	The EAG notes that high prevalence in people with Mediterranean, South Asian, South East Asian and Middle Eastern family origins is included in the background within the final scope for this appraisal, but that no other considerations are defined in relation to either the technology or the comparator. The EAG agrees that reducing health inequalities forms one of NICE's core principles, but notes also that on equity considerations the NICE reference case stipulates that an additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify evidence for the clinical efficacy and safety of exa-cel and comparator treatments. Information was provided in Appendix D of the submission, and the EAG requested missing information during the clarification stage. The EAG identified inconsistencies and inaccuracies in the SLR report, which are described below.

A SLR of evidence relating to economic evaluations and cost burden evidence of TDT treatment is critiqued in Section 4.1of the EAG report.

Searches

Searches were run initially on the 10th of May 2022 and updated on the 13th of May 2023. Table 63 in Appendix D (p. 58-59) states that the update was performed on the 13th of May 2022, which the EAG assumes to be an error.

Databases searched include MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and conference proceedings of associations relevant to haematology. From the CS, it appeared no evidence was sought from Health Technology Assessment (HTA) databases or individual clinical trial registries. In response to the EAG's request for clarification the company replied that HTA databases were explored in a 'desktop research search' and did not identify additional evidence. However, they did not provide search strategies or further details of these searches.

The EAG found numerous inaccuracies in the reporting of the search strategies and missed information on methods used to search the literature (Table 6). The EAG requested information on the following points:

- Accurate copies of exact searches run with correct details of: limits applied, database indexing, segments used, search dates, and correct number of hits per line.
- Missing search strategies of conference proceedings.
- Ambiguity in the PRISMA flowchart of study selection.

The company clarified that some of the inconsistencies were due to changes in database subscriptions, and they provided the search terms and number of hits for searches of conference proceedings. This information was inconsistent with the PRISMA diagram. The company's explanation did not address the wide range of errors across all databases searched and therefore, the search strategies could not be fully appraised.

Table 6 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	NO	The search strategies provided in the original company submission could not be fully appraised as the documentation provided was not an accurate representation of how the strategies were input and run on each of the databases. In the PfCs, the company were asked to provide accurate copies of the exact searches run with correct details of limits applied, database indexing, segments used, dates searches were run, and correct number of hits per line, as there were also many mistakes in these aspects of the documentation. In response to this PfC, the company did not resubmit the strategies with corrected, accurate documentation. The company explained that their database subscriptions had changed and that Embase was searched on Embase.com rather than via Ovid as represented in their original submission, and that the hits represented were 'anticipated to be correct' (p. 88, of 'ID4015_exa-cel_TDT_clarification_response [CON REDACTED]'). However, a study by Fortier et al has found differences in the search results between searching databases on Embase.com and Ovid even when the same strategy is used. The company's explanation does not address the wide range of errors across all databases searched. Therefore, the search strategies could not be fully appraised. In the original company submission, the search strategies for conference proceedings were not provided. This was raised as a PfC. The company provided these strategies in response to PfCs. These previously unseen strategies used in the original systematic literature review list 9 conference abstracts. However, the original submission described 12 conference abstracts on p. 59 of Appendix D, and 13 in the PRISMA on p. 60. The updated strategies of conference proceedings also list hits that are not shown in the PRISMA. In the original company submission, the searches of MEDLINE on p. 155 of Appendix D list 10 results but the PRISMA on p. 60 of Appendix D lists 12. This was raised as a PfC and the company corrected the figure to 12.
Were appropriate sources searched?	PARTLY	A limited selection of relevant databases and conference proceedings were searched. No trials registries or HTA sources were searched, which was raised as a PfC. The company responded that HTA sources were searched but did not identify relevant literature. However, these searches of HTA sources are not referred to in Appendix D and documentation for these was not provided. The company did not comment on why they did not search dedicated trialsubjec registries.
Was the timespan of the searches appropriate?	PARTLY	The original searches were not limited by date in the strategy. The update searches are described as being limited by date. However, the MEDLINE and Cochrane CENTRAL strategies do not document this. It is therefore unclear if the limits were applied appropriately. The date limits for Embase were applied on Embase.com which the EAG cannot appraise as we do not have access.
Were appropriate parts of the PICOS included in the search strategies?	PARTLY	The searches combined the population with the comparators and the study type. Beta thalassemia is a rare disorder – it would have been more sensitive to combine the population with the study type. One of the comparators used was 'best medical care' which is a very imprecise concept to search for.

Were appropriate search terms used?	PARTLY	Search terms for the condition were comprehensive, although the terms: TDT and transfusion dependent thalassemia were missed in all strategies. Search terms for the comparators were too narrow in places. For instance, the comparator 'best medical care' was searched for in the title and abstract and with exp medical care/ which is not a subject heading on Medline but appears in the updated Medline strategy. In additional to this error, there are numerous mistakes in the search terms used (too many to list). In the update search, the Emtree term zynteglo/ is used but this also does not exist.
Were any search restrictions applied appropriate?	PARTLY	It is better to remove non-English papers during screening rather than in the search strategy, as English language papers can be missed by the application of this limit on the Ovid platform. There are English language papers which have not yet been indexed with English language metadata.
Were any search filters used validated and referenced?	PARTLY	Search filters were used but not referenced. It is therefore unclear if filters were validated.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

The CS noted (on p137) that searches for a targeted literature review (TLR) were conducted for mortality inputs used in the model. However, the methodology and strategies were not documented, which was raised as a PfC. In response, the company submitted a spreadsheet '*Data on file – TDT Morbidity Algorithms TLR*' containing details on search strategies, sources searched, and relevant studies identified through abstract screening. However, the methodology for the TLR was not provided and the documentation did not provide detail on the dates of the searches – therefore the report of the search was not clear and comprehensive. Very few sources were searched: only Google Scholar and a backwards citation search. It is unclear whether any date restrictions were applied to the Google Scholar searches as this is not documented.

Selection criteria

Criteria for inclusion and exclusion of identified studies were summarised in Appendix D, table 63 (p. 58-59) of the CS.

The population criterion was broader than the proposed eligible population for exa-cel as it included all patients with TDT aged 12 years or older. Comparators included standard care, allogeneic stem cell transplantation, other gene therapies, and placebo.

Study outcomes eligible for inclusion in the SLR included all outcomes listed in the decision problem. Outcomes 'new or worsening haematological disorders' and 'reduction in the use of iron chelating agents', which were listed in the NICE scope but not included in the decision problem, were not part of the inclusion criteria.

Studies published in languages other than English were not included, which may lead to the exclusion of relevant literature.

Critique of data extraction

Following the update search, 100 unique studies were included for data extraction (Appendix D, Figure 32, p. 60).

The list of 185 excluded studies was provided by the company at the clarification stage. The most common reason for exclusion was that the outcome was out of scope (N=90).

The company identified seven publications relating to the CLIMB THAL-111 trial. In addition, three of the included studies were prioritised for detailed data extraction and inclusion in the indirect treatment comparisons (ITC): BELIEVE, Northstar-2, and Northstar-3.

The number of studies included for data extraction but not prioritised is inconsistently reported as either 96 or 97 studies. Reasons for not prioritising studies were not explained, but are listed in Table 66, Appendix D (p.63). These include 'lack of a transfusion-related outcome' (N=90) or incompatible outcome (N=1), not an FDA-approved treatment or formulation (N=4), and 'study included only four participants' (N=1). For these studies, only data relating to the intervention, geography, sample size, participant age, and definition of transfusion independence were extracted.

Quality assessment

The company reported the NICE quality assessment of the BELIEVE trial. Even though all domains received the most favourable rating, the evidence was judged to be 'low to moderate' (Appendix D, p. 73-74). The company explained following the EAG's request for clarification that this error was due to a misinterpretation of the evidence, and the company's conclusion was that BELIEVE is a high-quality study.

Quality appraisal of the two single-arm studies (Northstar-2 and Northstar-3) was not reported.

Evidence synthesis

An evidence synthesis was only presented for studies which reported transfusion-related outcomes. The three included trials evaluated luspatercept (BELIEVE) and betibeglogene autotemcel (beti-cel) (Northstar-2 and Northstar-3). As summarised in the CS (Table 6, p.34-35), neither of these treatments are used to treat TDT in the NHS. Data from these trials were synthesised using a matching-adjusted indirect comparison (MAIC) (see Section 3.4).

The absence of reporting of results data for other review-eligible outcomes e.g. iron-overload complication outcomes and mortality is an important limitation of the company's submission.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

The clinical efficacy and safety evidence used in the submission was based on data from a single-arm trial called CLIMB THAL-111 (clinicaltrials.gov reference: NCT03655678) which was conducted at 13 sites across five countries. CLIMB-131 is a long-term follow-up study (up to 15 years) for patients who received exa-cel in CLIMB THAL-111 and CLIMB SCD-121 (a study in patients with severe sickle cell disease). By the 6th September 2022 data cut-off, eight patients who completed CLIMB THAL-111 had entered the CLIMB-131 study.

3.2.1 CLIMB THAL-111

The primary outcome in CLIMB THAL-111 was the proportion of patients achieving transfusion independence (TI) for at least 12 consecutive months (TI 12). More specifically, this was defined as maintaining a weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion;evaluation begins 60 days after the last RBC transfusion for post-transplant support or TDT disease management. The EAG is concerned that this definition contrasts markedly with the definition used in the economic model, where TI was defined as patients who are transfusion-free starting 60 days after the last blood transfusion for post-transplant support or disease management, i.e. no minimum duration of transfusion independence, nor minimum Hb levels, were required to be met in the model definition. The use of this much easier to achieve definition means the company has used an outcome which has been defined post-hoc which has resulted in improved TI efficacy estimates when compared to the pre-defined TI outcomes reported in CLIMB THAL-111 (i.e. TI 12 and/or TI 6).

3.2.1.1 Quality assessment

The company presented quality assessment results for CLIMB THAL-111 in Table 69 of the appendices document. The value of the assessment was inherently limited, given that the trial has a single-arm design. Most of the criteria which could be completed for this study design related to aspects of study reporting (which all seemed adequate).

3.2.1.2 Applicability of the **CLIMB THAL-111** *study to the NHS setting*

Eligibility criteria

The EAG notes the exclusion of patients with high iron levels, specifically a liver iron content (LIC) of ≥15 mg/g dry weight on R2 MRI or cardiac T2* <10 msec by MRI or LVEF <45% by echocardiogram; the clinical advice given to the EAG was that these exclusion criteria were reasonable.

Patients also had to be aged between 12 and 35 years to be eligible for CLIMB THAL-111. Although 12 years is the lower age restriction in exa-cel's anticipated marketing authorisation, there is no upper age limit (i.e. patients aged over 35 years may receive exa-cel). The company expected the age range of patients treated with exa-cel in clinical practice to remain largely similar to that of CLIMB THAL-111, based on the age range of historical stem-cell transplant cohorts (CS, p111). The company said this view was supported by clinical expert feedback, noting that younger patients were likely to be prioritised for treatment initially. The EAG's advisers concurred with this outlook – they would only be comfortable using exa-cel in the over 35s once mature outcome data were available from younger cohorts. One of the EAG's advisers commented that the upper age limit of 35 relates to the use of myeloablative conditioning, which is often not suitable for older patients. The EAG's other adviser stated that some older patients would not want to receive exa-cel, not only due to the risk of the procedure but for a variety of other reasons such as loss of identity as a patient with thalassaemia and distrust of health services (which may have been exacerbated by the pandemic).

Baseline characteristics

The submission stated that the population enrolled in CLIMB THAL-111 was considered highly generalisable to those expected to receive exa-cel in UK clinical practice.

The company noted in its submission that the severity of β-thalassaemia depends on the type of mutation in the β-globin gene with β^0 mutations resulting in a complete absence of β-globin production and β^+ refers to a mild reduction in the β-globin production. Table 7 indicates that just over half the patients recruited to CLIMB THAL-111 had a severe genotype (either β^0/β^0 or β^0/β^0-like). The EAG's clinical advisers noted that in an NHS population there would be more south Asian patients than would be seen in the CLIMB THAL-111 trial. Since IVS-I-5 mutations are quite common in thalassaemia patients of Indian or Pakistani descent, in a point for clarification (PFC) (Question A.8) the EAG requested that the company provide data on patients with IVS-I-5 mutations. The company stated that [redacted] patients in the FAS had an IVS-I-5 mutation, adding that exa-cel treatment resulted in transfusion independence in [redacted] patients past the transfusion washout period, with a range of [redacted], starting 60 days after the last transfusion for post-transplant support or disease management.

An EAG clinical adviser thought that the proportion of patients who had had a splenectomy (31%) seemed quite high for the age group being considered - in the NHS younger patients are much less likely to have had a splenectomy. Moreover, the CS stated (on p133) that "*Given the recent shift in treatment patterns away from splenectomising patients, the model base-case assumes the ongoing risk of splenectomy to be 0% for all patients, regardless of transfusion status*." The EAG's adviser stated that the risks of infection or thrombosis (when being given treatment) might be higher in hyposplenic patients. Splenectomised patients may need fewer blood transfusions, although splenectomy is also

associated with a higher prevalence of cardiovascular comorbidities and diabetes.[3] The EAG considers that this is unlikely to affect the transfusion independence and transfusion reduction (from pre-baseline) trial outcomes, it may affect the average number of transfusions and units of blood received prior to receiving exa-cel; for the CLIMB THAL-111 cohort the average number of transfusions and units of blood may be less than those for an NHS cohort, given the proportion of patients who have had a splenectomy. The CS noted that [redacted] had prior treatment with luspatercept (an anti-anaemic therapy), which is not available in the UK. This may also have reduced the transfusion burden slightly. Nevertheless, the EAG has concerns regarding whether the CLIMB THAL-111 trial cohort necessarily represents the best source of evidence to inform the number of transfusions used in the cost-effectiveness modelling. This is because an alternative data source, the Shah chart review, is based on a UK cohort and because the company's economic model uses the Shah Chart Review cohort to inform several other model parameters, including iron load, distribution of baseline complications and the distribution of iron chelation agents (see Section 4.2.4).

[redacted] had type 1 diabetes, [redacted] had type 2 diabetes and [redacted] had a history of osteoporosis (CSR p168).

Table 7 Baseline characteristics of patients recruited to the CLIMB THAL-111 trial (adapted from CS Table 15)

Baseline Characteristics	FAS (n=48)	PES (n=27)
Sex, n (%)		
Male	23 (47.9)	14 (51.9)
Female	25 (52.1)	13 (48.1)
Age at screening (years), n (%)		
Mean (SD) Min, Max	21.4 [redacted] 12, 35	21.8 [redacted] 12, 32
Age category at screening (years), n (%)		
≥12 and <18 years	16 (33.3)	5 (18.5)
≥18 and ≤35 years	32 (66.7)	22 (81.5)
Race, n (%)		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Not collected per local regulation	[redacted]	[redacted]
Other	[redacted]	[redacted]
Multiracial	[redacted]	[redacted]
Genotype, n (%)		
β^0/β^0-like	28 (58.3)	15 (55.6)
β^0/β^0	16 (33.3)	6 (22.2)
β^0/IVS-I-110	9 (18.8)	6 (22.2)
IVS-I-110/IVS-I-110	3 (6.3)	3 (11.1)
Non-β^0/β^0-like	20 (41.7)	12 (44.4)
β^+/β^+	[redacted]	[redacted]
β^+/β^0	[redacted]	[redacted]
β^E/β^0	[redacted]	[redacted]
Annualised volume of RBC transfusion (mL/kg)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Annualised units of RBC transfusion[a]		

Mean (SD)	35.3 [redacted]	36.7 [redacted]
Median	[redacted]	[redacted]
Annualised number of RBC transfusion episodes		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Total Hb concentration (g/dL)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
HbF concentration (g/dL)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Serum ferritin level (pmol/L)[b]		
Mean (SD)	[redacted]	[redacted]
Median, Min, Max	[redacted]	[redacted]
Cardiac T2* (msec)[c]		
Mean (SD)	[redacted]	[redacted]
Median, Min, Max	[redacted]	[redacted]
Liver iron concentration (mg/g)[d]		
Mean (SD)	[redacted]	[redacted]
Median, Min, Max	[redacted]	[redacted]
Weight (kg)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]

FAS Full Analysis Set, HbF foetal haemoglobin, PES Primary Efficacy Set, RBC red blood cell. [a] An RBC transfusion episode was defined as all transfusions within 5 days, starting from the first transfusion in the episode. [b] Serum ferritin level is the measurement of tissue iron content. Normal serum ferritin is ≤2,247 pmol/L according to UKTS 2016 guidelines. [c] Cardiac T2* is the measurement of cardiac iron content. Normal cardiac T2* score is >20ms according to UKTS 2016 guidelines. [d] Liver iron concentration was derived from Liver R2. Normal score is <7mg/day according to UKTS 2016 guidelines

3.2.1.3 Recruitment of patients into CLIMB THAL-111

The EAG asked the company to clarify details regarding patient numbers for the CLIMB THAL-111 trial's pre-enrolment stage. The company stated that [redacted].

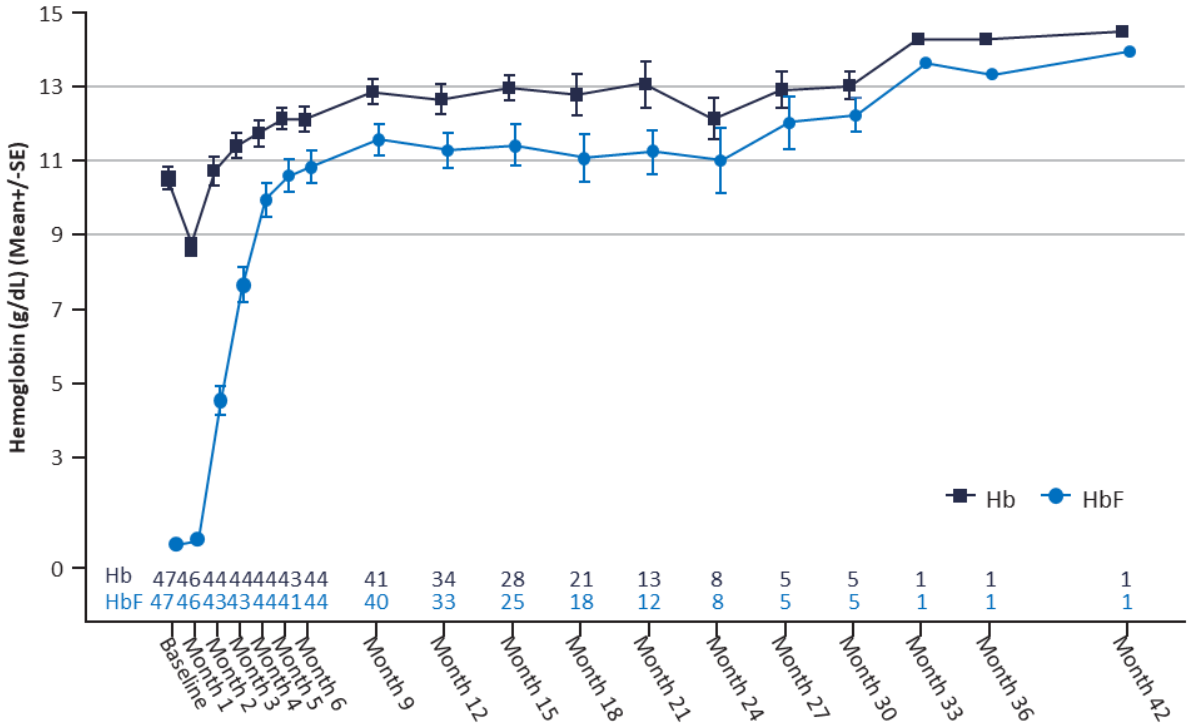
3.2.2 *Summary of key CLIMB THAL-111 efficacy results*

The CLIMB THAL-111 efficacy results were reported in Sections B.2.6 and B.2.7 of the CS. For the primary efficacy set cohort at data cut IA2, [redacted] at 12 months. [redacted].

Figure 16 in the CS (reproduced here as Figure 1) illustrates the increase in foetal haemoglobin (HbF) and total haemoglobin (Hb) over time. Clinical advisers on the company's advisory board indicated they would like to observe Hb levels of 11.5-12g/dL sustained over a 2-year period to be confident

that patients would not develop long-term complications;[4] The EAG's advisers agreed with this view. The EAG notes that it takes around 5-6 months for patients to reach and maintain near maximal levels of HbF.

Figure 1 Summary of total Hb (g/dL) and HbF (g/dL) levels over time (CLIMB THAL-111 and CLIMB-131)



Figures 18 and 19 in the CS presented data on the proportion of alleles with the intended genetic modification in CD34+ cells of the bone marrow and peripheral blood. The company stated that "*a high, stable proportion of alleles with the intended genetic modification was observed in both the CD34+ cells of the bone marrow and peripheral blood, indicating durable engraftment of edited long-term HSCs and reflecting the permanent nature of the intended edit*". The EAG is cautious in accepting the permanence of exa-cel engraftment in *all* patients, noting both the limited follow up available for the CLIMB THAL-111 cohort (median follow-up duration after exa-cel infusion was 16.7 months) and evidence on the existence of occasional very late relapses in β-thalassaemia major patients who have had an allogeneic SCT. A study by Santarone et al 2022 in an Italian cohort who had an allogeneic transplant indicated (in Figure 1b of the paper) that three of 137 patients had late recurrence of thalassaemia at around 9, 27 and 32 years respectively;[5] 13 patients died of transplant-related causes between day 12 and 212 post-transplant.

Figure 18 of the CS suggests that all patients still have some residual host cells present (i.e. 'mixed chimerism' exists), mostly at levels of between 10%-40% in bone marrow CD34+ cells. Although the EAG would accept an assumption that most mixed chimerisms are likely to remain persistent and

stable, with patients remaining transfusion independent, uncertainty remains regarding the factors which might lead to recurrence (e.g. whether there is a minimum level of modified cell chimerism required to prevent recurrence of β-thalassaemia).

An increase in LIC was observed following exa-cel infusion. Mean LIC at baseline was [redacted] mg/g in the FAS. After exa-cel infusion, LIC increased to a mean of [redacted] mg/g at Month 12 (n=[redacted]). At Month 24 (n=[redacted]), LIC remained above baseline levels at a mean of [redacted] mg/g. Cardiac iron levels were more stable following exa-cel infusion; the mean baseline cardiac T2* was [redacted] msec in the FAS, at month 12 (n=[redacted]), the mean was [redacted] msec and at month 24 (n=[redacted]), the mean was [redacted] msec. There was an increase in serum ferritin values after exa-cel infusion, although the levels subsequently decreased over time; by month 18 (n=[redacted]) the mean value was below the mean baseline value.

All patients received iron chelation agents before exa-cel infusion. After exa-cel infusion, iron chelation therapy for individuals was managed at the investigator's discretion though, if haematopoietic recovery was stable, chelation was recommended to be started as soon as possible >3 months (or >6 months for deferiprone) following infusion. Data on post exa-cel iron chelation use and/or phlebotomy was only available for the PES (n=27, i.e. all patients followed-up for at least 16 months after exa-cel infusion). [redacted] patients did not restart iron chelation therapy or receive phlebotomy after exa-cel infusion and were off such treatments for a mean of [redacted] months. Of the [redacted] patients who restarted iron chelation therapy/phlebotomy, [redacted] remained on their treatments and [redacted] subsequently stopped and were off treatment for a mean of [redacted] months.

The submission presented data indicating clinically-meaningful improvements in several health-related quality of life measures: EQ-5D-5L, EQ-VAS, FACT-BMT, FACT-G and BMTS (see CS, Tables 18-21). However, the company considered EQ-5D-5L to not be an effective tool for capturing the impact of transfusion-dependent β-thalassaemia on health related quality of life (HRQoL) and thought it may not be responsive to changes.

Although the trial subgroup analyses were limited by small sample sizes they nevertheless indicated a consistent effect across subgroups (age, genotype, and sex) for several outcomes, including: TI12, Total Hb levels, HbF levels and the proportion of alleles with intended genetic modification in CD34+ cells.

3.2.3 Safety results

Data on adverse events were reported in Section B.2.10 of the CS. Participants were administered busulfan for four consecutive days and exa-cel was infused between two to seven days after the last dose of busulfan. The most common grade 3 or 4 adverse events occurring after exa-cel infusion were [redacted]

[redacted] The CS stated that all common adverse events were consistent with myeloablative busulfan conditioning. The CLIMB THAL-111 CSR stated that [redacted]

Two patients (4%) had a SAE considered related, or possibly related, to exa-cel. One patient had SAEs of headache, haemophagocytic lymphohistiocytosis, and acute respiratory distress syndrome that were considered related or possibly related to exa-cel only, and one SAE of idiopathic pneumonia syndrome that was considered related to busulfan and possibly related to exa-cel. Another patient had SAEs of delayed engraftment and thrombocytopenia that were considered related or possibly related to both busulfan and exa-cel.

The availability of longer-term safety data was limited by the relatively short follow-up durations achieved so far in many patients (median 16.7 months). The company stated that exa-cel's mechanism of action (which utilises CRISPR/Cas9 gene-editing technology) eliminates the risk of insertional mutagenesis and transcriptional deregulation associated with viral vector-based gene therapies (i.e. the risk of treatment-related cancer was eliminated). The EAG's clinical advisers thought that although this was theoretically a reasonable statement, this level of safety should not be assumed so it is very important to keep the exa-cel safety data under ongoing review.

The longer-term data available so far for the outcome 'new or worsening hematologic disorders' from the CLIMB-131 long-term follow up study are presented in Table 8.

[redacted]

Table 8 Adverse events (any grade) of new or worsening hematologic disorders TDT safety set[1]

	n with event	N (total sample)	Proportion with adverse event
Before transfusion	[redacted]	[redacted]	[redacted]
Transfusion to month 24 visit	[redacted]	[redacted]	[redacted]
Enrolment to month 24 visit	[redacted]	[redacted]	[redacted]
After month 24 visit[2]	[redacted]	[redacted]	[redacted]

1. CLIMB -131 CSR, Table 14.3.2.5.1a, p. 2024 unless specified otherwise

2. CLIMB -131 CSR, Table 12-3, p.106

3.3 Critique of trials identified and included in the indirect comparison

The company conducted a feasibility assessment for its indirect comparison analyses. Relevant studies had to include patients with ages overlapping with CLIMB THAL-111 efficacy data and report a transfusion-related outcome. From its searches, the company identified three studies (in addition to CLIMB THAL-111): the BELIEVE trial of luspatercept versus placebo and two single-arm trials of the gene therapy beti-cel (Northstar-2 and Northstar-3). Given that neither beti-cel nor luspatercept were relevant comparators for the appraisal, the company performed only an indirect treatment comparison with standard of care (SoC), or established clinical management, which consisted of blood transfusions and iron chelation therapy. This was done using data from the placebo (plus SoC) arm of the 48-week, randomised, double-blind BELIEVE trial of luspatercept versus placebo. This trial's primary outcome was the percentage of patients who had a reduction in transfusion burden of at least 33% from baseline during weeks 13 through 24, plus a reduction of at least 2 red-cell units over this 12-week interval. 'Transfusion burden' was defined as the total number of red-cell units transfused.

3.4 Critique of the indirect comparison

The company only reported on transfusion independence as an outcome (not transfusion reduction) and reported that the re-weighted proportion of patients who were TI6 with exa-cel was [redacted] compared with no patients in the SoC group who were TI for at least three months. These results were highly predictable, given that transfusion independence at either three or six months was a clinically implausible outcome for patients taking placebo plus SoC. The EAG therefore thinks that the company could have more usefully directed its efforts to considering and discussing comparisons for transfusion reduction outcomes. Transfusion reduction is included as a relevant health state in the economic model and is a more plausible outcome for SoC patients (albeit for a small proportion).

The EAG notes that monthly relative reduction from baseline in blood transfusions was not reported as an outcome in the BELIEVE trial so a MAIC could not be conducted. However, it is worth noting that a small placebo response was observed for the transfusion reduction outcomes which were reported in the BELIEVE trial: 4.5% (5 of 112 placebo patients) had a reduction in transfusion burden of at least 33% from baseline during weeks 13 to 24, plus a reduction of at least 2 red-cell units; the figure was 3.6% during weeks 37 to 48. The results for a 50% reduction were 1.8% and 0.9%, at 13-24 weeks and 37-48 weeks, respectively.

In section B.3.3 of the CS the company stated that "*as evidenced in the SLR and ITC of clinical efficacy no TD patients on SoC can spontaneously revert to TI or TR without an active intervention*", and "*patients on SoC are therefore assumed to retain their baseline transfusion status, frequency and volume and iron distribution over the course of the model time horizon. This is of course a*

conservative assumption for the paediatric patients, whose transfusion and chelation requirements are likely to increase as they grow and reach adulthood." The EAG's adviser agreed that children would experience an increase in the volume of blood they receive as they age, though this would stabilise when they reach adulthood. However, given the above evidence from the BELIEVE trial, the EAG does not agree that all patients on SoC are assumed to retain their baseline transfusion status. A small number of placebo patients experience transfusion reduction at timepoints up to 70 months (after which trial treatment ended).

3.5 Conclusions of the clinical effectiveness section

The pivotal exa-cel single-arm trial (CLIMB THAL-111) recruited patients with a broad representation of genotypes and its results appear to have adequate applicability to the population likely to receive exa-cel in the NHS. Exa-cel is efficacious in allowing patients to achieve transfusion independence at 12 months, with *89%* of patients achieving this outcome. However, the CLIMB THAL-111 trial only recruited a small number of patients (n=*59*) and its results are still immature, so uncertainty exists regarding the proportion of patients who achieve successful engraftments and the longevity of exa-cel's effect in maintaining transfusion independence.

The EAG acknowledges the direct benefits of patients achieving TI, though notes that this represents only limited parts of the modelled benefits; the impact of TI on survival and onset of complications remains uncertain. There is also limited direct evidence to support an association between transfusion status and health-related quality of life. A limitation of the submission was that although the company's SLR sought to identify studies reporting iron-overload complication outcomes, survival and other outcomes relevant to the economic modelling, the synthesis presented (a MAIC) was entirely focussed on studies which reported transfusion-related outcomes. Consequently, no results data for the other relevant review outcomes were presented. The availability and appraisal of such data for studies of patients receiving SoC would have been very useful in this appraisal. The implication of this limitation is that the EAG has concerns about whether the most appropriate evidence has been used to represent SoC patients in the economic modelling.

The adverse event data available so far indicate that exa-cel has an acceptable short-medium term safety profile, with most of the safety issues relating to the well-known risks of myeloablative busulfan conditioning. The possibility of adverse events arising in the long-term as a consequence of mutagenic effects remains unknown.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The CS describes a systematic literature review (SLR) that was conducted to identify relevant economic evidence. The details of the methods and results of the SLR are reported in the CS, Appendix G.

4.1.1 Searches

A description of the searches and some of the search strategies used to identify cost-effectiveness studies for TDT were included in the CS, Appendix G, pp. 85-94.

In response to EAG's points for clarification (PfC), the company provided additional search strategies and some corrections to errors identified by the EAG.

Table 9 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE:
Is the report of the search clear and comprehensive?	NO	The search strategies provided in the original company submission could not be fully appraised as the documentation provided was not an accurate representation of how the strategies were input and run on each of the databases. In the PfCs, the company were asked to provide accurate copies of the exact searches run with correct details of limits applied, database indexing, segments used, dates searches were run, and correct number of hits per line, as there were also many mistakes in these aspects of the documentation. In response to this PfC, the company did not resubmit the strategies with corrected, accurate documentation. Therefore, the search strategies could not be fully appraised. The original company submission did not specify which of the 'Cochrane library' databases were searched and did not provide these strategies either. In the original company submission, no search strategies were provided for conference proceedings or any of the sources listed under 'following databases' on p. 87. This was raised as a PfC and the company provided these strategies in their response. However, the hits for conference proceedings are not shown in the PRISMA and the hits for the grey literature sources do not correspond with the PRISMA.
Were appropriate sources searched?	YES	A selection of relevant databases and conference proceedings were searched.
Was the timespan of the searches appropriate?	YES	The searches were not limited by date in the strategy, except for the Embase strategy (which was limited to 2013-2023, even though this is not referred to in the eligibility criteria).
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study type.
Were appropriate search terms used?	YES	Search terms for the condition were comprehensive, although the terms: TDT and transfusion dependent thalassemia were missed in all strategies.
Were any search restrictions applied appropriate?	NO	In the Medline strategy, the limits to humans and certain paper types applied on line 8 are risky and could have missed papers. In the Embase strategy, lines 6 and 7 would typically be removed from a search using the Boolean operator NOT. However, the strategy limits to these paper types (letters, editorials, commentary etc) and animal studies using the Boolean

		operator AND. In addition to limiting to these papers, the Embase strategy then applies further limits on line 10 (to the article types: article, article in press, review). It is unclear whether this is an error in the strategy that was run or the documentation only, as the company did not provide corrected, accurate documentation in their response to PfCs.
Were any search filters used validated and referenced?	PARTLY	Search filters were used but not referenced. It is therefore unclear if filters were validated.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

4.1.2 Inclusion/exclusion criteria used for study selection

The inclusion/exclusion criteria are summarised in the CS, Appendix G, Table 76 and follow the usual PICOS framework. In brief, the review included published economic analyses and cost and resource use studies of any treatment for patients with TDT. Outcomes were restricted to economic outcomes and included cost-effectiveness/utility analysis, incremental cost-effectiveness ratios (ICERs), discount rates, costs per annum, and resource use. No date limit was applied. Language restrictions required studies to be either published in English or to have English abstract/summary.

Two reviewers independently assessed the relevance of each study against the eligibility criteria. Any uncertainty regarding the inclusion of studies was resolved via consensus, with disagreements resolved by a third reviewer.

The EAG considers that the inclusion/exclusion criteria appear to be generally appropriate, although the EAG notes that the company's inclusion criteria covers both economic evaluations and resource use studies. These two study types have very different objectives and it is generally more appropriate for these reviews to be conducted separately.

4.1.3 Studies included and excluded in the cost effectiveness review

The CS presents a PRISMA flow diagram summarising the number of records included and removed at each stage of the review (Appendix G; Figure 34, CS).

A total of 6 studies were identified for inclusion in the review. This included three cost-effectiveness studies, two cost and resource burden studies and one NICE HTA document. The three identified cost-effectiveness studies evaluated alternative chelation agents and all considered a UK perspective. The NICE HTA document identified was the terminated appraisal of betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID968].[6] The EAG notes that two cost-effectiveness analyses identified in the ID968 appraisal: Delea et al. (2007)[7] and Pepe et al. (2017)[8] were not identified in the review; it is unclear why these were missed. The review also did not identify a US Institute for Clinical and Economic Review assessment (US ICER) of betibeglogene.[9, 10]

A high-level summary of the included studies is reported in CS, Appendix G, Table 76. However, the CS does not present an assessment of the appropriateness of the inputs and assumptions adopted in the studies identified in the review. The CS states that a critical appraisal was completed using the Drummond checklist; however, no quality assessment of the studies was reported as part of the CS.

4.1.3.1 Betibeglogene economic evaluations

Although the betibeglogene NICE appraisal[6] and US ICER assessment for betibeglogene[9, 10] do not provide direct evidence relevant to informing the cost-effectiveness of exa-cel, the EAG considers these existing economic evaluations to be relevant to the decision problem for treatments in TDT. The EAG presents a brief summary of both betibeglogene assessments, with a focus on highlighting the important similarities and differences between the approaches used in the company's *de novo* economic analysis and the economic evaluations of betibeglogene. The EAG also summarises the key committee considerations for the NICE appraisal of betibeglogene because many of the model parameters included in the company's analysis also formed part of the analysis for betibeglogene.

Comparison to exa-cel analysis

Table 10 presents a comparison of the betibeglogene and exa-cel economic analyses.

Table 10 Comparison of betibeglogene and exa-cel economic analysis

	Betibeglogene [ID968]	Betibeglogene US ICER	Current appraisal (exa-cel)
Model structure and drivers of costs and benefits	DICE simulation model based on transfusion status. Benefits are derived from patients achieving transfusion independence/reduction which directly improves quality of life and avoids costs associated with iron chelation. Reduction in complications associated with iron chelation leads to improved quality of life, longer life expectancy and avoids treatment costs.	Hybrid decision tree and Markov model. Decision tree used to establish whether patients successfully proceed to transfusion and transfusion status. Markov model developed for each transfusion status capturing the impact of iron overload related complications. Benefits are derived from patients achieving transfusion independence, which improves quality of life and avoids costs associated with iron chelation. Reduction in complications associated with iron chelation leads to improved quality of life, longer life expectancy and avoids treatment costs.	Markov model based on transfusion status. Benefits are derived from patients achieving transfusion independence/reduction which directly improves quality of life and avoids costs associated with iron chelation. Reduction in complications associated with iron chelation leads to improved quality of life, longer life expectancy and avoids treatment costs.
Time horizon	Life time	Life time	Life time
Discounting	1.5% company base case, scenario analysis exploring 3.5% discount rate. Evidence Review Group (ERG) and committee preferred a 3.5% discount rate	3% discount rate	1.5% company base case, scenario analysis exploring 3.5% discount rate.
Treatment waning effect	None. Assumes, 0% engraft failure and 0% relapse rate. ERG explored scenario analyses assuming non-zero rates of engraftment failure and relapse.	From year seven, 0.271% of patients reverted to transfusion dependent (TD) health state (with half the baseline frequency of transfusions per year) per year. This rate of reversion resulted in approximately 10% of patients reverting to TD by the end of the lifetime time horizon.	None. Assumes, 0% engraft failure and 0% relapse rate.
Mortality	Standardised mortality ratio (SMR) of 1.25 applied to transfusion independent patients. SMR of 3.9 applied to transfusion dependent patients. Mortality associated with cardiac complications modelled separately. ERG explored lower SMR of 2 which was preferred by the committee.	The base case risk of death from beti-cel infusion was 1.4%. SMR of 1.25 applied to transfusion independent patients. SMR of 3.9 applied to transfusion dependent patients. Mortality associated with cardiac complications modelled separately.	SMR of 1.25 applied to transfusion independent patients. SMR of 3.45 applied to transfusion dependent patients. Mortality associated with cardiac complications, and diabetes modelled separately.

Source of utilities	UK chart review (whole population; ERG and committee preferred to use age restricted sub group)	UK chart review (whole population), while other values based on published literature.	Vignettes in which health states were evaluated by the UK general public in a time trade off (TTO) exercise.
Resource use and costs	Betibeglogene administration costs were modelled using a micro costing approach. Distribution of chelation agents informed by UK chart review (whole population; ERG and committee preferred to use age restricted sub group). Costs associated with iron chelation complications informed by published literature.	The model included direct medical costs, including treatment acquisition and administration costs, treatment and condition related monitoring costs, and costs due to complications from iron overload (cardiac, liver, and endocrine complications).	Exa-cel administration costs were modelled using a micro costing approach. Distribution of chelation agents informed by UK chart review (whole population). Costs associated with iron chelation complications informed by published literature.
Severity modifier	Not applicable appraisal considered using 2013 NICE methods guide.	Not applicable.	Yes
DCEA	No	No	Yes, based in index of multiple deprivation

Committee recommendations

The NICE appraisal of betibeglogene autotemcel was discontinued following withdrawal of the technology by the company. This followed the issuing of draft guidance not recommending the use of betibeglogene. The published appraisal consultation document (ACD) outlines several committee considerations and preferences for model parameters, which share similarities to those included in the CS for exa-cel:

- Use the reference case discount rate for costs and benefits (3.5% per annum);
- Use the EAG's preferred approach to utilities, which implied a beta-thalassaemia related morbidity decrement of ~0.1 compared to the general population;
- Limit the UK Chart Review population data to match the population in the clinical-effectiveness data (see next section for further explanation);
- Set the time to normalisation for cardiac iron and liver iron to 5 years;
- Incorporate a non-zero mortality rate associated with myeloablative conditioning followed by betibeglogene autotemcel;
- Remove the utility impact associated with infertility from the model.

The EAG notes that the company's base-case analysis for exa-cel is inconsistent with all of the committee preferences stated above. At EAG points for clarification, the EAG requested information on why the company deviated from the committee's preferred judgements relating to model parameters that are relevant to the appraisal of exa-cel. The company response indicated that the appraisal of betibeglogene concerned a different technology, with a different mode of action and under different NICE guidance for the applicability of non-reference-case discounting. Consequently, the company stated that it is not relevant or appropriate to use the committee's preferred assumptions in appraisal ID968 as a benchmark against which to assess the assumptions used for exa-cel.

The EAG considers the company's argument invalid. The parallels between the two appraisals are very clear, as they both address gene therapies, with curative potential, for the treatment of TDT. Moreover, the company's economic analysis leans heavily on the betibeglogene model utilising a similar structure and uses many of the same input parameters particularly the UK chart review (see discussion below). The committee's preference for an annual 3.5% discount rate was a key theme of the company's advisory board meeting as documented in the supplied minutes. Importantly, while NICE methods guidance has subsequently been updated, the criteria for the application of the 1.5% discount rate are near identical with only minor differences in wording. Therefore, the EAG considers that the committee judgements made in ID968 are highly relevant to the current appraisal.

UK Chart Review

The Chart Review referred to in the previous section, was a retrospective chart review that documented healthcare management, clinical status and patient and carer-reported outcomes in a UK population of patients with TDT. The study was commissioned by Bluebird bio (the manufacturer of betibeglogene) and was used extensively to support the economic analysis presented in the betibeglogene appraisal. As noted above, the committee in the betibeglogene appraisal concluded that it was appropriate to limit the UK Chart Review population data to match the population in the clinical-effectiveness data. This reflected concerns that the population covered by the Chart Review did not match the population eligible for betibeglogene. Specifically, the Chart Review included patients under the age of 12 and over the age of 35, whereas the trial populations from which betibeglogene data were derived was limited to patients aged 12-35. The Chart Review has also been used to inform several parameters in the model presented as part of this appraisal where informs baseline iron levels, the distribution of iron chelation agents and several resource use parameters. The data used by the company in this appraisal is based on a subsequent publication (Shah et al. 2021).[11] Shah et al., however, only reports data for the whole population and not the optimised population preferred by the committee. At points for clarification stage, the company confirmed that they do not have access to the IPD from the Chart Review and therefore were unable to align with the committee preferences in the betibeglogene appraisal. The EAG is unable to fully assess the impact of using the whole Chart Review population because the data is redacted in the relevant committee papers; however, the EAG have provided comments on the likely impact of using the whole population wherever possible.

4.1.4 Conclusions of the cost effectiveness review

The CS did not identify any previous cost-effectiveness analyses assessing exa-cel. The company also did not make any statements as to the appropriateness of the studies identified for other interventions to inform the modelling of exa-cel. Although the EAG considers the company's model to provide the most relevant evidence for the cost-effectiveness of exa-cel, the NICE appraisal of betibeglogene provides an important basis for comparing key structural assumptions, data sources and parameter uncertainties.

The EAG 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. The EAG also note several evaluations were not identified in the company's review.

The EAG considers it unlikely that any studies which assess the cost-effectiveness of exa-cel in a TDT population have been published. The EAG consider the cost-effectiveness analysis reported in the CS to be the most relevant source of evidence to address the present decision problem.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 11 summarises the EAG's assessment of whether the company's economic evaluation meets NICE's reference case and other methodological recommendations.

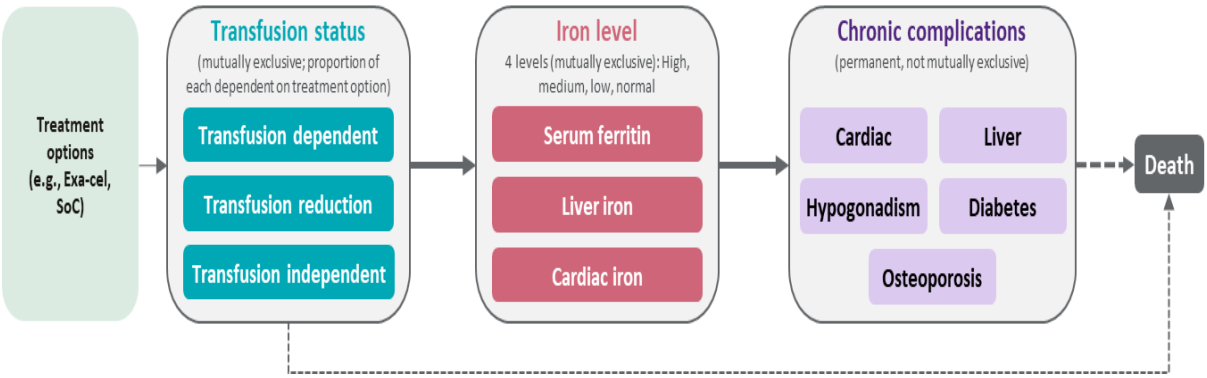
Table 11 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	Health effects from both patients and carers were included.
Perspective on costs	NHS and PSS.	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis.	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	The economic model had a lifetime horizon of up to 79 years. No patients were expected to be alive beyond this period.
Synthesis of evidence on health effects	Based on systematic review	Yes.
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.	Partial. Health states utility values were based on a time trade off (TTO) exercise reported in Matza et al. EQ-5D was not used.[12] Disutilities associated with complications were derived from published values. The EAG was however unable to identify the original sources used to generate the majority of decrements applied in the model. One exception to this was the decrement applied for diabetes which was based on EQ5D-5L.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No, utilities applied to health states were elicited using vignettes describing each health state.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	Utilities were elicited directly from members of the public.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No. QALYs were reweighted based on socioeconomic deprivation using a DCEA.
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.	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	No. A discount rate of 1.5% was applied for both costs and benefits. Scenario analysis considered a discount rate of 3.5%.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company developed a *de novo* Markov model in Microsoft Excel to estimate the lifetime cost-effectiveness of exa-cel for the treatment of TDT in patients 12 years of age and older for whom a HLA-matched related HSC donor is not available. The model compared exa-cel with standard of care, which comprises RBC transfusions and iron chelation therapy (ICT). Health states were determined by transfusion status, which drives patient iron levels, with an impact on complication risks, mortality, quality of life, as well as healthcare resource use and costs.

Figure 2 Model structure (Figure 20, CS)



The model consists of four mutually exclusive health states: transfusion independent (TI), transfusion reduced (TR), transfusion dependent (TD), and death. The model health states are determined by patient transfusion status, which drives patient iron levels and frequency of transfusions. A patient's iron level has an impact on complication risks from iron overload, which in turn determines mortality, quality of life, and health care resource use and costs. Iron levels are considered normal or abnormal (low, moderate or high) and based on SF, myocardial T2*, and LIC thresholds. All patients have abnormal iron levels at baseline and start in the TD health state. Patients receiving exa-cel can transition to the TR and TI health states. In the TI health state patients no longer receive RBC transfusions, and achieve iron normalisation after a fixed period following transfusion. A reduction in iron levels i.e., lower iron category from baseline, and RBC transfusions is assumed for patients in the TR health state. Patients with abnormal iron levels are assumed to receive full dose ICT until iron normalisation. To track time-to-iron normalisation following exa-cel treatment, several tunnel phases i.e., treatment phase (12 months), iron normalisation/change phase (48 months), and an ongoing phase, were included in the model time horizon. These model phases are not applicable to the SoC arm as SoC patients remain in the TD health state and do not experience changes to iron levels or reduced transfusions. The model uses a cycle length of one month, with half-cycle correction applied.

No treatment waning is assumed in the base case during the ongoing phase, therefore patient transfusion status and iron levels remain unchanged from the end of the iron normalisation/change phase until the end of the model horizon.

Patients enter the model at the point of exa-cel infusion, with pre-infusion costs and disutilities associated with transfusion applied once at model entry. The model assumes that patients remain in the TD health state with the same baseline iron levels until transfusion status is assessed at end of the treatment or response phase. Patients are also assumed to undergo premobilisation, mobilisation, and apheresis, myeloablative conditioning and infusion, and engraftment in the treatment phase.

4.2.2.1 Points for critique

Appropriateness of the Markov model approach

The EAG has significant concerns regarding the modelling approach adopted by the company. While the model structure used is superficially similar to the model used in the betibeglogene appraisal,[6] there are important differences in the modelling approaches adopted in the two appraisals. More specifically, the company employs a Markov model structure, whereas a patient-level simulation model was used in ID968.

The EAG considers this difference to be important in the context of treatments for patients with TDT. Markov models are aggregate-level models that define a limited number of mutually exclusive health states. They are most appropriate when disease progression can be captured within a small number of health states and where health state transitions do not depend on past states, or time spent in the current state. This contrasts with patient-level simulation models which are more flexible at tracking individual patients' unique characteristics, medical history, and response to treatments over time to determine appropriate transitions, costs and health-related quality of life.

TDT is a complex disease, and the EAG is concerned that a Markov model is not well suited to explicitly capturing the complicated dynamics of TDT without making significant simplifications that abstract from reality. The complications associated with TDT are particularly difficult to model using a Markov model structure and result in an overly complex model that inaccurately captures the burden of iron load related complications. This has important consequences for model outcomes, and the EAG does not consider the company's model suitable for decision-making. There are two main issues with the company's approach, which are described in detail below.

The EAG acknowledges that concerns were raised in the betibeglogene appraisal regarding the appropriateness of the model for decision-making.[6] However, the model critique in ID968 was related to the use of a DICE framework to implement the patient-level simulation model rather than the appropriate choice of model type. The EAG notes that it is possible to implement a patient-level simulation model in Excel without using the DICE framework. The EAG also notes that the US ICER assessment of betibeglogene[9, 10] used a Markov model approach; however, the model structure used in that assessment was simpler (and therefore more internally consistent for the choice of model type used) because it only modelled mortality associated with cardiac complications and did not attempt to

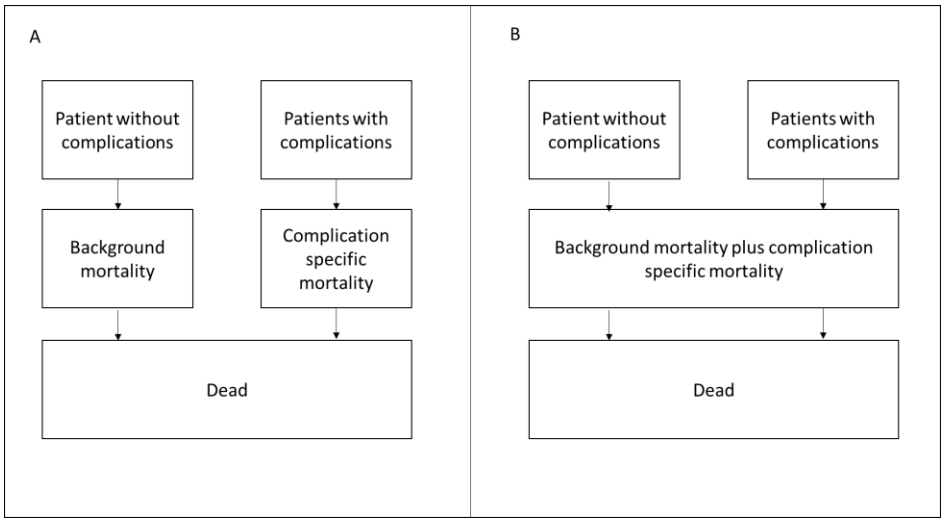
model multiple sources of complication-related mortality. Further, it is quite probable that the ICER model also suffers from at least some of the issues outlined below, though this is difficult to assess without access to the executable model.

Interaction between complications and mortality

The company's model attempts to track the overall proportion of patients with each complication (cardiac, liver, diabetes, hypogonadism and osteoporosis) within each health state. However, Markov models are unable to track individual patient history. Therefore, the company's model is forced to make several structural assumptions, which ultimately undermine the internal consistency of the model.

The most significant assumption is that a single mortality rate is modelled. This rate is a composite of general population mortality, excess mortality linked to transfusion status, and complication-related mortality. The EAG considers the application of a single mortality rate to lack face validity as it fails to correctly attribute mortality risks in the model and systematically leads to an over-accumulation of patients with complications, which, because mortality is a function of complication-related mortality, leads to a progressive overestimation of mortality in the whole cohort. Figure 1 attempts to illustrate this issue. Panel A describes a simplified, conceptualisation of how mortality should be calculated, while panel B presents how mortality is estimated in the company's model. The EAG has also illustrated this in a simple executable model, which we have provided to NICE, details of which are documented in Appendix 1.

Figure 3 Illustration of mortality calculations



The consequences of this issue are significant because the mortality rate associated with cardiac complications is very high (13% per annum). This leads to the model significantly underestimating life expectancy in both the exa-cel and SoC arms of the model, with implications for total QALYs. Furthermore, because the health state occupancy of complications is estimated incorrectly, the total

QALY loss and costs associated with complications are also incorrect. Moreover, because the model only tracks the overall proportion of patients and not the proportion of patients with each combination of complications, it incorrectly estimates the interactions between QALY loss and costs in patients who have multiple complications.

As stated above, this issue is a direct consequence of the company's use of a Markov model structure and the requirement to model multiple complications. Given that both cardiac and diabetes complications are associated with excess mortality, correctly estimating mortality requires that the proportion of patients with multiple complications is estimated. This cannot be achieved in a Markov framework without simplifying the model. For example, this could be done by modelling only one complication, or by assuming that complications are independent of mortality. Even with these simplifications, further assumptions about the disutility associated with individual complications are required because a Markov model cannot track which patients have multiple complications, without the introduction of excessive number of tunnel states.

Static distribution of iron levels

The model assumes a static and unchanging distribution of iron levels throughout the model time horizon, i.e. the same proportion of alive patients have low cardiac iron levels in cycle one as they do at the end of the model time horizon. This lacks face validity and misrepresents the impacts of iron overload-related complications. It is also inconsistent with the betibeglogene appraisal and US ICER models, where complication events were based on baseline iron load. The EAG recognises the complexity of accurately modelling the dynamics of iron levels and how they relate to complications. However, by assuming that the distribution of iron levels remains constant throughout the model time horizon fails to capture the link between iron levels, the onset of complications, and survival. Therefore, it does not capture the expectation that patients with higher iron levels will have lower life expectancy than those with low iron levels; under such circumstances, the distribution of iron levels will shift in favour of patients with lower iron levels through the model time horizon. This results in the model overestimating the risk of complications, particularly in the SoC arm, where patients do not experience iron normalisation.

This issue is linked to the mortality issue described above and is therefore a consequence of using the Markov model structure. Accurately tracking the relationships between iron levels, complications, and survival is computationally complex and impossible in a Markov model, which does not track individual patients. To make this tractable, the model assumes that iron levels are independent of mortality. This lacks face validity because patients with high levels are more likely to get complications and, consequently, are more likely to die.

Summary

The company's modelling approach is inconsistent with the complex dynamics of TDT and cannot explicitly capture the impact of complications on mortality, HRQoL and resource use. It is important to recognise that the issues identified by the EAG are not calculation errors. They cannot be "corrected" within the framework of a Markov model. The EAG outlines three options to address these underlying issues in Table 12 but notes that none of these options represent a perfect model and are all associated with limitations. For the purposes of the EAG base case, we have implemented Option 2, as it is the only option that is internally consistent within the Markov framework and could be implemented within the timelines of the appraisal process. This represents a significant simplification of the company's model and, importantly, does not capture the burden of complications on either individuals or the NHS. The EAG acknowledges that this model is likely to underestimate the value of exa-cel. However, unlike the company's model, it maintains internal consistency. Moreover, the direction of the bias is clear and, as such, can be accounted for in decision-making. Note when we implement options 2 in Section 6 this results in a decrease in the ICER. This is not an error. The company's approach to modelling mortality impacts both the exa-cel and SoC arms and results in the survival benefits associated with exa-cel being underestimated. In interpreting the results of the Option 2 is important to be clear that referent should not be the company's model but instead an internally consistent model that accurately captures the effect of complications on HRQoL and costs.

Table 12 Summary of alternative modelling approaches/structures

#	Summary of approach	Advantages	Disadvantage
1	Patient-level simulation model	• Consistent with the approach adopted in betibeglogene appraisal (ID968). • Can capture the complexities of TDT and reflect the impact of multiple iron overload related complications.	• Relies on a chain of evidence linking iron levels to the onset of complications, which is subject to considerable uncertainty because this evidence is unlikely to be available/limited in quantity (see discussion on surrogate outcomes in the next section). • Requires the consequences of complications to be captured, which is likely to be subject to considerable uncertainty. • Complex and time consuming to implement.
2	Markov model with no complications modelled.	• Simplified and transparent model structure. • Easy to implement in the current model.	• Systematically underestimates the burden of complications on patients with TDT. Likely to be biased in favour of SoC.
3	Markov model with one complication modelled.	• Retains the inherent simplicity of Markov modelling approach. • Captures some of the burden of complications. • Easier and quicker to implement than a patient-level simulation model.	• As with option 1, it relies on a chain of evidence to link iron levels with the onset of the modelled complication. • As with option 2, it systematically underestimates the burden of complications on patients with TDT, but to a less degree than option 2.

Surrogate relationship between transfusion status and final endpoints

An important feature of the economic analysis is that none of the final outcomes in the model such as survival, iron overload or onset of complications are informed by direct evidence from the trial. This reflects the short follow up in the single arm design of the CLIMB THAL-111 trial and the focus on intermediate outcomes. Instead, the model is structured around the chain of evidence linking intermediate outcomes, namely transfusion status, with final outcomes. The CS does not fully justify the implicit assumptions made in the model that transfusion status will positively impact on survival and the onset of complications, providing only limited indirect evidence based on risk equations used in the model. The EAG considers the lack of supporting evidence for a surrogate relationship between transfusion status and final outcomes to be an important omission and notes that the NICE methods manual states: "*When using 'final' clinical end points is not possible and data on other outcomes are used to infer the effect of the technology on mortality and health-related quality of life, evidence supporting the outcome relationship must be provided together with an explanation of how the relationship is quantified for use in modelling."*[13]

The EAG also highlights the reliance on surrogate relationships is an important area of uncertainty and that many of the claimed benefits of exa-cel rely on long chains of evidence. For example, a key claimed benefit of exa-cel is the avoidance of mortality associated with cardiac complications. This relies on a chain of evidence that links transfusion status to iron levels to cardiac complication risks to cardiac mortality. Each of these elements is subject to uncertainty and as such any inferences about how exa-cel impacts on cardiac related mortality are also subject to very high levels of uncertainty. This uncertainty is then further compounded by the use of multiple such chains of evidence. As such it is difficult to assess whether the predictions of the model are a realistic representation of the value of exa-cel to the NHS. This issue has an important bearing on the type of model used. As noted above, a patient-level simulation model would address the serious flaws in the current model structure, but it would be dependent upon multiple complex chains of evidence and as a result likely to represent a very opaque model. For this reason, the EAG considers that a simpler more abstract model structure has important advantages as it would reduce the need for long chains of evidence and as a result be more transparent to understand the direction of effects and implications for the cost-effectiveness of exa-cel.

Pre-transplant costs and treatment withdrawal from exa-cel

In the company's response to EAG points for clarification, the company stated that it typically takes 5-6 months from the cell cycle collection (apheresis) to patients being infused exa-cel and that some patients may require more than 1 round of apheresis, which must be spaced apart by several weeks. This represents a significant period of time, which is not explicitly accounted for in the economic analysis and in which patients may die, experience complications, or withdraw consent preventing

infusion with exa-cel. Patients who do not receive exa-cel will incur costs associated with treatment. The withdrawal rate of [redacted] is informed by the CLIMB THAL-111 trial in which 2 out of [redacted] patients did not proceed to infusion. Within the economic analysis it assumed that all patients withdraw in the period between mobilisation and conditioning and incur pre-transplant costs only, but not transplant-related costs or the acquisition costs associated with exa-cel. The EAG is, however, unclear if this fully captures the costs to the NHS and whether it is the company or the NHS who bears the cost of manufacturing exa-cel when patients withdraw or are otherwise ineligible for treatment after gene editing has been performed prior to infusion. As in precision medicine, edited cells are specific to an individual and cannot be reused. Therefore, patient withdrawal or ineligibility potentially represents a significant cost to the NHS. To explore this uncertainty the EAG presents scenario analysis in Section 6 assuming that [redacted] of insfusions would be wasted and chargeable to the NHS. Further clarity from the company and NHSE on the commercial arrangements in cases of withdrawal would be helpful in resolving this uncertainty.

4.2.3 Population

The modelled population included patients with TDT who are 12 years of age and older and are eligible for an autologous SCT without an HLA-matched donor. This population aligns fully with the marketing authorisation for exa-cel but it is narrower than that defined in the NICE scope, which does not define an age threshold. Section 2.2.3 provides further details on the population described in the licensed indication for exa-cel.

Table 29 of the CS summarises the baseline characteristics of the modelled population.

The age and gender of patients considered in the company's economic model are based on the 48 patients from the FAS of the CLIMB THAL-111 trial. This is inconsistent with the PES evaluable for transfusion independence from the CLIMB THAL-111 trial, which is used to inform the clinical effectiveness parameters. The EAG would expect the modelled patient characteristics to match the clinical effectiveness data used in the model. However, differences in patient characteristics between the FAS and PES are minor and do not have a material impact on the cost-effectiveness results.

Patient weight was estimated using data from CLIMB THAL-111 and data from the Health Survey for England.[14] The ratio of mean weight at baseline reported in CLIMB THAL-111 relative to a sex and age-matched UK population was estimated (0.76). This ratio was then applied to data from the Health Survey for England to inform changes in mean patient weight over the model time horizon. Patient weight was specified in the model in order to calculate the costs of chelating agents, which involve weight-based dosing.

The marketing authorisation for exa-cel describes that patients should be suitable for HSCT. This excludes patients with evidence of liver disease and patients with severely elevated cardiac iron (T2* <10 msec). The model, therefore, assumes that no patients have iron overload-related complications at baseline (although these may develop at a later stage). Other complications of TDT, including hypogonadism and splenectomy, were, however, modelled as non-zero at baseline and were informed by the FAS population of CLIMB THAL-111.

The model sought to account for the impact of myeloablative conditioning on infertility rates and, therefore, modelled arm-specific rates of infertility. In the SoC arm, infertility rates were assumed to match that of the general population and were informed by published values.[15] Patients treated with exa-cel were assumed to have elevated rates of infertility. This was estimated by applying a risk ratio of 1.24 in males and 1.57 in females. Risk ratios were informed by those applied in the betibeglogene appraisal.[6]

The baseline distribution of iron levels categorised patients into low, moderate, or high iron based on serum ferritin, LIC, and myocardial T2*. In contrast to the other modelled patient characteristics, the distribution of iron levels was informed by the Chart Review.[11] Scenario analysis using the CLIMB THAL-111 trial to inform the baseline distribution of iron levels was also presented in response to EAG points for clarification.

4.2.3.1 Points for critique

Patient weight

The EAG does not consider the modelling of patient weight to be valid. This is important because patient weight determines dose of ICT which makes up more than half of total costs associated with SoC. The EAG is concerned that the company's approach fails to recognise that a proportion of the patient cohort is from a paediatric population and, as such, is not fully grown. A constant ratio will not capture the growth effect. Moreover, the Health Survey for England data used to inform general population weight has several issues. Firstly, the Health Survey for England data only reports mean weight for broad age bands. The ratio estimated by the company is based on comparing the mean weight in CLIMB THAL-111 with the mean weight of people aged 16 to 24. This age band does not align with the age of patients in CLIMB THAL-111 (FAS population), which ranged between 12 and 35. The age distribution in each data set is also likely to be very different, likely near uniform in the Health Survey for England data and normally distributed in the CLIMB THAL-111 trial. Therefore, the estimated ratio is likely to be inaccurate. Secondly, the Health Survey for England data is a cross-sectional data set that reports on the mean weight of the current population by age. Associations between age and weight based on this data are therefore very likely to be confounded by the historical

attributes of previous generations, i.e. it does not reflect the fact that the population has gained weight over time.

The EAG believes that the company should have accounted for the fact that a proportion of the modelled population is under age 18. The EAG does not feel strongly about applying age-related trends in weight but considers this should ideally be informed by appropriate literature describing the relationship between age and weight rather than inferring such a relationship from a cross-sectional data set. The EAG cannot correct the calculations implemented by the company as it does not have access to the individual patient data from CLIMB THAL-111 with implications for ICT related costs. Moreover, the EAG is unclear on the likely direction of any bias, as this will depend on the distribution of patient weight across age groups in the trial.

Iron loading at baseline

The EAG considers the distribution of iron loading, derived from the Chart Review, to be broadly appropriate, notwithstanding the issues noted in Section 4.1.3.1 regarding the use of the whole population rather than the exa-cel eligible population. In the context of this specific set of inputs, it is not clear from the betibeglogene committee papers how baseline iron levels differed between the optimised and whole population. It is therefore not possible to comment on how this may impact the cost-effectiveness of exa-cel.

The EAG notes some differences between the distribution of iron levels reported in the Chart Review and the trial population; more patients in the Chart Review had high iron levels compared to the trial population (see Table 7 of Clarification response). The company attributed this difference to exclusion criteria applied in the trial, which excluded patients with high T2* and liver iron concentration at baseline. For this reason, the company do not consider it appropriate to use CLIMB-THAL-111 as a source of baseline iron levels and suggests that this would fail to capture the transition of TD patients to higher iron levels over their lifetime. The company also note that the mean age in CLIMB-THAL-111 is only three years younger than the Chart Review and consequently reflective of iron overload in a population eligible to receive exa-cel.

The EAG acknowledges that the trial exclusion criteria may be an important factor in explaining the difference in iron levels, but also notes that there is no specific reason to expect iron levels to vary by age, and any apparent relationship in the Chart Review population is likely to be confounded by changes in the management of iron overload complications over time. Given the limitations of using the whole Chart Review population, the CLIMB-THAL-111 trial represents a reasonable source of baseline iron levels. However, this remains an area of uncertainty in the model.

Iron overload-related complications

The modelled population excludes patients with osteoporosis and diabetes complications at baseline, despite the prevalence of these conditions being 10.4% and 6.3%, respectively in CLIMB THAL-111. The EAG requested justification for the exclusion of these complications at points for clarification. The company noted that the model only captures the cumulative incidence of complications and that prevalent cases could be treated and reversed following functional cure. As such, the company felt it more appropriate to capture only incident cases of osteoporosis. With regards to diabetes, the company considers the omission an error and confirms that 3/48 patients had baseline diabetes.

The EAG believes that osteoporosis and diabetes complications should be included in the model to reflect baseline comorbidities in the population. The EAG concurs with the company's assessment that modelling the treatment for a prevalent case of osteoporosis is not possible within the current model structure. The EAG, however, highlights that this is a direct consequence of using a Markov model rather than a patient-level simulation model. Importantly, it is also unclear whether treatment with exa-cel would permit the reversal of osteoporosis symptoms. The pathogenesis of beta-thalassemia-related osteoporosis is not well understood.[16] It is theorised to be the consequence of a multitude of factors, including inherent genetic factors, ineffective erythropoiesis, high iron levels, and low levels of vitamin D. Treatment with exa-cel may disrupt several of these pathological links but not necessarily all of them and therefore the impact of treatment with exa-cel on prevalent osteoporosis is not clear. With regards to the omission of baseline diabetes, the EAG notes that the company has not updated its base case results despite acknowledging this omission as an error.

4.2.4 Interventions and comparators

Exa -cel treatment

As explained in Section 2.2.1, exa-cel is a gene therapy and involves the transplantation of autologous CD34+ haematopoietic stem cells which have been transduced using CRISPR-Cas9 gene-editing to encode the BCL11A gene. Exa-cel is a personalised medicine and is produced from patients' own stem cells. The manufacturing process consists of a number of stages and begins with the harvesting of the patient's stem cells through a process known as leukapheresis. The harvested stem cells are then genetically engineered to produce the final cell product, exa-cel. Exa-cel is administered as a single intravenous infusion in a hospital setting after patients have undergone a busulfan conditioning regimen.

The duration of the manufacturing process for exa-cel is expected to take several months, and the company anticipate a period of 5-6 months from the cell cycle collection to patients being infused with exa-cel. During the manufacturing period, patients may require continued use of chelation agents to stabilise iron levels until they can be infused with exa-cel.

The minimum recommended dose of exa-cel is 3.0×10^6 CD34+ cells/kg. In cases where multiple rounds of mobilisations are required, patients receive more than one product lot of exa-cel, and these were administrated in succession and considered one dose. The base case analysis also includes the costs of plerixafor (0.24 mg/kg/day for 3 days) administered as part of the mobilisation procedure. Other drug costs including those associated with busulfan conditioning are assumed to be captured within the NHS reference cost, see Section 4.2.8 for further details.

Current standard of care

The comparator considered in the company's model is 'current care' for patients with TDT. This consists of regular RBC transfusions and ICT. The company used data from the CLIMB THAL-111 trial and the Chart Review[11] to define the management of standard of care (SoC) patients in the model.

Based on data from the CLIMB THAL-111 trial, SoC patients are modelled to receive 16.4 transfusions per year, with patients assumed to receive 2.2 units per infusion. At the points for clarification stage, the EAG noted that the modelled frequency of transfusions was substantially higher than that observed in the. Chart Review (16.4 vs. 13.7) and that total transfusion volumes also appeared to be higher (195.3mL/kg/year vs. 175.5 mL/kg/year). The company acknowledged in their response that the frequency of transfusions was higher in the CLIMB THAL-111 trial but justified this as the most appropriate source, noting that patients in the Chart Review may include patients with less serious diseases due to more severely affected patients with higher transfusion burden being more likely to opt for gene therapy. The company also noted that the Chart Review included older patients who may only have milder genotypes.

To determine the cost of chelation therapy, patients were allocated to either oral (deferasirox, deferiprone), subcutaneous (desferrioxamine) or a combination of oral and subcutaneous ICT 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 13).

Table 13 Distribution of chelating agents in the company model (Table 44, CS)

Iron chelator	Mode of Administration	Distribution in full Chart Review population n (%)
Deferasirox	Oral	94 (58%)
Deferiprone	Oral	11 (7%)
Desferrioxamine	Subcutaneous	23 (14%)
Deferiprone and Desferrioxamine	Oral and Subcutaneous	18 (11%)
Deferiprone and Deferasirox	Oral	8 (5%)
Deferasirox and Desferrioxamine	Oral and Subcutaneous	8 (5%)

At the clarification step, the EAG highlighted that the committee in the appraisal of betibeglogene [ID968] preferred to base the mix of iron chelation agents on a subgroup of the Chart Review population who matched the population eligible to receive the use of combination therapy (under 35's).[6] The company's response outlined that they could not use this subgroup of the Chart Review as they do not have access to the IPD. They further outlined that they consider the use of the whole population conservative because scenario analysis undertaken by the Evidence Review Group (ERG) in [ID968] demonstrated that using the optimised subgroup lowered the ICER for betibeglogene.[6]

4.2.4.1 Points for critique

The EAG considers the intervention as implemented in the economic model to be in line with the licence for exa-cel. The comparator, i.e. blood transfusions and iron chelation therapy, is appropriate and in line with current practice in this population.

Frequency of blood transfusions and volume of blood

The EAG considers the modelled number of transfusions to be uncertain and potentially higher than would be expected in a UK patient eligible for treatment with exa-cel. The company clarification response outlined several explanations as to why transfusion frequency may be higher in exa-cel treated patients compared to the broader TDT population. The EAG, however, considers these justifications to be largely speculative and there remains uncertainty about whether the CLIMB THAL-111 trial represents the best source of evidence to inform the number of transfusions in NHS practice.

While it is possible that the difference in transfusion frequency is a result of more severe patients opting for treatment, the EAG notes that the eligibility criteria for exa-cel already defines the population as those with more severe disease. Moreover, the reasons why specific patients opt for treatment are likely to be determined by a large number of factors personal to that patient, and it is unclear whether the severity of the disease would be a primary driver of the decision to undergo

treatment with exa-cel. The company also speculates that the inclusion of older patients biases the Chart Review data; however, no mechanism is described by the company whereby age could impact upon frequency of blood transfusions.

The EAG considers the strongest argument for using the CLIMB THAL-111 to be that it is internally consistent with the modelled population. There are, however, several reasons to prefer the Chart review. Firstly, the Chart Review is based on a UK population. Therefore, it is more likely to be representative of UK patients eligible for treatment with exa-cel. It is also consistent with the betibeglogene [ID968] appraisal.[6] Secondly, the model uses the Chart Review to inform several other model parameters, including iron load, distribution of baseline complications and the distribution of iron chelation agents. The use of the CLIMB THAL-111 for number of transfusions only is therefore inconsistent with the other data used in the model to characterise UK SoC. The EAG, therefore, on balance, prefers to use the Chart Review to inform infusion frequency, but notes the uncertainty in the most appropriate parameter values. The EAG also notes that the company declined to provide a scenario using the Chart Review due to it not reporting mean patient weight. The EAG does not consider this a significant barrier to using this data and provides a scenario analysis in Section 6.

Distribution of iron chelation agents

The EAG notes the company's response to clarification and agrees that the current position of using the whole population is reasonable given that the company do not have access to the necessary IPD data from the Chart Review. The ERG, in the betibeglogene appraisal, highlighted that a greater proportion of patients aged 12-35 were receiving combination therapy than the unrestricted whole population, which would tend to increase costs. Therefore, as noted by the company, the modelled distribution is likely to be conservative. Clinical advice to the EAG considered the distribution of iron chelation broadly reasonable, but noted that the modelled proportion of patients receiving subcutaneous deferoxamine was higher than expected based on their experience. They also noted that the proportion of patients receiving combination treatment was low, estimating that between 25% and 30% of patients would receive combination therapy.

The EAG considers that the use of combination therapy remains uncertain, obtaining further clinical perspectives on the use of combination iron chelation may be helpful.

4.2.5 Perspective, time horizon and discounting

Consistent with the NICE methods guide, the company's analysis adopted an NHS and Personal Social Services (NHS & PSS) perspective. The company used a lifetime horizon of 79 years (patients are followed until 100 years of age), which was considered sufficient to capture all relevant differences in costs and benefits between the comparators. The EAG consider this to be an appropriate time horizon, as it is unlikely that any patients would remain alive beyond this point.

The economic model presented in the CS used a non-reference case discount rate of 1.5% per annum for both costs and outcomes.

4.2.5.1 Points for critique

The EAG has significant concerns regarding the company's justification for the use of the non-reference case discount rate of 1.5% per annum. The NICE methods guide provides criteria for the application of the non-reference case 1.5% discount rate.

The company's justification for these criteria is discussed in turn below.

Exa-cel restores people who would otherwise die or have a very severely impaired life to full or near-full health

The EAG has significant concerns regarding the company's position that patients would otherwise die or have a severely impaired life.

It is the EAG's understanding that there is limited evidence available reporting the life expectancy of patients treated optimally with current management strategies. Given recent therapeutic advances in beta thalassemia, and the expected improvement in prognosis over time, estimates of life expectancy should be based on a cohort of patients who have received the current SoC. The improvements in the management of beta thalassaemia include the introduction of oral iron chelation agents, deferiprone and deferasirox, and the declining use of desferrioxamine. Given the importance of the mode of chelation agent on adherence and ultimately complications and survival, Weidlich 2016 reports that these advances are likely to have resulted in improved survival outcomes for patients with TDT.[17]

Existing studies that report the life expectancy of patients with beta thalassaemia often have limited follow-up and are largely based on cohorts of patients managed with different techniques and chelation agents. The company cites a 55-year expected life expectancy and a mortality rate five times that of the general population for the modelled population. [18-20] However, these sources suffer from a lack of follow-up and mortality is likely to be skewed by older patients who for a large part of their life have not received optimal care. The EAG notes that in the most recent edition of *Standards* published by the UK Thalassaemia Society, it is stated that patients are expected "to live a normal or near normal lifespan" and that "in the UK we now have a cohort of beta thalassaemia major patients who are approaching their sixties".[21] These statements, and the lack of generalisable survival data casts doubt on the claim that patients would "otherwise die".

The EAG also has concerns regarding the company's assertion that patients would otherwise have a severely impaired life because this is not supported by existing evidence. As stated in the CS, the baseline EQ-5D scores from the CLIMB THAL-111 trial are close to those reported for the UK

general population, i.e., 0.90 in the FAS compared to 0.93 in an age-matched UK general population. Other studies have reported similarly high EQ-5D values,[6, 22, 23] indicating that the disease is associated with only a modest decrement in health-related quality of life. and does not result in a "very severely impaired life" from the perspective of the patient. The company makes the argument that the EQ-5D instrument is inappropriate in this population for deriving health-related quality of life utility values due to a lack of content validity, potential for ceiling effects and does not adequately capture fatigue (discussed further in Section 4.2.7) and as a result argues that the full burden of disease is not captured by the EQ-5D. The company uses vignettes, elicited from the UK general population, to inform the health state utility values in the model, which indicate an approximate 0.2 decrement in utility for TD patients compared to the general population. As discussed in Section 4.2.7, the EAG considers that the company have not provided adequate evidence to support the assertion that the EQ-5D instrument is insufficient for deriving health-related quality of life in this patient population. Therefore, the evidence from the CLIMB THAL-111 trial and the wider literature indicates that this patient population do not consider their quality of life to be "severely impaired".

The EAG has concerns regarding the company's position that exa-cel restores patients to full or near-full health, both in terms of length and quality of life.

Firstly, for patients with pre-existing complications, developed as a result of TDT (e.g., cardiac or liver complications), these are unlikely to be reversible following treatment with exa-cel. Therefore, morbidity associated with the condition is likely to continue even if exa-cel represents a functional cure. The EAG notes that in the company's model, patients in the exa-cel arm are at a significantly higher risk of mortality than the general population. If there remains significant morbidity in treated patients, these patients cannot be considered to be restored to "full or near-full" health. In addition, as discussed in Section 4.2.6.2, direct evidence supporting the permanence of the treatment effect is lacking, and although indirect evidence and data from surrogate outcomes is supportive of a persistent treatment effect, the lack of direct evidence means that this is a key area of uncertainty.

"The benefits are likely to be sustained over a very long period"

As discussed in Section 3.2.2 and 4.2.6.2, the EAG notes that there is insufficient evidence to determine whether permanent long-term engraftment occurs and therefore whether the benefits are sustained over a long-term. Published evidence for engraftment failure in patients receiving allogeneic HSCT indicates that it typically occurs within 2 years of transplantation and that rates tend to be below (<10%).[5, 24]

The EAG considers there be uncertainty about whether the benefits of exa-cel are likely to be "*sustained over a very long period*". Follow-up data from the CLIMB THAL-111 trial will provide additional evidence.

Exa-cel will not commit the NHS to significant irrecoverable costs

The NICE guidance states that the "committee will need to be satisfied that any irrecoverable costs associated with the technology have been appropriately captured in the economic model or mitigated through commercial arrangements."

The EAG consider the [redacted] acquisition cost of exa-cel to be significant, and, potentially irrecoverable if the benefits of exa-cel are not realised. For example, if i) patients relapse at any point following treatment, the NHS will incur the cost of iron chelation therapy and transfusions; and ii) if there are delayed clinical problems associated with exa-cel treatment (or myeloablative conditioning) the NHS will bear the cost of resolution of these complications.

[redacted]

In conclusion, the EAG considers that insufficient evidence has been provided by the company to justify the application of the non-reference case 1.5% discount rate. It is also worth noting that in NICE appraisal of betibeglogene [ID968],[6] the committee agreed its preferred approach to use the reference case discount rate of 3.5% per annum for costs and benefits.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Transfusion dependence

The clinical effectiveness of exa-cel in the model is informed by the proportion of patients achieving transfusion independence. Transfusion independence is defined as those patients who are transfusion-free starting 60 days after the last RBC transfusion for post-transplant support or disease management. This was estimated from the CLIMB THAL-111 trial. This definition of transfusion independence is inconsistent with all primary and secondary outcomes pre-specified in the CLIMB THAL-111 trial and represents a post-hoc analysis of the trial data.

Of the 27 patients evaluable for TI status at the time of the submission, a total of 25 patients achieved TI (92.6%). Of the two patients who did not achieve TI, both experienced significantly reduced transfusions, requiring 87.6% fewer transfusions. The model assumes that the two patients who did not achieve TI were transfusion-reduced.

Points for critique

The EAG considers that the use of the post-hoc definition of transfusion status to lack justification. The pre-specification of outcomes in a trial is undertaken to prevent post-hoc analyses of data. The EAG notes that the definition of transfusion independence used to inform the economic analysis is less restrictive than the T12 primary outcome defined in the trial. The EAG specifically notes that this more relaxed definition employed in the economic analysis means that patient 002 is classified as transfusion independent despite not meeting the requirements of the T12 primary outcome. The proportion of patients achieving transfusion independence is a key driver of the model (as indicated by the company's deterministic sensitivity analysis; see Section 5.1.1.2), and so it is imperative that the model accurately reflects the supporting clinical data.

4.2.6.2 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 CLIMB THAL-111 trial. The model also assumes that there would be no loss of graft, i.e., no patient would lose their transfusion independence status, either by experiencing reduced haemoglobin levels or a return to transfusions, and that transfusion-reduced patients would not experience an increase in the need for transfusions or return to transfusion dependency over time.

Points for critique

The EAG considers the assumption of 100% initial engraftment success to be potentially over optimistic. The EAG considers it possible that initial engraftment failure is likely to occur in a small number of patients and the failure to observe any events in the CLIMB THAL-111 trial is indicative of its rarity, but does not necessarily indicate that none will occur in practice. The need to collect back-up cells for rescue treatment, acknowledges that such a risk exists. Furthermore, initial engraftment failure in patients treated with HSCT is well established with a recent publication estimating a rate of 6.9%.[24] The EAG explores applying non-zero rates of initial engraftment success in Section 6.

As discussed in Section 3.2.2 direct evidence supporting the permanence of engraftment is limited by the short trial follow up and therefore there is insufficient evidence to determine whether permanent long-term engraftment occurs. However, as of the IA1 data cut there are no recorded events of loss of transfusion independence. Evidence from surrogate makers also appear to be generally supportive of the persistence of the treatment effect, although it also remains limited by the short trial follow up. The company note increased and stable HbF as proportion of Hb as well as stable levels of the proportion of modified alleles in the bone marrow and peripheral blood are indicative of a permeant treatment effect. Indirect evidence from betibeglogene is also cited by the company; at 7 years follow

up all patients maintained their initial response to treatment with no loss of transfusion independence.[25]

The EAG considers that the base case assumption of a permanent treatment effect is reasonable given the evidence from the trial but it remains an important area of uncertainty given the limitations of the evidence base and its impact on the cost-effectiveness of exa-cel. The EAG notes that there is precedent for cure in TDT.Allogeneic HSCT is accepted as being a curative treatment but it is rarely used in older patients due to high mortality rates. While late engraftment failure is not unknown for patients receiving allogeneic HSCT,[5] published evidence indicates that engraftment failure typically occurs within 2 years of transplantation and that rates tend to be <10%.[5, 24] This is consistent with clinical expert advice received by the company which indicates that a sustained treatment effect at 2 years is indicative of long-term and permanent treatment effect. Follow-up data collected in CLIMB THAL-111 trial will provide more evidence to support this assumption. This uncertainty may also be resolved by an appropriately implemented managed access arrangement. The EAG explores uncertainty in the permanence of the treatment effect assumption in Section 6.

4.2.6.3 Organ-specific iron overload

Baseline levels of iron overload (discussed in Section 4.2.3) were based on the population studied in the Chart Review, and assumed patients were in one of three overload risk categories (low, medium, high risk) for the cardiac, liver and endocrine systems. As described in Section 4.2.2, 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 SoC arm, and the proportion of patients receiving exa-cel who remained transfusion dependent.

Transfusion-independent and reduced patients

Transfusion-independent patients were assumed to achieve normalised iron levels in all organ systems by four years from initial treatment with exa-cel. Since the evidence for long-term changes in iron levels following exa-cel is limited, the company assumed a normalisation period of 4 years based on clinical expert opinion. Patients who achieved meaningful transfusion reduction were also assumed to achieve reduced levels of iron and transition to the next lowest ferritin, T2* and LIC values (i.e., high to medium, medium to low) by the end of the normalisation period.

Points for critique

The EAG considers there to be limited evidence to support the modelled base case assumptions. There is limited direct evidence on iron levels from CLIMB THAL-111; follow-up is too short to draw inferences about how long iron normalisation may take. The EAG notes that in the betibeglogene appraisal [ID968] the committee concluded that the minimum iron-normal period should be 5 years for all organ systems.[6] Evidence on iron normalisation in patients who achieve transfusion

independence following betibeglogene suggest that there remained a number of patients with moderate to high levels at 48 months. The EAG considers that the evidence considered by the committee in ID968 is informative and represents the best available evidence to inform the iron normalisation period following treatment with exa-cel.

4.2.6.4 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 14. Risk equations were modelled for the following complications: cardiac, liver, osteoporosis, diabetes and hypogonadism. Based on clinical advice, the risk of splenectomy was assumed to be 0% reflecting a shift away from splenectomising patients in NHS practice. Risk equations were selected following a literature search and according to the generalisability of the study population to the model population as well as the appropriateness of the results to the model health states (i.e., iron level stratification).

Table 14 Predicting complications of iron overload (Table 32, CS)

Variable	Value	Reference
Cardiac: annual risk based on myocardial T2* level (%)		
Myocardial T2* Normal	0.26	Matched control cohort, UK BoI study [19, 20]
Myocardial T2* Low	1.12	Pepe et al., 2018 [26]
Myocardial T2* Moderate	1.88	Pepe et al., 2018 [26]
Myocardial T2* High	3.99	Pepe et al., 2018 [26]
Liver: annual risk based on LIC level (%)		
LIC Normal	[redacted]	Matched control cohort, UK BoI study [19, 20]
LIC Low	[redacted]	Matched control cohort, UK BoI study [19, 20]
LIC Moderate	[redacted]	Matched control cohort, UK BoI study [19, 20]
LIC High	8.5	Angelucci et al., 2002 [27]
Osteoporosis: monthly incidence rate in general (non-TDT) population (by gender and age group)		
Male		
< 30	0.0000225	Hippisley-Cox et al., 2009 [28]
30-34	0.0000450	
35-39	0.0000475	
40-44	0.0000475	
45-49	0.0000508	
50-54	0.0000600	
55-59	0.0000725	

60-64	0.0000883	
65-69	0.0001242	
70-74	0.0002117	
75+	0.0003625	
Female		
< 30	0.0000208	Hippisley-Cox et al., 2009 [28]
30-34	0.0000417	
35-39	0.0000517	
40-44	0.0000733	
45-49	0.0001100	
50-54	0.0001642	
55-59	0.0002250	
60-64	0.0003325	
65-69	0.0004767	
70-74	0.0006708	
75+	0.0010092	
Increased risk of osteoporosis by transfusion status: rate ratio		
TI	1.00	Assumed same as general (non-TDT) population
TR	[redacted]	Assumed average of TI and TD
TD	[redacted]	UK BoI study [19, 20]
Diabetes		
Annual risk for normal iron level		
When both serum ferritin and myocardial T2* are normal	[redacted]	Matched control cohort, UK BoI study [19, 20]
Risk equation (log-odds of 8-year risk) for non-normal iron levels		
Intercept	-8.019	Ang et al., 2014 [29]
Serum ferritin (moderate or high)	2.695	Ang et al., 2014 [29]
Myocardial T2* (moderate or high)	2.960	Ang et al., 2014 [29]
Age	0.095	Ang et al., 2014 [29]
Hypogonadism		
Annual risk for normal iron level		
When both serum ferritin and myocardial T2* are normal	[redacted]	Matched control cohort, UK BoI study [19, 20]
Risk equation (log-odds of 8-year risk) for non-normal iron levels		
Intercept	-4.422	Ang et al., 2014 [29]

Serum ferritin (high)	1.065	Ang et al., 2014 [29]
Myocardial T2* (moderate or high)	1.361	Ang et al., 2014 [29]
Age	0.095	Ang et al., 2014 [29]
Splenectomy: annual risk based on transfusion status		
TI	0.0%	Assumption
TR	0.0%	Assumption
TD	0.0%	Assumption

BoI: Burden of Illness

Points for critique

Accurately modelling complication rates

The EAG considers the broad approach to modelling iron complications appropriate and note that the same sources were used to populate both the models considered as part of the betibeglogene NICE appraisal[6] and US ICER assessment.[9, 10]

There are, however, a number of important limitations to the company's approach. Firstly, accurately modelling the ongoing risk of iron overload related complications is exceptionally challenging as there is limited data on both how iron load changes with time and age, as well how iron levels relate to the onset of complications. Secondly, an important limitation of the risk equations identified is that they do not reflect the cumulative risk of iron over-load and the risk equations are likely to reflect a long-term history of iron loading, beyond the period in which iron load was directly observed. The mechanisms by which iron levels relate to complication onset may be affected by a multitude of factors, which are not adequately explored. These may include evolving practice around the use of combination ICT, the frequency of monitoring visits and better management of adverse events, which lead to improvements in adherence rates. It is therefore unclear if the risk equations used in the model truly reflect the risks faced by current NHS patients.

The EAG considers the issue to be intractable and, while the company have done their best with the available evidence, this represents an important uncertainty with the current model. As described in Section 4.2.2, the EAG has fundamental concerns about the use of a Markov model. In reflecting on the appropriateness of alternative approaches it is important consider the inherent uncertainty in these risk equations. A patient-level simulation model would correct the issues outlined in Section 4.2.2 but would still be informed by the same risk equations for complications and, therefore, subject to the inherent uncertainty associated with them. Because of these uncertainties the EAG considers there to be a case for using a more simplified model that does not attempt to directly model iron overload related complications.

Pre-existing and irreversible damage

The company do not account for the long-term consequences of iron damage in patients who achieve transfusion independence and assume that patients who have normalised iron levels are no longer at risk of developing complications beyond background levels. While eligibility to receive exa-cel is conditional on the absence of iron-related complications, clinical advice to the EAG suggests that there may be a degree of pre-existing and irreversible iron overload-related damage in patients prior to treatment.

In the allo-HSCT population, occurrence of late hepatic, endocrine and cardiovascular complications related to past and residual iron overload have been acknowledged.[30] 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.[31, 32]

The long-term consequences of iron damage in patients who achieve transfusion independence remains an area of uncertainty, and it is possible that the elevated risk of mortality modelled for these patients captures only a proportion of the impact of complications that may occur.

4.2.6.5 Mortality

In the absence of direct long-term survival data for a TDT population after treatment with exa-cel, the company uses a range of external sources to predict long-term survival. To model mortality in each treatment arm, the company applied a standardised mortality rate (SMR) based on transfusion-dependency status to the age- and gender-matched general population mortality. Mortality following the development of cardiac complications and diabetes were accounted for in the model separately. As described in Section 4.2.2, mortality is modelled using a single mortality rate, which is a function of background (general population) mortality, disease related mortality (dependent on transfusion status) and complication specific mortality. This is achieved in the model by estimating the proportion of the cohort that will die from each source of mortality (background, disease related and complication related) and then multiplying these together to estimate the proportion of the cohort who die in each cycle. As discussed in Section 4.2.2, the EAG does not consider this 'averaging' approach to be appropriate as it does not attribute mortality to the correct patients within the cohort and consequently leads to significant underestimation of life-expectancy in the cohort.

Transfusion-independent mortality

To capture the potential mortality impact of myeloablative conditioning associated with the exa-cel procedure, TI patients in the model are assumed to have survival with slightly elevated mortality

compared to the general population This was achieved by applying a SMR of 1.25 to general population mortality rates. The SMR was not informed by literature-derived evidence due to insufficient evidence of the natural history following transplant in patients with thalassaemia. The SMR matches that assumed in ID968.[6]

Transfusion-dependent and reduced mortality

To capture disease related mortality not attributable to cardiac or diabetes complications, an SMR of 3.45 was applied to patients who are TD. The SMR was estimated by calibration to predict an SMR of 5.0 over the modelled time horizon, in order to align with literature identified the by company. [18-20] Full details of how the calibration of the model was undertaken are not included in the CS or executable model but it appears to have been conducted by comparing the cumulative survival in the SoC arm with that of the general population at the end of the model time horizon (last cycle of the model). The EAG were unable to replicate this calibration exercise and note that application of an SMR of 5, in the absence of complication specific mortality, results in a considerable increase in life-expectancy compared with the base case model predictions.

In the absence of a specific SMR for patients with reduced transfusions, the company assumed the mid-point of transition-dependent (3.45) and transfusion-independent (1.25), resulting in an SMR of 2.35 for the TR health state.

Complication related mortality

Cardiac and diabetes complications are assumed to be associated with complication specific mortality rates. Cardiac disease is assumed to be associated with an annual mortality rate of 13%,[33] based on a study of 52 patients with β-thalassaemia and heart failure. Diabetes is associated with an elevated mortality risk of 1.5 times that of the general population mortality rates, informed by data from the UK National Diabetes Audit.[34] As noted above and elsewhere, the rates are not applied in the model specifically to patients with that complication, but instead used to inform a single mortality rate applied to the whole cohort.

Points for critique

Mortality in transfusion-independent patients

The EAG considers it appropriate to model an elevated mortality for patients with TDT compared to the general population in order to capture the potential mortality impact of myeloablative conditioning associated with the exa-cel procedure. While there is no data available to determine the extent of this, the EAG considers that the SMR used by the company to be reasonable and aligns with assumptions accepted in ID968.

Mortality in transfusion-dependent patients

The EAG have a number of concerns surrounding the evidence presented in the CS to support the elevated mortality rates modelled, which are based on the company's own burden of illness (BoI) study (presented in slide deck format)[35] and published literature sponsored by Bluebird bio, the manufacturer of betibeglogene autotemcel.[18] No formal synthesis of peer-reviewed literature was performed by the company to support the modelled mortality rates.

The EAG considers that the studies used to model transfusion-dependent mortality are outdated and of limited generalisability to the present decision problem. Both studies include older patients and as such reflect historical practice. This is evident in the Jobanputra *et al.*[18] study where ~ 60% of the mortality events are recorded in patients who would be ineligible to receive exa-cel. Greater clinician experience, alongside improved monitoring and iron chelation practices observed over the last decade, means that iron levels in TDT are more likely to be well controlled, and TDT will have better mortality than is predicted by these older studies. Furthermore, patients in the current decision problem population would have lower iron levels and fewer iron overload-related complications than an unrestricted TDT population, with eligibility for exa-cel requiring patients to be sufficiently fit to undergo the procedure. In addition, the EAG notes that similar arguments and evidence was used to justify excess disease related mortality in ID968 and these arguments were rejected by both the ERG and committee in favour of a much lower SMR of 2.[6]

The EAG also highlights that there is no direct evidence to support a survival benefit for patients receiving exa-cel and that unlike patients receiving SoC, patients receiving exa-cel will be exposed to additional mortality risks due to the long-term effects of myeloablative conditioning. Given improvements in ICT and the serious long-term complications associated with myeloablative conditioning it is unclear to what extent exa-cel will result in substantial improvements in overall survival relative to SoC.

Complication related mortality rates

The EAG is concerned that the modelled rate of cardiac mortality of 13% per annum is excessively high and unlikely to reflect the mortality rate associated with cardiac complications in current NHS practice. The study used to justify this mortality rate was based on a historical cohort of patients treated in the mid-to-late 1990s.[33] The impact of both of oral chelation therapies and T2* cardiovascular magnetic resonance (CMR) for identifying myocardial siderosis means that outcomes reported in this study are unlikely to reflect current practice. The widespread application of T2* CMR rapidly changed the clinical management of cardiac complications, allowing direct visualisation of cardiac siderosis as a guide to the need for intensified iron chelation therapy and as a means of assessing response. These improvements in monitoring of cardiac symptoms have led to substantially

improved outcomes for patients developing cardiac complications and imply a mortality rate much lower than that adopted in the company's base case analysis.

The EAG is broadly satisfied with the source used to model diabetes related mortality, although it is important to highlight that the National Diabetes Audit[34] used to inform the SMR reflects the excess mortality risk in a non-TDT population. It is unclear if this excess risk observed in type I diabetes patients in general is transferable to a TDT population. The EAG also notes that a principle source of diabetes related mortality is from cardiac complications.[34] The application of both a cardiac specific mortality risk and a diabetes specific mortality risk is likely to double count the impact of each complication on mortality.

4.2.6.6 Adverse events of treatment

Adverse events specifically associated with exa-cel (Section 3.2.3), are not explicitly modelled as it is assumed that the cost impact of 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. Adverse events associated with ICT are also not modelled, and, the model assumes that each adverse event disutility is captured in the health state utility. Cost impacts of adverse events associated with ICT are not explicitly accounted for; however, the impact of this simplification is expected to be small.

Points for critique

The EAG is satisfied that the company's approach to modelling adverse events is appropriate.

4.2.7 Health related quality of life

The CS considers health-related quality of life (HRQoL) relating to (i) the health states of TI, TR and TD; (ii) disutilities associated with complications (cardiac, liver, diabetes, osteoporosis, hypogonadism, splenectomy and infertility); (iii) disutility associated with receiving subcutaneous ICT; and (iv) disutility associated with treatment with exa-cel in the transplant year. A disutility due to engraftment failure is not included in the base case analysis because the base case assumes no patients experience engraftment failure from exa-cel. An age- and gender-related utility adjustment is applied to health state utilities over the model time horizon to reflect decreases in HRQoL in the general population. Caregiver disutilities for patients up to the age of 26 is considered in a scenario analysis only.

The company conducted a systematic literature review to identify studies reporting HRQoL in patients aged ≥12 years with TDT (see Appendix H of CS). Fifteen studies were selected for data extraction. Of these, three studies reported EQ-5D-3L index scores, valued with a UK population tariff [Locatelli et al., 2022 (abstract only);[36] Javanbakht et al. 2015[22] for a population in Iran; and Shah et al. 2021,[11]

TDT Chart Review study], while one study used time trade off (TTO) methodology to elicit utilities from the UK general population for treatments associated with TDT, including pre- and post-stem cell transplantation (Matza et al. 2020,[12] TDT vignette study).

Despite the availability of EQ-5D data from CLIMB-THAL-111, the company argues that the EQ-5D instrument does not adequately capture the symptoms and experience of patients with TDT. Therefore, the company opted to use HRQoL values reported in the vignette study that used TTO interviews with members of the UK general population, unaffected by TDT, to inform health state utilities and ICT- and transplant-related disutilities. The company obtained values from the published literature to inform disutilities associated with complications considered in the model.

In the economic model, patients' HRQoL depends on their transfusion status, mode of ICT (oral vs. subcutaneous) and complications experienced. Utilities associated with patient transfusion status are applied as health state utilities. Base-case HRQoL inputs are summarised in Table 15.

Table 15: Summary of base-case HRQoL inputs (adapted from Table 36. CS)

Health state	Company base-case value	Assumption source
Transfusion status health utilities		
Transfusion independent (TI)	0.93	Matza et al. 2020 (vignette)[12]
Transfusion reduced (TR)	0.75	Matza et al. 2020 (vignette)[12]
Transfusion dependent (TD)	0.73	Matza et al. 2020 (vignette)[12]
Complication disutilities		
Cardiac	-0.11	Karnon 2012[37]
Liver	-0.11	Tsochatzis 2014[38]
Diabetes	-0.06	Jalkanen K., et al. 2019[39]
Osteoporosis	-0.08	Sawka et al. 2005[40]
Hypogonadism	-0.03	Assumption – half the disutility of diabetes
Splenectomy	0.00	Assumption
Infertility	-0.06	Krol et al. 2019[41]
Transplantation-related disutilities		
Treatment with Exa-cel in transplant year	-0.11	Matza et al. 2020 (vignette) [12]
ICT-related disutilities		
Oral ICT	0.00	Matza et al. 2020 (vignette)[12]
Subcutaneous ICT	-0.10	Matza et al. 2020 (vignette)[12]

4.2.7.1 Trial-based EQ-5D utility values

The EQ-5D-5L instrument was used in the CLIMB THAL-111 and CLIMB-THAL-131 trials to collect utility data. The company describe how this data was subsequently mapped to EQ-5D-3L, in

line with the NICE reference case; however, the number of patients providing data to month 24 after exa-cel infusion is limited (█ patients) and the company have not presented a scenario analysis using the EQ-5D data in the model, despite requests from the EAG at Points for Clarification (PfC 12b, Pf C 13).

The company noted that high baseline EQ-5D utility values were reported, 0.90 (n=32) in the FAS and 0.87 (n=22) in the PES of CLIMB THAL-111 and CLIMB-THAL-131, which the company states are greater than the average UK population score of 0.87 (CS, p88).

The company considers that the high baseline utility values reported in the trial are suggestive of "adaptation" by patients to their condition resulting in potential ceiling effects when examining the impact of Exa-cel on patients. The company describe how in a subset of eight patients in the PES with 24 months of follow-up, an increase in utility of 0.19 was observed, where this magnitude of gain is not possible in the remainder of patients due to higher baseline EQ-5D scores and corresponding ceiling effects.

Further, the company argue that the EQ-5D descriptive system lacks content validity in this population and as a result may not be responsive to changes in HRQoL. The company argue that the fluctuating nature of symptoms for patients at different points on the RBC transfusion cycle make it difficult for the EQ-5D to capture the impact of the condition on HRQoL, because the EQ-5D is collected at a single point in time. The company also suggest that the EQ-5D lacks a 'fatigue' domain, which the company suggests is an important symptom of TDT. The company conducted and presented a mixed methods study (presented in slide deck format) in support of their argument that the EQ-5D instrument does not capture the symptoms of TDT adequately. As a result, the company opted not to apply the EQ-5D data collected in the CLIMB trials in the economic model.

Points for critique

The EAG first notes that the preference in the NICE reference case for the measurement of HRQoL is to use the EQ-5D measurement instrument to ensure consistency across NICE evaluations. In circumstances where the EQ-5D is considered to be inappropriate, the NICE manual states that qualitative empirical evidence on the lack of content validity for the EQ-5D, showing that key dimensions of health are missing, is required and that this should be supported by evidence showing that the EQ-5D performs poorly on construct validity and responsiveness based on a synthesis of peer-reviewed literature.

The EAG have a number of concerns surrounding the evidence presented in the CS to support the company's argument that the EQ-5D is inappropriate in this patient population. No formal synthesis of peer-reviewed literature was performed by the company to support the assertion that the EQ-5D is

unresponsive to the symptoms of TDT. Instead, the company refer to their own mixed methods study (presented in slide deck format),[42] which evaluates the appropriateness of the EQ-5D-5L descriptive system (DS) in adults with TDT. The EAG considers that the mixed methods study presented by the company to be insufficient justification for their argument. First, the methodology underpinning the study is unclear. In particular, the study claims that the EQ-5D-5L DS did not capture 11 out of 16 (68.8%) symptoms using a 'concept mapping' approach through interviews with adults with TDT (n=30). However, the methodology and criteria used to classify each of these symptoms is unclear and not reported in the slide deck. Second, the 11 dimensions of health reported as missing from the EQ-5D are heart palpitations, shortness of breath, dizziness, weakness, sleep problems, concentration difficulties, reduced appetite, relationships and, with partial coverage, fatigue, time and planning, and emotional wellbeing, which the EAG considers to represent limited evidence of missing dimensions from the EQ-5D as most of these symptoms are attributable to most chronic conditions with fluctuating symptoms. Third, the company states that the most significant contributor to poor quality of life in TDT is fatigue, which is not captured by the EQ-5D; however, the EAG considers that fatigue is partially represented by the 'usual activities' domain of the EQ-5D DS and is a key symptom of most chronic conditions. Fourth, the company states that the EQ-5D-5L DS lacks the capacity to capture fluctuating symptoms that are highly dependent on where patients are in their RBCT cycle (given the recall period of "today" in the EQ-5D-5L DS); however, the EAG notes that the mixed methods study describes how participants completed the EQ-5D twice – first, based on a typical day when they felt at their worst and second, based on a typical day when they felt at their best. The EAG would expect to see presentation of the difference in EQ-5D responses for these two extreme health states to support the assertion that quality of life differs significantly depending on where the patient is in their RBCT cycle, but this data has not been presented by the company. Therefore, overall, the EAG considers the mixed methods study by the company to provide relatively weak evidence of the lack of content validity for the EQ-5D.

The company's main argument against the use of EQ-5D data appears to lie with the high baseline EQ-5D values reported for participants in clinical trials of TDT, which is expected to lead to ceiling effects for the increase in HRQoL following treatment with exa-cel. The high baseline values are reported to be a result of the fact that TDT is an inherited condition, the symptoms of which are experienced from early childhood, and patients 'adapt' to their condition with time. The EAG notes that the finding of high baseline EQ-5D values in the TDT population is consistent with the betibeglogene trials and other studies that have reported EQ-5D values in this population (Javanbakht 2015, Seyedifar 2016).[22, 23] However, the EAG notes that the company have not presented sufficient evidence from CLIMB-THAL-111 and CLIMB-THAL-131 to demonstrate the inappropriateness of the EQ-5D measure to adaptation and ceiling effects. The CS only presents EQ-5D data from a subset of patients in CLIMB-THAL-111 and no evidence of ceiling effects in this subset of patients. The

mean utility value in the subset of 8 patients at 24 months following exa-cel infusion is 0.96, which represents a utility gain of 0.19, suggesting a mean baseline utility score of 0.77 for this subset of patients. The company states that this utility gain of 0.19 applied to the average baseline utility score in the PES population (n=22) of the trial of 0.87 would result in a ceiling effect on the utility gain from treatment. The EAG considers that there may be differences in patient characteristics, or history of symptoms, that could explain the variation in baseline scores between this subset of patients and the remainder of the PES population. For example, this subset of patients may represent a subpopulation with more severely impaired HRQoL (hence, their lower average baseline utility value) and therefore may be expected to gain more from treatment in terms of improvements in HRQoL and willingness to undergo transplantation. Importantly, the company have not presented any evidence to demonstrate that the magnitude of utility gain of 0.19 from exa-cel at month 24 would be expected to be similar in the remaining patients, who have a higher average baseline utility value before treatment, in order to justify the concerns about ceiling effects. In response to EAG points for clarification (PfC B12b), the company states that the "*baseline age of these* 8 *patients is unknown*", leaving open the possibility that this subset of patients may differ according to their baseline characteristics such as age. Furthermore, the company states that the average baseline EQ-5D utility value from the trial population is greater than the average UK population score of 0.87 (CS, p88). However, the EAG notes that the age- and gender-matched population utility value for the average trial population age of 21.4 years old and 52.1% female that is used in the model is 0.940 (Ara and Brazier 2010), which represents a difference of [redacted] from the trial mean baseline value of 0.87 in the PES of CLIMB THAL-111 and CLIMB-THAL-131, indicating a modest decrement in utility associated with TDT before exa-cel infusion.

Despite requests from the EAG at points for clarification (PfC 12b, PfC 13), no scenario analysis has been implemented using the EQ-5D utility values from the trial. As a result, it is unclear how use of vignettes, valued by samples of the general population rather than patients with TDT, impacts the cost-effectiveness results compared to EQ-5D utility values reported by patients with TDT.

4.2.7.2 Health state utility values

The company used a published vignette study (Matza et al.)[12] to inform the health state utility values for TI, TR and TD in the model. This study used TTO interviews with members of the general population in England, unaffected by TDT (n=207, mean age = 43.2 years), to elicit utility values in TDT pre- and post-transplant for gene addition therapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT) and allo-HSCT with acute graft-versus-host disease (GvHD). Participants were asked to value eight hypothetical health states (or 'vignettes') using the TTO methodology, where each vignette described the relevant treatment processes including the ongoing cycle of

transfusion and iron chelation, as well as health states describing patients with TDT pre- or post-transplant.

The study reported a TDT pre-transplant mean utility value of 0.73 for individuals managed with ongoing transfusion and iron oral chelation therapy, and 0.63 for subcutaneous chelation – the difference between these values (0.10) was used in the company's model to represent the decrement associated with subcutaneous ICT vs. oral ICT in the model. During the transplant year, a mean utility value of 0.62 was reported for gene therapy, which the company used in the model to represent a 0.11 decrement in utility associated with transplant in the year of exa-cel. Post-transplant mean utility values of 0.93 and 0.75 were reported for transfusion independent and 60% transfusion reduction, respectively. Therefore, the company used the values of 0.93 and 0.75 to represent the utility values associated with the TI and TR health states in the model, respectively. The pre-transplant mean utility value of 0.73 was used to represent the TD health state in the model.

The company states that the TI post-transplant utility value aligns with the UK general population norm for the 18-24-year-old age group (0.93) and is supported by the literature that reports SCT-treated TDT patients report HRQoL close to that of the general population.

Points for critique

The EAG's key concern relates to the appropriateness of using vignettes, valued by a sample of the general population, as the main source of utility values used in the model. In the NICE manual, when evidence shows that EQ-5D is not appropriate, the hierarchy of preferred HRQoL methods is other generic preference-based measures of HRQoL, elicited directly from patients, followed by condition-specific preference-based measures elicited directly from patients, and only after that the use of vignettes, which should be developed using the 2020 DSU report on best practice recommendations (Rowen et al. 2020)[43] and valued by a sample of the general population using an appropriate preference elicitation technique. The Matza et al.[12] vignette study uses an appropriate preference elicitation technique of TTO, but it does not follow the DSU best practice recommendations, which were published after the vignette study was conducted. The EAG notes that one of the DSU best practice recommendations for vignettes is that in the formulation of vignette descriptions, investigators "should not use value-laden or irrelevant phrases or content (such as 'devastating')". However, the EAG notes that in the description of vignettes provided by Matza et al.,[12] the pre-transplant state description reads "*Without regular blood transfusions, this disease would be fatal*", which the EAG considers to be a value-laden description. Importantly, the NICE manual states that, in the event that alternative HRQoL measures are used, these "*must be accompanied by a carefully detailed account of the methods used to generate the data, their validity, and how these methods affect the utility values*", which is not presented in the CS. The company justifies the choice of Matza et al.[12] on the basis that it was the only study identified in the literature search that valued health states for

TDT relevant to treatment with curative therapies, which the company considers to be most relevant to exa-cel, and it provides lower utility values than observed in the CLIMB THAL-111 study. The EAG notes that the vignette study was not used as the source of utility values in the NICE appraisal of betibeglogene for treating TDT because the company considered that patient-elicited utility values were more appropriate for inclusion in the model.[6] Importantly, the use of vignettes to compensate for inadequate evidence generation introduces unnecessary uncertainty into the appraisal.

The utility values reported from the vignettes do follow a logical pattern, with higher utility values for post-transplant TI and TR compared to TDT pre-transplant, and a higher utility value for oral ICT compared to subcutaneous ICT; however, the EAG considers that the magnitude of the impact of transplant on the utility values derived from the vignettes is impossible to assess without reference to other findings, such as the EQ-5D utility values from the trials. Given that the TI post-transplant utility value (0.93) from the vignettes aligns quite closely with the general population norm for the average age and gender used in the model (0.94), the EAG considers that a utility decrement of [redacted] for the trial population at baseline (0.87) appears plausible and not an insubstantial decrement associated with TDT before exa-cel infusion; therefore, it may not be reasonable for the company to dismiss the patient-derived EQ-5D baseline values from the trial. The EAG also notes that a utility decrement of about 0.1 compared with general population values for the age group 12 to 35 years was favoured by the committee in the NICE appraisal of betibeglogene for treating TDT.[6] The EAG considers the application of the utility for the treatment year appropriate and in line with the magnitude of disutility applied in the NICE appraisal of betibeglogene.

The key driver of HRQoL in the model is the utility value applied to the post-transplant TI health state relative to the pre-transplant TD health state because all patients are TD at model entry and response to treatment is assessed based on transfusion status. The company's base case analysis assumes a utility decrement of 0.2 for TD relative to TI based on the findings of the vignettes. The EAG considers a utility decrement of [redacted] for TD based on the trial population at baseline to be plausible and not dissimilar to the decrement of about 0.1 used in the NICE appraisal of betibeglogene.[6] In Section 6, the EAG considers a range of scenarios for utility decrements of 0.15, 0.1 and [redacted] for TD relative to TI in order to assess the impact of this highly uncertain, but critical parameter, on the cost-effectiveness results.

4.2.7.3 Utility decrements associated with complications

The company captures disutilities associated with complications by applying separate decrements to each of the broad categories of complications considered in the model: cardiac, liver, osteoporosis, diabetes, hypogonadism, and infertility associated with myeloablative conditioning (see Table 3 above for a summary of the utility decrements).

A disutility of 0.114 was used for cardiac complications, which was sourced from a cost-utility analysis by Karnon et al. (2012),[44] based on a 1993 study by Fryback et al.[45] This study comprised TTO interviews with 1,356 people from a single US town between 1988 and 1990. For liver complications, a disutility of 0.11 was used, which was sourced from Tsochatzis et al. (2014)[38] that cites Wright et al. (2006);[46] however, the company provided insufficient information for the EAG to determine the exact source of the data. A decrement of 0.06 was used to represent the disutility associated with diabetes, which was sourced form Jalkanen et al. (2019)[39] on the impact of type 2 diabetes treated with non-insulin medication and number of diabetes-coexisting diseases on EQ-5D-5L index scores in the Finnish population, and weighted according to the proportion of patients with coexisting morbidities from Jobanputra et al. (2020).[18] For osteoporosis, a decrement of 0.08 was sourced from Sawka et al. (2005),[40] which reports quality of life measurements in an elderly population in Canada. For hypogonadism, a decrement of 0.03 was assumed, based on half the disutility associated with diabetes.

The company used a decrement of 0.06 to represent the disutility associated with infertility, which was sourced from Krol et al. (2019)[41] and applied in the model over a fertile age of between 16 and 51 years. Krol et al.[41] present utility weights reported by respondents from the Dutch general population (n=767) using a visual analogue and TTO method; however, the CS does not provide sufficient information to determine how this decrement was derived and the EAG is unable to identify the value in Krol et al (2019).[41] The upper bound of the fertile age range considered by the company was based on the average age of menopause in women in the UK reported by the British Menopause Society.[47] The lower bound was based on the minimum age of respondents to a cross-sectional population survey, investigating the prevalence of infertility in the UK.

Points for critique

The EAG first notes that the company have provided very limited information on how the decrements associated with complications were derived. A systematic literature review was not undertaken to identify the values. The values appear to have been selected arbitrarily from different sources, with no justification for their use over other published values in the literature, or no synthesis of available data. Furthermore, the source of utility values for each of the broad categories of complications are based on non-UK data. The EAG considers the utility decrements associated with complications to be highly uncertain and not adequately justified. The utility decrements for complications are a relatively small driver of the cost-effectiveness results compared to the utility decrement associated with TD (vs TI), but are responsible for a difference in approximately [redacted] between exa-cel and SoC in the company's base case results, which the EAG considers not an insubstantial difference that is highly uncertain. Moreover, because the company's model structure does not track patient history for the onset of complications over time, and treats all complications as independent events, the model

overestimates the risk of complications and, therefore, the magnitude of HRQoL impact associated with complications.

In line with committee preference for NICE appraisal of betibeglogene, the EAG questions the appropriateness of including a utility decrement for infertility in the base case analysis.[6] The impact of infertility 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 from associated co-morbidities and underlying causes. The CS also provides insufficient information for the EAG to verify the source of the utility decrement for infertility. The lower 'age of fertility' bound also raises the question of whether a 16-year-old would consider their HRQoL to be impaired by infertility concerns. In addition, it cannot be assumed that all individuals incur an equal decrement associated with infertility. The EAG notes that the committee's preference in ID968 was to remove the impact of infertility on HRQoL from the model. Given the uncertainties, the EAG explores the impact of removing the infertility-related utility decrement from the cost-effectiveness results in Section 6.

4.2.7.4 Utility adjustment for age

Age-adjusted utility decrements were derived using general population UK data from Ara and Brazier (2010) and applied additively per cycle.

Points for critique

The EAG considers the source used for the age-adjusted utility decrements to be appropriate, given that it is used extensively in previous NICE technology appraisals, but notes that the company applied these additively per cycle rather than using multiplicatively approach. The multiplicative method for age adjustment is recommended in NICE DSU guidance[48] and is specified as the preferred approach in the NICE methods guide.[13]

4.2.8 Resources and costs

The costs included in the model comprise: i) treatment-related costs, including exa-cel acquisition, mobilisation, and ongoing monitoring; ii) blood transfusion and chelation costs; iii) ongoing state-dependent disease management costs; iv) complication-related costs; v) adverse event costs; and vi) terminal care costs.

Costs were obtained from a number of sources, including NHS Reference Costs, British National Formulary (BNF), and from Drugs and Pharmaceutical Electronic Market Information Tool (eMIT). A summary of the base case inputs is described in Table 16 below. Full details on base-case cost inputs are described in the CS, Section B.3.5 (Tables 37 – 40).

Treatment acquisition costs are applied to all patients assigned to exa-cel at the beginning of the model. In addition to the acquisition cost of exa-cel ([redacted]), costs related to pre-mobilisation, mobilisation, and hospital costs are applied. The company's base case does not explicitly consider costs related to myeloablative conditioning but instead assumes that these are included in the NHS tariff for SA26A and SA26B, a tariff for autologous-SCT which the company assumes to represent the cost associated with exa-cel delivery (£26,602). In the CS, the company argues that the resources required for delivery of exa-cel are likely to be similar to those required for autologous-SCT and CAR-T therapies. The company states that only auto-SCT have published reference costs and therefore the company opted to use this cost in the model. Post-treatment monitoring costs are applied annually until year 15 following treatment. Patients are assumed to undergo phlebotomy throughout the normalisation/change phase. Fertility preservation costs are included in pre-mobilisation costs.

The cost associated with blood transfusions are based on NHS reference costs for packed RBC infusions and administration cost per RBC procedure. These reference costs are applied in the model based on the blood quantities derived from the CLIMB THAL-111 FAS population. Costs related to ICT depend on the mode of administration and are weighted by age-dependent weight-inputs in the model. Patients receive a full dose of ICT in the treatment/response phase of the model, regardless of transfusion status, and in the ongoing phase among those patients in the TD and TR health states.

Ongoing state-dependent disease management costs are applied in the model to account for complications related to iron overload and other costs associated with the disease. Unit costs associated with emergency room, inpatient, and outpatient visits are based on the weighted average of 2022/2023 NHS reference costs for SA11Z and applied to state dependent HRU weights for each cost item. The company describe how HRU weights associated with the TI health state are based on expert opinion, while the weights used for the TD health state are based on the Shah Chart Review,[11] which reported HRU values for TDT patients in the UK. For the TR health state, HRU values were calculated as the midpoint of the weights for the TD and TI states.

Each tracked complication incurs a cost in the model. Costs for cardiac, liver, osteoporosis, diabetes, and hypogonadism incur costs, which are differentiated between the first and subsequent years. Infertility costs are also applied in the model, which incorporate the cost of IVF treatment for females (one-time cost), as well as the cost for ongoing storage of sperm/oocyte in both males and females. Adverse event costs are applied in the model for SoC and the adverse event costs for exa-cel are assumed to be zero and explored only in scenario analyses.

Table 16 Summary of the costs included in the economic model

Description of cost	Value	Source
Treatment & transplant-related costs (exa-cel)		
Exa-cel acquisition cost	[redacted]	Vertex Pharmaceuticals
Pre-mobilisation costs (screening and fertility)	£3,483	NHS reference costs[49]
Mobilisation costs	[redacted]	BNF,[47] NHS reference costs[49]
Hospitalisation costs for procedure	£26,602	NHS reference cost SA26A and SA26B[49]
Monthly post-transplant monitoring costs – Years 1 & 2	£99.8	NICE ID968[6]
Monthly post-transplant monitoring costs – Years 3+	£82.0	NICE ID968 (applied until year 15)[6]
Phlebotomy - monthly cost	£10.18	NHS reference cost[49]
Blood transfusions and chelation		
Monthly RBC transfusion costs	£822.58	NHS blood and transplant price list,[50] NICE TA743[51]
Deferiprone (DFP) – cost per unit	£4.66	NHS drug tariff[52]
Desferrioxamine (DFO) - cost per unit	£4.20	NHS drug tariff[52]
Deferasirox (DFX) – cost per unit	£1.30	NHS drug tariff[49]
Disease management costs (monthly)		
Transfusion independent	£34.83	NHS reference costs, [49] expert opinion
Transfusion reduced	£103.33	NHS reference costs[49]
Transfusion dependent	£171.83	NHS reference costs, [49] Shah et al. 2021[11]
Complication & other condition costs (monthly)		
Cardiac – Year 1	£625.23	Karnon et al. 2012[37]
Cardiac – Year 2+	£322.01	Karnon et al. 2012[37]
Liver – Year 1	£259.03	National reference costs[49]
Liver – Year 2+	£259.03	National reference costs[49]
Osteoporosis – Year 1	£690.50	Ivergard et al. 2013[53]
Osteoporosis – Year 2+	£38.10	Ivergard et al. 2013[53]
Diabetes – Year 1	£485.60	Karnon et al. 2012[37]
Diabetes – Year 2+	£485.60	Karnon et al. 2012[37]
Hypogonadism – Year 1	£52.59	Karnon et al. 2012[37]
Hypogonadism – Year 2+	£52.59	Karnon et al. 2012[37]
Infertility (IVF, one-time cost – female)	£2,631.55	NHS fertility centre[54]
Infertility (monthly cost of sperm/oocyte storage, male/female)	£19.79	NHS fertility centre[54]
Adverse event costs		
Monthly AE costs (SOC)	£2.39	NHS reference costs[49]
Miscellaneous costs		
Terminal care costs – one time	£12,397	Personal Social Services Research Unit (PSSRU)[55]

4.2.8.1 Points for critique

Acquisition costs for chelation agents are based on the NHS tariff and not the cost of treatment

In EAG points for clarification, the EAG requested information on why the company used NHS drug tariff costs rather than electronic information tool (eMIT) costs to represent the acquisition cost associated with ICT regimes, and requested that the company (PfC question B18) update all drug acquisition costs used in the model using up-to-date eMIT costs. In response, the company argued that it was inappropriate to use eMIT costs for retail pharmacy drugs, as eMIT reports hospital-sector prices, which the company states have a different cost to the NHS than retail pharmacy costs. As a result, the company retained the original NHS tariff costs used in the model. Following discussions with NICE, the EAG were advised to use the eMIT costs for all drug acquisition costs, which the EAG explores in a scenario in Section 6, whereby eMIT costs are used to represent ICT acquisition costs in the model.

Table 17 below shows a comparison between NHS tariff costs applied in the company's base case and the eMIT costs applied in the EAG's base-case analysis.

Table 17 Electronic market information tool (eMIT) ICT acquisition costs

Parameter	Value – NHS Tariff (company base case)	Value – eMIT (EAG base case)
Desferrioxamine – 10 x 500mg	£46.63	£40.54
Deferasirox – 30 x 90mg	£126	£48.74
Deferiprone – 100 x 500mg	£130	£94.57

Exa-cel administration tariff costs

The company apply an NHS tariff cost in the model to represent the cost of delivery of exa-cel. The cost applied in the company's base-case is the tariff cost for autologous SCT (SA26A and SA26B), which the company states is similar to the resource requirements for delivery of exa-cel, along with CAR-T therapy (which the company state doesn't have published tariff costs). The EAG pointed out in a clarification question to the company (PfC B17) that previous appraisals, ID3980 and ID1684,[56, 57] describe an NHS tariff cost developed by NHSE for the administration of CAR-T, amounting to £41,101. In response, the company state that this tariff cost is likely to represent an inflated estimate of the cost of administering exa-cel. The EAG invite input from NHS England to inform the appropriate tariff costs for administration of exa-cel.

Ongoing disease management costs

The EAG has concerns regarding the company's application of state-dependent disease management costs. In the company's model, monthly costs of £34.83, £103.33, and £171.83 are applied to the TI, TR, and TD health states, respectively. The company describe how they use HRU weights from Shah

et al.,[11] along with unit costs, to calculate monthly disease management costs associated with the TD state. For the TI state, the company cite expert opinion as the source for the applied HRU weights. Given the high costs associated with the TD state over and above the specific costs associated with complications in the model, and the low costs associated with the TI state, the EAG are concerned that the model overestimates the ongoing costs associated with transfusion dependent patients. The Shah study presents HRU associated with TDT patients, however, this is likely to include 'background' resource usage that would also apply to patients who are TI and which may not be reflected in the current costs applied to the TI state. The resource use described in Shah also reflects resource usage related to complications which is accounted for separately in the model. As a result, the EAG considers scenarios in which health state costs are removed from the economics analysis – these are presented in Section 6.

Differential complication costs applied to first and subsequent years

The EAG has concerns about the application of differential complication costs for the first and subsequent years following a complication. The Markov structure used by the company to model the disease process makes it difficult for the model to accurately track the proportion of patients with complications, as well as accurately tracking the proportion of patients who are in their first (as opposed to subsequent) year of the complication. The EAG consider this a limitation of the chosen model structure as discussed previously in Section 4.2.2.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

This section summarises the results of the company's corrected and updated analysis following the clarification response. These results are based on a cost-effectiveness threshold of £30,000 and a 1.5% discount rate (company's base case analysis) or a 3.5% discount rate (company's scenario analysis). No interventions assessed in this submission, including transplant related, transfusion and iron chelation therapy costs have an associated PAS. The results presented in Sections 5.1.1 and 5.1.2 are presented with and without severity weighted ICERs, as per the company submission. Severity weighted ICERs are estimated in line with the company's assessment of the appropriate severity weight and do not necessarily correspond with the EAG assessment, See Section 7 for further discussion. Additionally, the company presents results reweighted using a DCEA. These are presented in the CS as a co-base case. Results inclusive of the DCEA are presented in Section 5.1.3. The appropriateness of the DCEA and its relevance to decision making is discussed in Section 8.

5.1.1 Base-case results

Table 18 presents the results of the company's base-case analysis with a 1.5% discount rate. The results show that at the 1.5% discount rate, exa-cel is associated with increased costs (cost difference of [redacted]) and increased QALYs (gain of [redacted] QALYs) compared with SoC. The company's base-case ICER exclusive of severity reweighting is [redacted] per QALY gained. Inclusive of the severity modifier (1.7 multiplier) the ICER is [redacted] per QALY gained.

Table 18 Base-case results with 1.5% discount rate

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years

At the 3.5% discount rate in the company's scenario analysis, exa-cel is associated with increased costs (cost difference of [redacted]) and increased QALYs (gain of [redacted] QALYs) compared with SoC. Exclusive of severity reweighting the ICER is [redacted] per QALY gained. Inclusive of the severity modifier (1.2 multiplier) the ICER is [redacted] per QALY gained.

Table 19 Scenario results with 3.5% discount rate

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years

5.1.1.1 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) by running 1,000 iterations. The model parameters were simultaneously varied by +/- 20%, or by their standard errors when available, to characterise uncertainty in the results. The severity modified cost-effectiveness acceptability curves for both comparators at the 1.5% and 3.5% discount rates are provided in Figure 4 and Figure 5, respectively.

The mean probabilistic ICER was [redacted] per QALY at the 1.5% discount rate, including the severity modifier. This was [redacted] lower compared with the deterministic ICER. At the 3.5% discount rate, the mean probabilistic ICER was [redacted] per QALY, including the severity modifier. This was a difference of [redacted] per QALY compared with the deterministic ICER. The notable difference between the probabilistic and deterministic ICERs is a result of the design of the PSA functionality of the model which assesses eligibility for the severity modifier during each iteration of the PSA rather than on a 'post-hoc' basis, see Section 5.2. The probability of exa-cel being cost-effective compared to SoC at the WTP threshold of £20,000 and £30,000 per QALY is [redacted] at both the 1.5% and 3.5% discount rates.

Table 20 PSA results (1.5% discount rate)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years

Table 21 PSA results (3.5% discount rate)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years

Figure 4 Cost-effectiveness acceptability curve, 1.5% discount rate (severity modified) (from company model)

[redacted]

Figure 5 Cost-effectiveness acceptability curve, 3.5% discount rate (severity modified) (from company model)

5.1.1.2 Deterministic sensitivity analysis

The company presented a series of univariate deterministic sensitivity analyses (DSA) to assess the impact of varying key model input parameters on the ICER results. Tornado diagrams summarising the most influential parameters with the severity modifier included at the 1.5% and 3.5% discount rates are presented in Figure 6 and Figure 7.

At the 1.5% discount rate, the results indicate that varying the frequency of moderate and high myocardial T2* levels at baseline, mortality risk from cardiac complications and the frequency of blood transfusions have the greatest impact on the ICER.

At the 3.5% discount rate, the results indicate that varying the frequency of moderate and high myocardial T2* levels at baseline, utility value for TD disease and the frequency of blood transfusions have the greatest impact on the ICER.

Figure 6 DSA results for Exa-cel vs SOC (1.5%) disc rate with severity modifier without DCEA modifier (from company model)

Figure 7 DSA results for Exa-cel vs SOC (3.5%) disc rate with severity modifier without DCEA modifier (from company model)

5.1.2 Company's sensitivity analyses

At the clarification stage, the EAG requested that the company present several scenarios exploring alternative assumptions and parameter inputs. The results of these analyses are presented in Table 22. The scenarios explored are as follows:

i. Baseline iron levels from CLIMB THAL-111
ii. Baseline prevalence of osteoporosis (10.4%) and diabetes (6.3%) from CLIMB THAL-111
iii. Adherence by ICT regimen according to Shah et al. 2021
iv. Assuming different myocardial iron risks
    a. Low T2* risk (0.3%) & TD SMR of 3.93
    b. Zero risk for Normal T2*
    c. Zero risk of complications in Normal and Low T2* & TD SMR of 4.12
v. Assuming a 0.1 decrement from general population utility
vi. Applying carer disutilities
    a. Health state and death-related disutilities
    b. Health state disutilities only
vii. Costs associated with additional hospitalisation days.

Table 22 Company's additional scenario analyses

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER
i. Baseline iron levels from CLIMB THAL-111						
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ii. Baseline prevalence of osteoporosis and diabetes from CLIMB THAL-111						
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
iii. Adherence by ICT regimen according to Shah et al. 2021						
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
iv. Myocardial iron risks:						
a. Low T2* risk (0.3%) & TD SMR of 3.93						
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b. Zero risk for Normal T2*						
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c. Zero risk of complications in Normal and Low T2* & TD SMR of 4.12						
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
v. Assuming a 0.1 decrement from general population utility						
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vi. Carer disutilities:						
a. Health state and death-related disutilities						
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b. Health state disutilities only						
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vii. Costs associated with additional hospitalisation days						
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years

5.1.3 Results inclusive of DCEA reweighting

The company base-case results and scenario analysis inclusive of severity and DCEA reweighting are presented in Table 23. Results are presented in NHB form as the DCEA reweighting explicitly assumes that the NICE threshold represents the opportunity cost of health forgone elsewhere in the health system. Note that the NHB values presented in the company's initial submission were

incorrectly calculated and were corrected at the clarification stage, this correction is reflected in the table below. The DCEA approach is discussed in detail in Section 8.

Table 23 Company base-case, severity-weighted and DCEA-weighted NHBs (1.5% discount rate)

Scenarios	NHB at £30,000			
	Base-case	Severity weighted	DCEA weighted	DCEA and severity weighted
Company base-case (1.5% discount rate)	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case (3.5% discount rate)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline iron levels from the CLIMB THAL-111 trial	[redacted]	[redacted]	[redacted]	[redacted]
Baseline prevalence of osteoporosis and diabetes from CLIMB THAL-111	[redacted]	[redacted]	[redacted]	[redacted]
Adherence by ICT regimen according to Shah et al. 2021	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial iron risks: – Low T2* risk (0.3%) & TD SMR of 3.93	[redacted]	[redacted]	[redacted]	[redacted]
– Zero risk for Normal T2*	[redacted]	[redacted]	[redacted]	[redacted]
– Zero risk of complications in Normal and Low T2* & TD SMR of 4.12	[redacted]	[redacted]	[redacted]	[redacted]
Assuming a 0.1 decrement from general population utility	[redacted]	[redacted]	[redacted]	[redacted]
Carer disutilities: – Health state and death-related disutilities	[redacted]	[redacted]	[redacted]	[redacted]
– Health state disutilities only	[redacted]	[redacted]	[redacted]	[redacted]
Costs associated with additional hospitalisation days	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: NHB, net health benefit; DCEA, distributional cost-effectiveness analysis				

5.2 Model validation and face validity check

The company performed model validation in which the internal validity, face validity, and external validity of the model was assessed. The internal validity check consisted of several quality control procedures, with line-by-line audit of code and model structure, assumptions, inputs and data reviewed by health economists. Face validity was assessed by comparing the model's predicted survival output with real-world estimates for SoC reported in the literature and to the undiscounted life years and discounted QALYs for SoC predicted by the ERG in the NICE appraisal of betibeglogene [ID968]. External validation of the model compared SoC outcomes of mean survival and rates of complications (cardiac, liver, diabetes and osteoporosis) with those reported in a UK study with a 10-year prospective cohort analysis for the period 2009–2018 using HES admitted

patient care, outpatient data and linked HES/Office of National Statistics mortality data for patients with two or more primary diagnoses of TDT in England (Jobanputra et al. 2020).[18]

The survival outcomes from the model for SoC are within the range of survival estimates reported in the studies used for validation purposes. The company notes that the undiscounted life years (37.79) and discounted QALYs (15.48) for SoC in the betibeglogene appraisal are greater than the estimates from the company's base case of [redacted] life years and [redacted] QALYs (discounted at 1.5% per annum). The company states that the reasons for this discrepancy is difficult to determine due to differences in model structure, approach to modelling mortality, and use of an age and gender distribution in the betibeglogene model rather than a cohort starting age of 21.4 years.

5.2.1.1 Points for critique

The EAG considers the company's validation procedures to be appropriate. However, the EAG is concerned about the discrepancy between the estimated life years and QALYs for SoC from the betibeglogene appraisal and the company's base case analysis. Although the model structure (Markov model vs. patient-level simulation model) and approach to modelling mortality differs between the appraisals, the fact that the estimated outcomes differ substantially for SoC, which is the same treatment in both appraisals, only serves to demonstrate the importance of characterising the disease pathway in an appropriate model structure and accurate approach to modelling mortality. The QALY difference for SoC reported in the CS between the betibeglogene appraisal and the company's base case analysis is using different discount rates. The discounted QALYs of 15.48 for SoC reported in the betibeglogene appraisal is based on a discount rate of 3.5% per annum, whereas the discounted QALYs of [redacted] for SoC in the company's model is based on a 1.5% discount rate. The corresponding discounted QALYs from the company's model for a 3.5% discount rate are [redacted], which is a substantial difference of [redacted] QALYs between the two appraisals for the same treatment. The EAG also notes that although the survival estimates are reported to be within a range of estimates from the literature, the range is quite wide, varying between a mean or median age of death of between 45 and 55 years for SoC. The EAG also notes that the rates of complications from the company's model do not align well with those reported in the 10-year retrospective cohort analysis by Jobanputra et al. 2020 (see Appendix J.1.1 of CS); therefore, although the validation procedures reported in the CS are appropriate, the findings suggest that the model is not externally valid with other UK sources of data for the SoC arm.

The EAG reviewed the model in detail and applied the TECHnical VERification (TECH-VER) checklist.[58] Overall, the model was coded well and the errors identified by the EAG largely pertain to the DCEA. In relation to the DCEA, the EAG notes that the company made use of proprietary functions in its programming, which are not available as standard within the software package of

Excel. The University of York's version of Excel does not support the use of dynamic arrays, which were used for the DCEA calculations; as a consequence, the EAG had to adapt the model to generate the DCEA results without the use of dynamic arrays, which were unnecessary because a combination of standard functions in Excel (e.g., use of OFFSET and MATCH) were sufficient to derive the DCEA weights. The EAG also noted the following errors in the DCEA:

- On the DCEA Weights worksheet the distribution of the incremental cost from the intervention across IMD groups and the distribution of the health opportunity cost from the intervention across IMD groups is not a function of the percentage of each group that would uptake the intervention. This does not affect the base case analysis as uptake is assumed to be 100% in all groups; however, in any sensitivity analysis where uptake is adjusted, this only feeds through into the QALY gain from the intervention across IMD groups and not to the costs.
- The model submitted in response to clarification uses the incorrect figures for the QALE by IMD. Table 21 in the clarification response shows the correct figures, but the model instead uses the figures for females only from the Love-Koh 2023 reference.
- The clarification response and the model use incorrect figures for the health opportunity cost gradient from Love-Koh et al, where the model divides the number of females in each IMD group by the total number of males and females combined. This means that the proportions do not sum to one, and any calculations based on these proportions are therefore incorrect.

These errors were corrected by the EAG (see Section 8).

The EAG considers that the severity modifier and DCEA are applied incorrectly for the reporting of the ICER results from the PSA. In each PSA iteration, the company applies the relevant severity modifier and QALY reweighting according to the output of that iteration; therefore, the PSA results presented in the CS represent the reweighted results. Decision-making modifiers are factors that have not been included in the estimated QALYs under the NICE reference case (because it is not possible to include them in the QALYs) and where the committee makes a value judgement to account qualitatively through committee discussion or quantitatively through QALY weightings on the reference case QALYs. The EAG considers it inappropriate for the company to make a value judgement on decision modifiers for each PSA iteration output. Therefore, the PSA results should be presented without the weightings and any QALY weighting applied to the reference case unweighted PSA results.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified several limitations and areas of uncertainty in the company's cost-effectiveness analysis. These issues are discussed in detail in Section 4. The following sections present additional analyses by the EAG, where the EAG explores alternative approaches and assumptions in scenario analyses to the company's base case analysis.

Descriptions of the EAG exploratory analyses are provided in Section 6.1 and the impact of these analyses on the company's base case are presented in Sections 6.2 and 6.3, along with the EAG's preferred base case. Additional scenarios are included to explore the impact of alternative assumptions on the EAG base-case. All results in this section are presented with and without a 1.2 QALY weighting for severity as per the company's QALY shortfall calculations at a 3.5% per annum discount rate, see Section 7.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The following exploratory analyses were conducted by the EAG based on identified uncertainties. Some of the scenarios were implemented by the company in response to EAG points for clarification and are included in this section. Each of the following analyses are based on the updated version of the model provided by the company in response to EAG points for clarification:

1. Alternative assumptions for mortality associated with complications

As discussed in Section 4.2.2, the EAG considers the assumption of a single mortality rate to lack face validity. Since mortality is modelled as a function of general population mortality, excess mortality linked to transfusion status, and complication-related mortality, a single mortality rate does not appropriately attribute mortality risks and leads to an over-accumulation of patients with complications. The EAG presents a scenario based on simplifying the Markov model to include no complications, which ensures internal consistency within the Markov model framework (i.e., the model cannot track which patients have multiple complications, without the introduction of excessive numbers of tunnel states). The EAG acknowledges that this approach does not capture the burden of complications on either individuals or the NHS but the direction of bias is clear, and it is expected to underestimate the value of exa-cel.

2. Accounting for cost and health outcomes where patients are unable to receive exa-cel transfusion

As discussed in Section 4.2.2, the company assumes that all patients who withdraw from exa-cel infusion do not incur transplant related costs or acquisition costs associated with exa-cel. However, the EAG is unclear whether it is the company or the NHS who bears the cost of manufacturing exa-cel

when patients withdraw or become ineligible for treatment after gene editing has been performed prior to infusion. The EAG presents a scenario in which the modelled dropout rate of [redacted] from the CLIMB THAL-111 trial is used to adjust exa-cel acquisition costs and health outcomes.

3. Baseline prevalence of osteoporosis and diabetes based on the CLIMB THAL-111 trial

As discussed in Section 4.2.3, the EAG requested that the company include osteoporosis and diabetes complications in the model to reflect baseline comorbidities in the population. This scenario replicates the analysis implemented by the company at the clarification stage in which the prevalence rates of 10.45% and 6.3% for osteoporosis and diabetes, respectively, are used.

4. Baseline iron levels based on the CLIMB THAL-111 trial

The EAG requested that the company update the baseline distribution of iron levels used in the model to represent those of the CLIMB THAL-111 trial who are eligible for exa-cel. The company noted that the categorised baseline iron levels were obtained via post-hoc analysis and presented a scenario analysis in response to EAG points for clarification with these inputs. The results of this scenario are replicated below.

5. Frequency of blood transfusions based on Shah et al., 2021

As discussed in Section 4.2.4, the EAG considers the use of CLIMB THAL-111 data on the frequency of transfusions to be inconsistent with the data used to inform the other model inputs characterising SoC in the UK, which are based on the Chart Review. The modelled number of transfusions based on the trial is higher than that reported in the Chart Review, which is representative of the UK population. The company were unable to conduct this scenario in response to EAG points for clarification because the model bases blood transfusion utilisation on RBC units, whereas Shah et al., 2021 reports RBC volumes per kg body weight but does not report the mean patient weight. The EAG explores a scenario by using an annualised transfusion frequency of 13.7 from Shah et al., 2021 and assuming 2.2 units of blood per transfusion.

6. Using a 3.5% discount rate

As discussed in Section 4.2.5, the company argues that exa-cel meets the criteria for the use of a 1.5% discount rate. The EAG does not consider the company's justification for the use of the non-reference case discount rate of 1.5% to be sufficient and emphasises that the committee had a preference for a 3.5% discount rate in the betibeglogene appraisal [ID968]. The EAG presents a scenario with the 3.5% discount rate applied.

7. Aligning the definition of transfusion independence to the T12 primary outcome in CLIMB THAL-111

As discussed in Section 4.2.6.1, the company's post-hoc definition of transfusion independence is inconsistent and less restrictive compared with the primary and secondary outcomes pre-specified in the CLIMB THAL-111 trial. As a consequence, patient 002 from the trial is classified as transfusion independent despite not meeting the requirements of the TI12 primary outcome. This has a significant impact as transfusion independence is a key driver in the model. The EAG presents a scenario where patient 002 is reclassified as transfusion reduced to be more consistent with the pre-specified primary and secondary efficacy endpoints as reported in the company submission. The EAG assumes that 88.9% of patients (24 out of 27 patients) achieve TI12 as per the company submission.

8. Alternative assumptions for the rate of (late) relapse from engraftment

The model assumes a 0% engraft failure and 0% relapse rate. The EAG considers this assumption reasonable given that the current data cut from the CLIMB THAL-111 trial supports the assumption of permanence of the treatment effect in patients who achieve transfusion independence following exa-cel treatment. However, uncertainty remains as this data is based on short trial follow up and thus provides limited direct evidence for long-term treatment effect.

The EAG explores two alternative rates of relapse of 2.19% based on values reported by Santarone et al 2022 and 10% based on values from the Betibeglogene US ICER report.

9. Alternative assumptions for time to iron normalisation

The company assumed an iron normalisation period of 4 years from initial exa-cel infusion in the base-case based on expert opinion. As discussed in Section 4.2.6.3, there is limited evidence available to inform this time period and the CLIMB THAL-111 follow-up is short. The EAG notes that in the betibeglogene appraisal [ID968] the committee concluded that the minimum iron-normal period should be 5 years for all organ systems. A scenario using 5 years is implemented in the company's updated model.

10. Alternative assumptions for iron normalisation in patients with low iron levels

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 experience complications risks in line with the general population. As discussed in Section 4.2.6.4, 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. The EAG presents a

scenario whereby patients in the TI health state continue to experience complication risks associated with low iron overload.

11. Assuming a lower SMR for patients who are TD

The company applies a SMR of 3.45 to transfusion dependent health state which was estimated following calibration of the model to predict a SMR of 5.0 over the modelled time horizon. As discussed in Section 4.2.6.5, the EAG considers the source that it was derived from to be outdated and of limited 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 EAG therefore explores the impact of lower SMRs of 2.5 and 2 in TD patients. The latter being selected as this was the preferred SMR in the betibeglogene appraisal [ID968].

12. Exploring a non-zero mortality risk associated with myeloablative conditioning

The mortality risk associated with myeloablative conditioning is assumed to be 0% in the company's base case. The company states that this risk is captured in the SMR of 1.25 applied in the model for TI. The EAG considers it appropriate to model a non-zero mortality risk associated with myeloablative conditioning because this was the committee's preferred approach in the betibeglogene appraisal [ID968] and it captures the potential mortality impact of myeloablative conditioning associated with exa-cel treatment. The EAG presents a scenario applying a 1.4% mortality risk for myeloablative conditioning based on the value used in the US ICER model.

13. Exploring the HRQoL decrement for TD relative to the general population

As discussed in Section 4.2.7, the company uses values from a published vignette study to inform the health state utility values in the model rather than EQ-5D data from CLIMB THAL-111. The vignette provides lower utility values than those observed in the CLIMB THAL-111 trial. The company's base case analysis assumes a utility decrement of 0.2 for TD relative to TI based on the findings of the vignettes. The EAG explores a range of scenarios applying utility decrements of [redacted], 0.1 (similar to that used in the NICE appraisal of betibeglogene), and 0.15 relative to the general population. For consistency, it is assumed that the utility applied to the TR health state are an average of the utility values applied in the TI and TD heath states.

14. No infertility-related decrements on HRQoL

The company's base case applies a decrement of 0.06 to represent the disutility associated with infertility. As discussed in Section 4.2.7, and in line with the committee's preference in the betibeglogene appraisal [ID968], the EAG considers there to be uncertainty about the appropriateness

of including the impact of infertility upon HRQoL. In this scenario, the EAG explores the impact of removing the infertility-related utility decrement.

15. Using drug acquisition costs from eMIT

As discussed in section 4.2.8, the EAG requested that the company update the ICT acquisition costs in the model from NHS drug tariff costs to eMIT costs. In response, the company states that it is inappropriate to use eMIT for retail pharmacy drugs, as eMIT reports hospital-sector prices. The company argues that these costs may be a different cost to the NHS than retail pharmacy costs. NICE have advised the EAG that eMIT costs should be used for all drug acquisition costs. The EAG presents a scenario using eMIT costs to represent ICT acquisition costs in the model.

16. Ongoing disease management costs

As described in Section 4.2.8, the EAG is concerned that the model overestimates ongoing costs associated with TD patients as this is likely to include 'background' resource usage that would also apply to patients who are TI and TR patients. The EAG is also concerned that the TD health state costs double count some care costs as it includes resource usage related to complications which are accounted for separately in the model. The EAG explores the magnitude of impact from removing these health state costs.

17. Using a multiplicative approach for age-adjusted utility decrements

The company applies the age-adjusted utility decrements additively per cycle rather than multiplicatively. The NICE DSU guidance recommends the multiplicative method for age adjustment. The EAG presents a scenario with this correction.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 24 presents the results of the scenario analyses described in Section 6.1. All results are presented deterministically.

Table 24 EAG Exploratory Scenario Analyses

Scenario	Technology	Total		Incremental		ICER	Severity weighted at ICER (1.2 multiplier)
		Costs	QALYs	Costs	QALYs		
Company base case	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Modelling no complications	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Costs and outcomes from exa-cel withdrawal	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Baseline prevalence of osteoporosis and diabetes based on CLIMB THAL-111	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Baseline iron levels based on CLIMB THAL-111	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Frequency of blood transfusions based on Shah et al., 2021	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. 3.5% Discount rate	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Align transfusion independence to the T12 primary outcome in CLIMB THAL-111	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 (a). Relapse based on published values from Santarone et al. 2022	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 (b). Relapse based on US ICER report	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. Assuming 5 years to iron normalisation	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. Iron normalisation in patients with low iron levels	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11 (a). SMR of 2.5 for TD patients	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11 (b). SMR of 2 for TD patients	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12. 1.4% mortality risk for myeloablative conditioning	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]				

13 (a). [redacted] utility decrement	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13 (b). 0.1 utility decrement	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13 (c). 0.15 utility decrement	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14. No infertility-related decrements	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15. Use of eMIT costs	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16. No health state costs	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17. Multiplicative age-adjustment	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3 EAG's preferred assumptions

The cumulative impact of the EAG's preferred assumptions on the base-case are presented in Table 25 and Table 26. The EAG base-case adopts the following scenarios described in Section 6.1:

- Scenario 1: Alternative assumptions mortality associated with complications,
- Scenario 2: Costs and outcomes from exa-cel withdrawal,
- Scenario 5: Frequency of blood transfusions based on Shah et al., 2021,
- Scenario 6: Using a 3.5% discount rate,
- Scenario 7: Aligning the definition of transfusion independence to the T12 primary outcome in CLIMB THAL-111,
- Scenario 9: Assuming 5 years to iron normalisation,
- Scenario 11: Assuming an SMR of 2.5 for TD patients,
- Scenario 13: HRQoL decrement of [redacted] relative to the general population,
- Scenario 15: Use of eMIT costs,
- Scenario 17: Multiplicative approach to age-adjustment.

Table 25 EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY
Company base-case	5.1.1.1	[redacted]
1. Alternative assumptions mortality associated with complications	4.2.2	[redacted]
2. Costs and outcomes from exa-cel withdrawal	4.2.2	[redacted]
5. Frequency of blood transfusions based on Shah et al., 2021	4.2.4	[redacted]
6. Using a 3.5% discount rate	4.2.5	[redacted]
7. Aligning transfusion independence to the T12 primary outcome in CLIMB THAL-111	4.2.6	[redacted]
9. Assuming 5 years to iron normalisation	4.2.6	[redacted]
11. Assuming an SMR of 2.5 for TD patients	4.2.6.5	[redacted]
12. HRQoL decrement of [redacted] relative to the general population	4.2.7	[redacted]
15. Use of eMIT costs	4.2.8	[redacted]
17. Multiplicative approach to age-adjustment	4.2.7.4	[redacted]

Table 26 EAG preferred base-case

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Severity weighted ICER (1.2 multiplier)
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3.1 Additional scenario analysis on the EAG's base case

The selection of changes made to the EAG base-case analysis were driven by the available evidence; however, a number of important uncertainties remain. To address the remaining uncertainty, the EAG 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 by the company in their base-case analysis. The second and third relate to the permanence of the treatment effect and the possibility of late engraftment failure. The fourth relates to the potential for transplantation-related mortality. Results of these additional analysis are presented in Table 27.

Table 27 Results of scenario analyses on the EAG alternative base case analysis

Scenario	Technology	Total		Incremental		ICER	Severity weighted at ICER (1.2 multiplier)
		Costs	QALYs	Costs	QALYs		
EAG base case	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.5% Discount rate	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse based on published values from Santarone et al. 2022	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse based on US ICER report	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.4% mortality risk for myeloablative conditioning	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.4 Conclusions of the cost effectiveness section

The EAG considers the submitted evidence to broadly reflect the decision problem defined in the final scope, but note that the submitted analyses did not meet the requirements of the NICE reference case with regards to the use of a non-reference discount rate and the use of a non-reference case elicitation study to generate the applied utility set. The EAG's review of the company submission identified several areas of uncertainty, and a number of significant methodological issues which the EAG has sought to address its additional economic analysis.

In terms of thier likely impact on the ICER the most of important of these issues centered on the modelling approach adopted by the company. While superficially similar to the model considered in ID968, the company's economic analysis is based on a Markov model which contrasts with the patient simulation model used in ID968. The company's modelling approach is inconsistent with the complex dynamics of TDT, which is not well suited to explicitly capturing the complicated dynamics of TDT without making significant simplifications that abstract from reality. The consequences of this issue are significant and lead the model to incorrectly attribute mortality risks. This issue leads to an over-accumulation of patients with complications, and a progressive overestimation of mortality in the whole cohort overestimate. Because of this issue and several related issues, the EAG does not consider the company's model fit for decision making. Correcting the company's model is non-trivial and requires judgments to be made about the most appropriate modelling approach, with all options being subject to limitations. In scenario analysis the EAG presents a simplified version of the company's economic analysis which does not capture the burden of complications on either

individuals or the NHS. The EAG acknowledges that this model may underestimate the value of exa-cel. However, unlike the company's model, it maintains internal consistency.

The small sample size of the CLIMB THAL-111 trial and short-follow up also have important implications in terms of the predicted cost-effectiveness estimates. Assumptions around the durability of transfusion independence, as modelled in both the company's and EAG base-case, assume that the benefits of exa-cel will be highly durable and persist for the life time of the patient. There is however, little direct evidence to inform this assumption and generally a lack of clinical experience of the gene therapies such as exa-cel. The limitations of the current evidence base both in terms of the length of follow- up, but also importantly the impact of exa-cel on HRQoL and mortality, makes characterisation of the benefits of exa-cel difficult and highly uncertain. There is currently no direct evidence to support any of the model benefits of exa-cel which all rely on surrogate relationships between transfusion status and improvements in both HRQoL and mortality.

The EAG has substantive concerns regarding the health state utilities applied in the company's economic model. There are serious flaws in the non-reference case elicitation study used by the company to generate the applied utility set and significant evidence of bias. As a result, EAG considers that the applied values to lack face-validity and likely overestimate the quality of life impacts of TDT. The EAG takes issue with company's disregard for EQ-5D data collected as part of the CLIMB THAL-111 trial and refusal to appropriately analyse these data so that they may inform the economic. The EAG considers the CLIMB THAL-111 trial to be the most appropriate source of evidence on HRQoL and that this should be addressed as part of technical engagement.

The EAG also takes issue with the company's characterisation of SoC which is informed by data from UK Chart Review and BoI study. The populations recruited to both of these studies do not match the NICE scope of the exa-cel trial population. A large proportion of Chart Review patients were aged over 35, with some over 60 years of age, and had a number of co-morbidities that would have precluded treatment with exa-cel. The representativeness of this cohort for key parameters such as iron loading and the distribution of ICT used in practice is unclear. The BoI study used to inform mortality in patients is similarly problematic as it is outdated and of limited generalisability to the present decision problem, being based on an unrestricted TDT population and reflecting historical use of ICT. Clinical practice regarding the use of iron chelation agents has evolved significantly in the last 20 year, due to improvements in evidence, availability of oral ICT and increased confidence around the combination ICT.

The EAG also does not consider the company's justification for the use of the non-reference case discount rate of 1.5% in the economic evaluation sufficient. The company argue that exa-cel restores people who would otherwise die or have a very severely impaired life to full or near full health. The

EAG is concerned that the literature cited in support of this assumption is unrepresentative of current SoC and identified recent sources stating that patients optimally managed with currently available therapies could have a near-normal life expectancy. Further, a number of evidence sources, including the company's own trial, support the notion that the impact of TDT and current management on HRQoL is not as severe as argued by the company. The EAG also notes that the NICE committee in ID968 firmly rejected application of the 1.5% discount rate in a near identical indication.

7 SEVERITY MODIFIER

The company undertook a QALY shortfall analysis by calculating the expected quality-adjusted life expectancy (QALE) for the general population, in line with methods described by Schneider *et al.* (2022). Life expectancy for the modelled population was calculated using ONS population mortality data from 2018-2020 and did not account for specific patient characteristics associated with this population other than age and sex mix. Life expectancy was quality-adjusted using UK population norm values as reported by Hernández Alava *et al*. (2022).

The company estimated the QALY shortfall considering the base case 1.5% discount rate and 3.5% discount rate applied in scenario analysis. The results of the company's QALY shortfall analysis are presented in Table 28, along with the values generated in the EAG base-case. The absolute QALY shortfall associated with the condition was above the threshold of 18 QALYs when a 1.5% discount rate is assumed and was between 12 and 18 when considering a 3.5% discount rate. Therefore, the company applied a severity modifier of 1.7 in the base-case results and severity modifier of 1.2 in scenario with a 3.5% discount rate. The EAG base case results in absolute and proportional QALY shortfall that fall below the threshold of 12 and 0.85 respectively. These imply that TDT does not meet the criteria for application of the severity modifier.

Table 28 Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs achieved on SoC	Absolute QALY shortfall	Proportional QALY Shortfall
Company base-case (1.5% discount rate)			
34.51	13.31	21.20	61.42%
Company Scenario analysis (3.5% discount rate			
22.51	10.48	12.03	53.5%
EAG base case (3.5% discount rate)			
22.51	18.73	3.78	16.8%

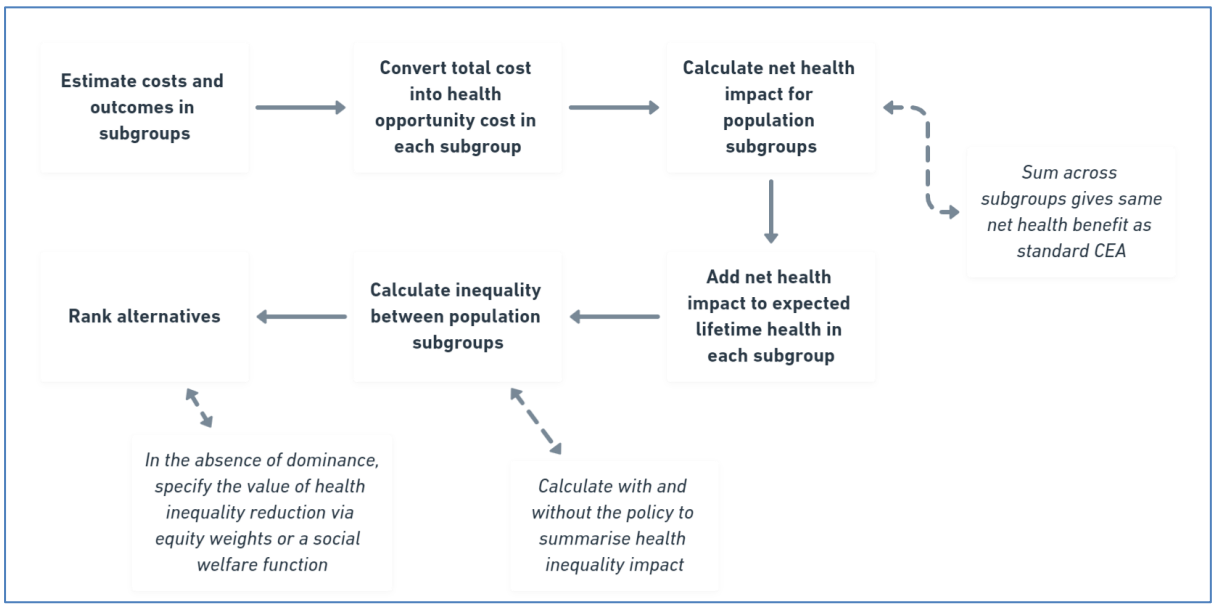
The NICE methods guide states that: *"Absolute and proportional shortfall calculations should include discounting at the reference-case rate."* The EAG therefore do not consider it appropriate to consider a non-reference discount rate when considering eligibility for the severity modifier and that qualification for the severity modifier should be considered using the reference case discount rate of 3.5%. The company's base-case analysis would therefore imply that a severity modifier of 1.2 is appropriate, not 1.7 as proposed by the company.

8 DISTRIBUTIONAL COST-EFFECTIVNESS ANALYSIS

Distributional cost-effectiveness analysis (DCEA) is a methodology that integrates health inequality concerns into the economic assessment of health sector interventions. The DCEA is a distinct, non-reference case approach to health technology evaluation that goes beyond the methods outlined by the NICE methods guide. NICE has requested the EAG to review and critique the DCEA provided by the company. In DCEA, societal preferences regarding aversion to health inequality are formally integrated into health economic assessments, including the consideration of NHBs. This means that not only are these preferences factored into the decision-making process, but they are also reflected in the results of economic analyses. This ensures a more nuanced evaluation of healthcare interventions that accounts for societal values related to fairness and equity.

DCEA is a supplementary approach to standard CEA that is used to evaluate the impact of healthcare interventions on different subgroups within a population, such as income, age, ethnicity, or socioeconomic status. This represents a modified approach to assessing healthcare interventions where equity and fairness in the allocation of healthcare resources is of importance. DCEA involves two stages: modelling the social variations in health (QALYs) linked to different interventions, and assessing the societal disparities in health for the objectives of improving overall population health and reducing unfair health inequalities[59]. This process expands on the traditional CEA by integrating equity concerns and addressing how model outcomes in terms of costs and benefits of an intervention are distributed across different subgroups within a society.

Figure 8 Conducting a full DCEA



The process of conducting a full DCEA, summarised in Figure 8, generally involves breaking down the outcomes of different alternative interventions based on equity-relevant variables by simulating

QALY benefits, and opportunity cost distributions. When combined with the distribution of pre-intervention baseline QALYs, these distributions simulate the post-intervention distribution. This method involves evaluating how an intervention affects different subgroups in terms of costs incurred and benefits gained. The resulting distributions pre- and post-intervention can then be formally evaluated and ranked in terms of cost-effectiveness, equity, and, where necessary, a comprehensive evaluation of social welfare that considers both cost-effectiveness and equity. Importantly, the distribution of treatment benefits and the total cost of treatment is estimated within the patient population that receives the treatment of interest, but the health opportunity costs can fall outside of the patient population and the inequality measures are expressed at general population level. Therefore, the extent to which an intervention can impact on population level health inequalities depends on the size and distribution of the treated population and the distribution of the opportunity costs of NHS expenditure within the general population. NICE has previously considered incorporating possible concerns relating to health inequalities across all appraisals, including whether an intervention could address inequality or unfairness in the distribution of health, but opted not to in the 2022 methods update.

The company applied an aggregate approach to DCEA, which relies on aggregate data, including the summary results from a cost-effectiveness analysis, without explicitly considering variation in cost-effectiveness analysis inputs across specific subgroups. This approach uses the results from a standard CEA model in terms of incremental costs and QALYs, the equity-relevant characteristics of the target population or the disease, variation in healthcare utilisation and the health opportunity costs based on equity-relevant variables such as socioeconomic status or ethnicity. To approximate distributional breakdowns, costs and effects are assigned to equity subgroups using differences in prevalence of the condition and uptake of treatment across subgroups.

This aggregate approach is a simpler version than a 'full' or standard DCEA, and it estimates the distribution of summary level health outcomes to specific population subgroups. In contrast, the standard DCEA can incorporate other differences across subgroups, including short- and long-term differences in treatment efficacy and costs. An aggregate DCEA could be considered an extension to a completed CEA, whereas a standard DCEA would allow integration of the equity concern throughout the modelling.

The DCEA produces simulated distributions of QALY outcomes and health opportunity costs that can be combined into a distribution of net health benefits and then formally evaluated using inequality metrics, as intended in this submission. Some metrics compare distributions based on inequality only i.e., to measure equity impacts, rather than both cost-effectiveness and equity. A bivariate equity metric, the slope index of inequality (SII) is used to measure the association between the health variable (quality-adjusted life expectancy), and the equity relevant variable (e.g. socioeconomic

status). To compare distributions based on cost-effectiveness and equity, specific weights are required to specify the value of reducing health inequality relative to the value of increasing overall population health. Indirect equity weighting compares interventions using an equity parameter within a social welfare function to reflect the degree of societal concern for the worse off by giving priority to specific groups depending on their level of health. This differs from the direct equity weighting which gives priority directly to specific groups. The NICE severity weights are an example of a direct equity weight. The submission used a level-dependent indirect equity weight derived from an Atkinson social welfare index. Level-dependent means that the indirect weight varies in accordance with the health level, i.e., the QALE, in each subgroup. A key parameter in this function is the Atkinson inequality aversion parameter, which quantifies the degree to which societies are averse to health inequality; a higher parameter value indicates more priority is given to the least healthy group (i.e., with the least QALYs) relative to the overall population.

The health measure used In this analysis was the quality-adjusted life expectancy (QALE) and the socio-economic measure used was the Index of Multiple Deprivation (IMD), classified into five quintiles ranging from the most deprived (IMD 1) to the least deprived group (IMD 5). The IMD measures deprivation across seven domains (health, income, employment, education, crime, housing and living environment) for all lower layer super output areas (LSOAs) in England. The LSOA that an individual is associated with is determined by their postcode, and each LSOA contains about 1,500 residents. Thus, the IMD does not measure an individual's socio-economic status directly, but rather the socio-economic characteristics of their area of residence.

The total general population size was based on ONS (2022) population estimates for England. Other inputs included the proportion of the eligible treatment population by IMD group derived from the Vertex Burden of Illness Study[35, 60], the general population distribution by IMD group from Love-Koh et al, 2020[60], and QALE estimates at birth by IMD derived from Love-Koh et al., 2015.[61] Incremental costs and QALYs derived from the company's CEA and the eligible treatment population estimates were used to calculate population-level effects. In the base-case, health opportunity costs were assumed to be equally shared between the different IMD groups i.e., it was assumed that each IMD group bears 20% of health opportunity costs. Full uptake by the eligible population in all subgroups of the interventions was also assumed in the base-case.

Changes in lifetime health inequality following an intervention i.e., the post-intervention QALE values, were calculated by adding the net health benefits from an intervention to the IMD-specific QALE. The company chose an absolute measure of inequality, the slope index of inequality (SII), to assess the inequality impact on QALE by IMD. The difference between the SII value pre- and post-intervention gives the net inequality impact. The company scaled the change in health inequality at population level by multiplying the change in SII by the total general population size. A negative

difference in SII is interpreted as the intervention reducing population-level health inequality, a difference in SII of 0 indicates the same inequality level as baseline, and a positive difference in SII indicates an intervention increases health inequality.

Additionally, the DCEA was used to re-weight the incremental QALYs and costs from the standard CEA to derive an equity-weighted ICER. To do this, the company applied the Atkinson social welfare function and used an inequality aversion parameter estimate of about 11 reported in Robson et al. (2017).[62] As this parameter does not assign fixed weights to different groups, the company used the derivative of the health function in the Atkinson index to calculate the ratios between each IMD group compared to the least deprived group (IMD 5). The ratios were interpreted as the relative indirect equity-weighting by IMD group; a higher ratio output value means more variation in the rate of change in health inequality in an IMD group compared to the least deprived group. The company applied these weightings to indicate the values required to move all IMD groups to 'equal' health distribution.

The company also used the equity-weighting ratios to re-weight QALYs and financial opportunity costs by IMD group. The resulting aggregate weighted incremental QALYs and costs across IMD groups were used to derive the equity-weighted gross population health benefit and financial opportunity costs. The equity-weighted financial opportunity costs were divided by the re-weighted QALYs for each intervention (calculated by dividing the gross population health by the eligible treatment population size) to calculate the equity-weighted ICER.

Points for critique

Aggregate DCEA approach

The submission applies an aggregate DCEA approach which provides an estimate of the treatment impact on health inequality but inherently cannot incorporate equity relevant variation in model inputs. The company reasons in their clarification response that a full DCEA would need to incorporate all social variables relevant to equity. However, there is no limitation to conducting a full DCEA using the same equity characteristics used in the aggregate approach, i.e., distribution of total QALY benefits by IMD group according to indicators of disease prevalence and utilisation. A full analysis of distributional consequences can be conducted using these distributions combined with a simulation of the baseline QALY distribution and the distribution of health opportunity costs; these can be based on available information or appropriate assumptions. The purpose of a full DCEA is to reflect model input and treatment effect variation across subgroups such as IMD or based on ethnicity.

The company clarified that cost-effectiveness is assumed to be constant across IMD groups, implying that efficacy and costs of exa-cel are expected to be consistent across patients living in different levels

of deprivation. On this basis, results from a full DCEA would not differ substantially from an aggregate approach. Therefore, the EAG is satisfied with an aggregate DCEA approach in this submission.

IMD as a proxy for ethnicity

While the submission focused on how the prevalence and management of TDT affects individuals based on ethnicity, the DCEA focusses on inequality by area level deprivation. In relation to ethnicity, in the UK TDT predominantly affects individuals of Pakistani and South Asian origin as evidenced by the National Haemoglobinopathy Registry (NHR) 2021 data and the BoI study respectively.[63 35, 64]The issue of scarcity of ethnically matched blood supplies for management of patients from minority ethnic backgrounds with TDT is also raised in the submission. The EAG recognises that the issue of ethnically matched transfusions may imply inequality in the effect of SoC, and as a consequence may impact on the distribution of treatment effects from exa-cel, dependent on how treatment effects are specified. As explained in Section 4.2.6.4, the company do not account for long-term consequences of iron damage in patients who achieve TI. However, uncertainty remains on whether the risk of developing complications for patients who achieve iron normalisation returns to background levels as this fails to recognise impacts related to past and residual iron overload. There is also uncertainty on whether these risks are associated with ethnicity or socio-economic status; where there is an association, a full DCEA may be more appropriate to account for these impacts. If the lack of ethnically matched transfusions affects HRQoL, mortality, or other SoC factors, and treatment normalises these across groups, this would denote a differential treatment effect across subgroups (e.g., greater HRQoL gain for those worse off initially) even as efficacy from exa-cel is assumed to be constant across population groups. Nevertheless, the DCEA does not appropriately reflect an equity concern on ethnicity, as the analysis solely focused on socio-economic deprivation. The company justify this based on the reasoning that most ethnic minority groups within the UK are also disproportionately affected by socio-economic deprivation. Therefore, the company used socio-economic deprivation as a proxy to reflect ethnicity.

Socio-economic deprivation and ethnicity are distinct dimensions of inequality. Simplifying assumptions may mask potential variation in the impact of TDT across different ethnic groups as a single ethnic group can have varying levels of deprivation and health outcomes. The submission also references that individuals of Asian and Southeast Asian origin with TDT face lower life expectancy and HRQoL, attributed to the development of secondary morbidities later in life, in comparison to individuals of different ethnic backgrounds. Ethnicity as a social determinant of health can also intersect with the different aspects of socio-economic deprivation captured by IMD. For these reasons, using IMD as a proxy for ethnicity is inappropriate and cannot be regarded as a conservative approach. Further to this, the study used to inform the level of inequality aversion in the submission

asked the UK general population for their concern about inequality between rich and poor groups. The strength of aversion to health inequality is likely to vary according to the way in which the different groups are specified, and so a value derived on the basis of comparing rich to poor would differ to one derived on the basis of comparing different ethnic groups. The EAG considers that the results presented by the company approximate the impact on health inequality across IMD groups only, and they do not capture inequality between ethnic groups. The EAG considers adopting an intersectional approach that incorporates both ethnicity and socio-economic concerns would be a more nuanced approach.

The company also judged the available ethnicity data for patients identified in the BoI study as inadequate for analysis based on ethnicity in the TDT population. This is because data for some ethnic minority groups, specifically Black and Mixed ethnicities, were masked due to low numbers. This presents implications for any data sourced from the BoI that has been matched on ethnicity. The EAG also note that any issues with the quality of ethnicity data in the study would not be resolved by using IMD as a proxy for ethnicity, and if anything may be exacerbated by this approach.

In principle the DCEA method can be applied by exploring the distribution of health across any equity relevant group, including groups defined based on ethnicity. To apply the aggregate DCEA approach used in the company submission to groups defined by ethnicity, the following distributions are required; treatment population distribution (available from the BoI study), health opportunity cost shares, general population proportions (available from the ONS) and QALE by ethnicity. Data on health opportunity costs by ethnicity is not readily available but this could be based on assumption, as the company has done so for IMD in the submission. Data on QALE by ethnicity is also not readily available, although the ONS provides data on mortality, burden of disease, and disease-free life expectancy by ethnicity. The EAG is not aware of studies that have attempted to estimate the Atkinson inequality aversion parameter in relation to health inequalities between ethnic groups, and so a DCEA based on ethnicity may be limited to measuring the change in inequality based on inequality metrics such as the SII and to estimating the threshold level of inequality aversion that might alter the recommendation.

An aspect to consider is that ONS analysis on ethnic differences in life expectancy in England and Wales (2011-2014) [65]suggests that life expectancy at birth is higher in ethnic minority groups compared to White British and Mixed ethnic groups. These results revealed complex patterns in life expectancy with potential explanations including health-related behaviours, socio-economic compositions, and clinical and biological factors. Hence from a health inequality perspective, the general population ethnic minority group may have the highest baseline health level.

DCEA inputs

At the clarification stage the company updated the distribution of QALE to the most recent estimates from Love-Koh et al., (2023)[66] and updated the general population proportions by IMD group to values reported in this reference. The general population estimates were based on pooled Health Survey for England sample data. It is inappropriate to use these proportions without adjusting for individual sampling weights for the sample to represent the larger population more accurately. Individual sampling weights adjusts for the fact that not all individuals share the same probability of being included in a sample. This is particularly significant in addressing potential disparities among different ethnic or socio-economic groups and avoids misrepresentation of certain subgroups in the analysis. The EAG prefers using ONS data which shows that IMD quintiles should represent around 20% of the total sample population i.e., a general population share distribution of 0.20 for each IMD group[67]. These values are applied in the EAG base-case DCEA analysis.

The total eligible treatment population size is set to 1,000 in the model with no reference. The EAG notes that this figure is different to the size of the prevalent population of 920 TDT patients provided in the submission. This discrepancy has insignificant impact on the results.

Estimation of health opportunity cost shares

Health opportunity cost shares in the model were based on assumption and applied as an equal share (20%) to each IMD quintile. The reference used in the submission for the general population proportions (Love-Koh et al., 2020)[60] provides an estimate of the distribution of the health opportunity cost in England by IMD, based on secondary healthcare utilisation. The company updated these values at the clarification stage, however, these were incorrectly calculated based on the distribution of the female population compared to the total population distribution reported in the publication. This error explains substantially increases the DCEA-weighted ICERs and reduces net health benefit. The EAG has updated this to reflect the total population distribution of health opportunity costs by IMD group.

Uptake proportions, which define the proportion of the population in each IMD quintile that uptake exa-cel, were assumed to be at 100%. Clinical advice to the EAG suggest that uptake may be less than 100% and this may be influenced by fear of potential side effects associated with therapy. It is possible that uptake may also be socially patterned if related to factors such as access to health services. The EAG notes that health opportunity costs were not further adjusted for the rate of uptake in exa-cel in the DCEA, however this does not affect base-case results where full uptake is assumed.

Inequality aversion parameter

An Atkinson inequality aversion parameter of 11 is applied in the analysis, based on an estimate reported in Robson et al. (2017)[62] that used data from an online survey of the general public in

England (n = 244). The EAG identified a more recent estimate of 3.5 based on further studies and a UK representative sample (n = 337) Robson et al., (2023).[68] The company expressed concern regarding the source suggested by the EAG, reasoning that it is based on a participant sample distribution that was skewed towards higher income groups, sampled via an online survey. The EAG notes that this was also the case in the 2017 study as there is similarity in the sample and methods used to identify aversion to health inequality. The company explains further that the source for an aversion parameter value was based on expert consultation and values reported in a systematic literature review on inequality aversion[69], ranging between 5.76 to 28.9. Therefore, the company deems the 3.5 estimate as a pessimistic scenario value. The EAG highlights that the referenced review included studies that explored inequality aversion based on varying contexts i.e., socioeconomic groups and neutrally labelled groups, some of which estimated low or no aversion to health inequality.

The EAG maintains its preference for sourcing the aversion parameter value of 3.5 from Robson et al., (2023)[68] and recognises that this value is smaller than previous UK estimates.

Indirect equity weighting approach

The submission applied indirect equity weights on the basis of QALE at birth by IMD using the Atkinson social welfare function. This was based on the derivative of the Atkinson social welfare function for each IMD group baseline QALE to the derivative of the baseline QALE in the least deprived IMD quintile (IMD 5). This resulted in weights equal to or greater than one across all IMD quintiles. The company cites Cookson et al. (2020)[70] to justify this approach but do not provide a chapter reference. To the EAG's knowledge, this reference does not address use of the derivative of the Atkinson SWF to calculate indirect equity weights in the manner used by the company. The EAG also notes that these indirect equity weights were calculated using the 'baseline distribution' and would have resulted in marginally different weights if calculated using the post-intervention distribution.

The EAG emphasises that this equity-weighting approach is not standard to DCEA and is not necessary as the Atkinson social welfare function allows equity impacts to be measured in the same units as total health in terms of equally-distributed equivalent (EDE) health. EDE health is a form of equity-weighted net health benefit variable that illustrates how far the actual QALY distribution across subgroups reduces the value of the QALYs gained compared to an equal distribution. Hence, the EDE health is more comparable to the standard CEA net health benefit variable. Neither an indirect weighted or a threshold weighted approach is required when using EDE. The EAG recognises that the equity-weights used in the submission gives some indication of the priority assigned to QALY gains in each IMD quintile as they were calculated relative to the least deprived group.

Application of indirect equity weights to financial opportunity costs

The company based the indirect equity weights on the aversion to inequality in the level of health across IMD groups. These weights were applied to the financial opportunity costs rather than the health opportunity costs to calculate the DCEA-weighted ICER. The company cites Cookson et al (2020) to justify this approach but does not provide a chapter reference. However, Cookson et al (2020, p.176) state that the proportion of opportunity costs that fall on each group is not determined by the proportion of costs generated by each group, but rather by the proportion of health benefits of the forgone activities that could have otherwise been funded.

The company's approach in applying derived indirect equity weights to the incremental QALY gains and to the incremental cost from the intervention represents an important point of departure from the standard DCEA methodology. Under standard DCEA methodology, the incremental costs from the intervention are converted into forgone QALYs in each equity relevant subgroup. These are subtracted from the incremental QALY gain from the intervention in each group, and the DCEA metrics are then calculated in relation to the net health benefit in each equity relevant subgroup. The Atkinson SWF, and the derived equity weights, applied in the submission are only relevant to different health levels and not applicable to financial impacts. DCEA incorporates health opportunity cost rather than monetary costs.

Equity-weighting to financial opportunity costs would also require that that there be some direct relationship between financial opportunity costs and health opportunity costs. Within cost-effectiveness methods, DCEA methods, and the NICE reference case, a link between incremental costs and health opportunity costs is provided by the cost-effectiveness threshold. However, the company's approach breaks this link having presented an equity-weighted ICER to the non-equity weighted NICE cost-effectiveness threshold. Additionally, in a reference case analysis the NICE cost-effectiveness threshold does not consider the distribution of opportunity costs. Therefore, the equity-weighted financial opportunity costs presented in the submission are not a function of the cost-effectiveness threshold.

The NICE cost-effectiveness threshold is primarily used to evaluate the incremental benefit gained from an intervention, expressed as the cost per QALY gained. This is useful in the NHS context; however, it may not fully capture the distributional impact of an intervention across different population subgroups and the broader societal considerations in DCEA. The company reasons that the application of indirect equity-weights to the incremental QALYs and costs results in the ICER being proportionally weighted. The EAG is not satisfied with this reason as the company does not provide clear justification or sources to support this.

8.1 EAG preferred DCEA analyses

In addition to scenario analyses to the cost-effectiveness analysis presented in Section 6, the EAG presents a few scenarios specific to the DCEA analysis, one of which incorporates an equity-weighting approach that aligns with the standard DCEA methodology. The Atkinson social welfare function can be used to estimate the equally distributed equivalent (EDE) of the incremental net health benefit. This number can be interpreted as the value of the incremental net health benefit adjusted for the equity impact of the intervention. If an intervention reduces inequality, the EDE incremental net health benefit will be greater than the incremental net health benefit. If an intervention increases inequality, the EDE incremental net health benefit will be smaller than the incremental net health benefit. The following scenarios shows the impact of the DCEA on the cost-effectiveness analysis result when the level dependent weighting introduced by the Atkinson social welfare function is shown directly in terms of the EDE:

18. Scenario 18: Updated company base-case with corrected DCEA inputs

At the request of the EAG, the company updated the DCEA inputs for the general population distribution, the QALE distribution, and the share of health opportunity costs to more recent figures. However, as discussed in Section 8, the distribution of the share of health opportunity costs were incorrectly calculated. The EAG presents results of the company base-case with the corrected calculation and updated input values.

19. Scenario 18b: Scenario 18 with an inequality aversion parameter value of 3.5 applied

The company reports its DCEA results for an Atkinson inequality aversion parameter value of 11 based on an estimate sourced from Robson et al., (2017).[62] The EAG maintains its preference for using a more recent value of 3.5, sourced from Robson et al., (2023)[68], to present the impact of the DCEA on the net health benefit. This scenario explores the impact of using an inequality aversion parameter value of 3.5. The EAG uses ONS data for the general population proportions which shows that IMD quintiles should represent around 20% of the total sample population.

20. Scenario 19: Scenario 18b with social welfare measured in terms of EDE health

As discussed in Section 8, the company's approach to indirect equity weighting is not standard to DCEA methodology. The EAG presents a scenario on the company's updated and corrected base case incorporating a more appropriate approach to DCEA using EDE health to measure social welfare. The EAG conducts analysis applying the £20,000 and £30,000 thresholds under the assumption that the threshold is representative of health opportunity costs. This scenario represents the EAG DCEA preferred base case.

Table 29 and Table 30 presents the NHB results of the DCEA scenario analyses described at a discount rate of 1.5% at £20,000 and £30,000, respectively. The results from the EAG preferred DCEA approach (Scenario 19) are presented in Table 31 and Table 32 at £20,000 and £30,000, respectively. Equity-weighted ICERs and NHBs are not presented in this section as the approach used by the company is non-standard to DCEA methodology. The EAG notes that the company used a custom dynamic array function within an external licenced software application that is neither built in nor supported by Microsoft Excel. The EAG has removed the dynamic array function in order to replicate the company and the EAG analyses in Sections 5, 6, and 8.

Table 29 EAG preferred DCEA inputs at a £20,000 threshold

	Individual level incremental NHB at £20,000 (1.5% discount rate)	
Scenarios	**Base-case**	**EDE**
Company base-case	[redacted]	[redacted]
Corrected DCEA company base-case	[redacted]	[redacted]
Corrected DCEA company base-case with an inequality aversion parameter value of 3.5 applied	[redacted]	[redacted]

Table 30 EAG preferred DCEA inputs at a £30,000 threshold

	Individual level incremental NHB at £30,000 (1.5% discount rate)	
Scenarios	**Base-case**	**EDE**
Company base-case	[redacted]	[redacted]
Corrected DCEA company base-case	[redacted]	[redacted]
Corrected DCEA company base-case with an inequality aversion parameter value of 3.5 applied	[redacted]	[redacted]

Table 31 Scenario 19: summary measures of impact on health distribution at a £20,000 threshold

Social welfare index	**SoC**	**Exa-cel**
Mean health (inequality aversion = 0)	[redacted]	[redacted]
Slope index of inequality	[redacted]	[redacted]
Atkinson EDE* (inequality aversion = 11)	[redacted]	[redacted]
Atkinson EDE* (inequality aversion = 3.5)	[redacted]	[redacted]
Incremental EDE* (inequality aversion = 3.5)	[redacted]	
Change in SII* (x 1000)	[redacted]	

Individual level incremental EDE NHB	[redacted]
Abbreviations: EDE, equally distributed equivalent health; SII, slope inequality index *The higher the EDE the better *As EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality *A positive change in SII indicates an increase in inequality after the intervention	

Table 32 Scenario 19: summary measures of impact on health distribution at a £30,000 threshold

Social welfare index	**SoC**	**Exa-cel**
Mean health (inequality aversion = 0)	[redacted]	[redacted]
Slope index of inequality	[redacted]	[redacted]
Atkinson EDE* (inequality aversion = 11)	[redacted]	[redacted]
Atkinson EDE* (inequality aversion = 3.5)	[redacted]	[redacted]
Incremental EDE (inequality aversion = 3.5)	[redacted]	
Change in SII * 1000	[redacted]	
Individual level incremental EDE NHB	[redacted]	
Abbreviations: EDE, equally distributed equivalent health; SII, slope inequality index *The higher the EDE the better *As EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality *A positive change in SII indicates an increase in inequality after the intervention		

The results for scenario 19 are presented in a health equity impact plane as shown in Figure 9 and Figure 10. The equity impact plane shows the relationship between the cost-effectiveness of an intervention (shown on the vertical axis) and its impact on health inequality (shown in the horizontal axis).

If an intervention falls in the northwest quadrant, it is cost-effective but inequality increasing compared to the comparator. If an intervention falls in the southeast quadrant, it is cost-ineffective but inequality decreasing. If an intervention falls in the northeast quadrant, the intervention is cost-effective and decreases inequality. As shown in Figure 9 and Figure 10, exa-cel falls in the southwest quadrant, indicating that the intervention is both cost-ineffective and inequality increasing. Given that the cost and equity impact fall in the same direction, trade-offs between cost-effectiveness and an alternative health equity objective become irrelevant hence further analysis is not required.

Figure 9 Health equity impact plane at 1.5% discount rate (EAG analysis)

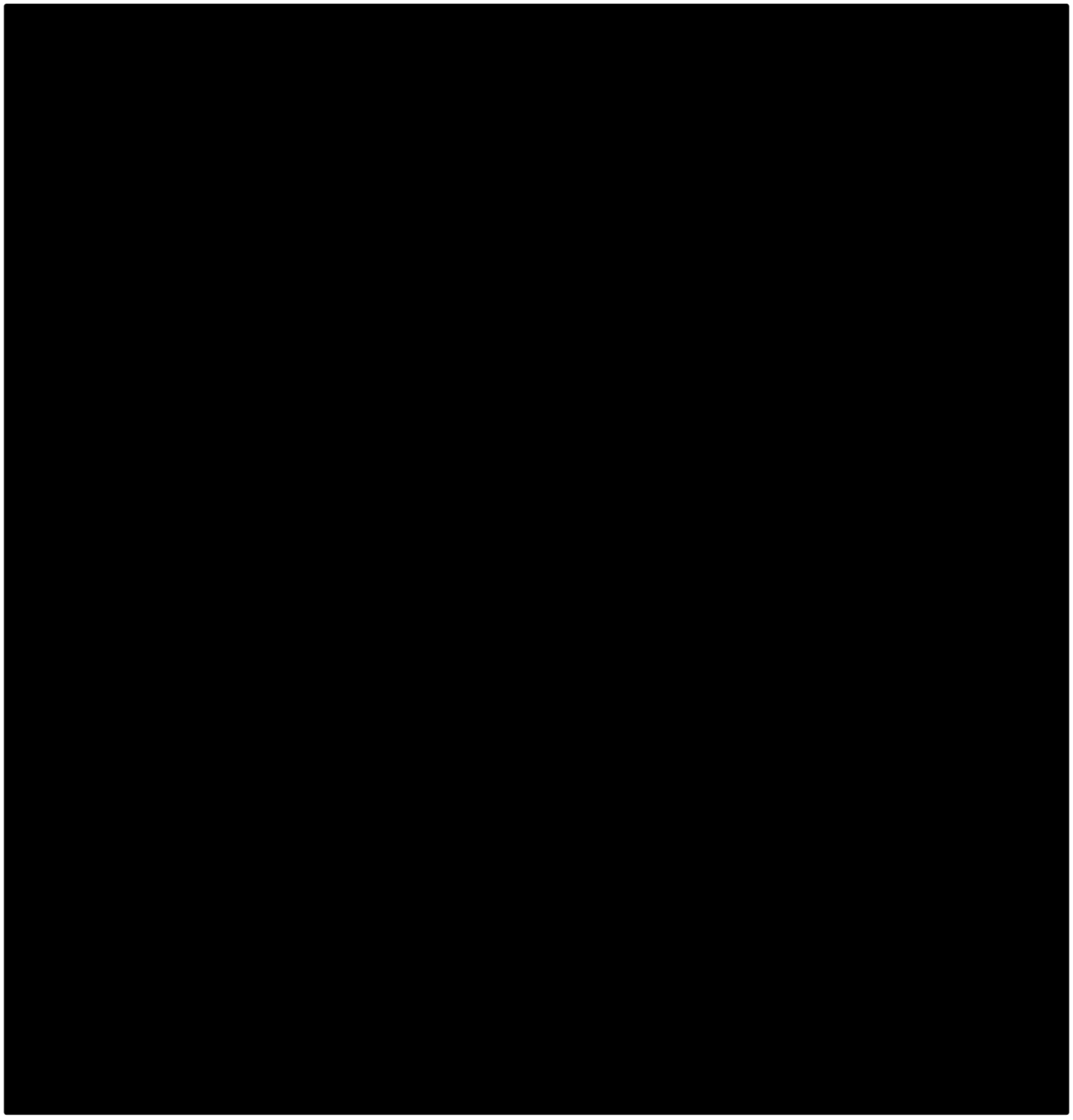


Figure 10 Health equity impact plane at 1.5% discount rate (EAG analysis)

EAG base case analysis

The impact of scenario 19 on the EAG preferred base-case (described in Section 6.3) is presented in Table 33 and Table 34 at £20,000 and £30,000, respectively.

Table 33 EAG DCEA exploratory analysis at £20,000

Scenarios	NHB at £20,000	
	Base case	EDE*
Company base-case (1.5% discount rate)	[redacted]	[redacted]
Company base-case scenario (3.5% discount rate)	[redacted]	[redacted]
EAG preferred base-case (3.5% discount rate)	[redacted]	[redacted]

EAG preferred DCEA on EAG base-case	[redacted]	[redacted]
*Where EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality		

Table 34 EAG DCEA exploratory analysis at £30,000

	NHB at £30,000	
Scenarios	**Base case**	**EDE**
Company base-case (1.5% discount rate)	[redacted]	[redacted]
Company base-case scenario (3.5% discount rate)	[redacted]	[redacted]
EAG preferred base-case (3.5% discount rate)	[redacted]	[redacted]
EAG preferred DCEA on EAG base-case	[redacted]	[redacted]
*Where EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality		

8.1.1 DCEA, Discounting and Severity modifier

The company have applied a non-reference case discount rate of 1.5%, a decision modifier in terms of the severity modifier, and have conducted a DCEA. All three of these departures from the reference case have the impact of inflating the estimated incremental QALY gain associated with the technology. In addition, the non-reference case discount rate and the DCEA adjusts the incremental costs associated with the technology.

The NICE methods manual does not address the combination of the non-reference case discount rate and decision modifiers. There is likely to be an association between meeting the criteria for the non-reference case discount of 1.5% (when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health), and a larger proportionate or absolute QALY shortfall. Indeed, while criteria for non-reference case discount of 1.5% are open to interpretation the EAG consider that the non-reference discount rate is primarily intended for severe conditions. This may have consequence for how the criteria for the non-reference discount rate of 1.5% are interpreted and whether it is considered appropriate to apply both the non-reference discount rate and severity modifier simultaneously.

When the NICE methods were updated in January 2022 the severity modifier was introduced but at the same time it was determined that there would be no introduction of formal methods to account for health inequalities. As such, the NICE methods manual does not directly address the issue of whether it is appropriate to combine a severity modifier with a DCEA. However, according to the methods manual, decision-making modifiers are factors that have not been included in the estimated QALY.

Due to the way that IMD affects the QALY shortfall estimation undertaken by the company, the severity weighted QALYs provided by the company include the influence of IMD.

The QALY shortfall that the company have estimated to justify the application of the severity modifier is determined by a crude comparison between QALE in the target patient population and QALE in an age and sex matched general population. It does not reflect the difference in QALE attributable to the disease alone, as it captures differences in QALEs from other factors that are correlated with presence of the disease, including socioeconomic deprivation. In the case of this appraisal, the patient population are on average living in lower IMD quintile areas compared to the general population, and as a result are expected to have a QALE shortfall compared to an age and sex matched general population regardless of the presence of TDT. This means that IMD is to some degree influencing the shortfall calculation, and informs the application of the NICE severity weights.

To illustrate, consider the model inputs in terms of the QALE in the general population by IMD, the distribution of the TDT population by IMD, and the distribution of the general population by IMD, as shown in Table 35. Without accounting for the health impacts of TDT, a population with the same IMD distribution as individuals with TDT would have an expected QALE of 67 years. In contrast, the general population has an expected QALE of 68.4 years. This implies 1.4 years of the QALY shortfall for individuals with TDT may be explained by the association of IMD with QALE.

Table 35 QALE shortfall associated with IMD

	IMD1	IMD2	IMD3	IMD4	IMD5
A. QALE	62.17	65.28	69.55	71.59	73.42
B. TDT population share	0.26	0.30	0.20	0.14	0.10
C. General population share	0.20	0.20	0.20	0.20	0.20
Sum product A and B					67
Sum product A and C					68.4

If the severity modifier is to be applied in combination with a DCEA that accounts for health inequalities between IMD quintiles, it would be appropriate to calculate the QALY shortfall between QALE in the target patient population and QALE in an age, sex and IMD matched general population. This would avoid any double counting or double weighting of differences in QALE associated with IMD. The EAG requested that the company provide this estimate in the points for clarification, but the company did not undertake this calculation.

8.1.2 DCEA Conclusions

The NICE reference case stipulates that an additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit. The use of a DCEA therefore represents a departure from the reference case. The final scope for the appraisal and the background in the company submission highlight equity concerns in relation to ethnicity. However, the company chose to perform a DCEA in terms of a measure of area-level deprivation, and hence the EAG consider that the results of the DCEA do not address equity concerns in relation to ethnicity, and may only be relevant to equity concerns regarding socioeconomic deprivation. The company apply aggregate DCEA methodology, but present the results using an equity weighted ICER that does not align with DCEA methodology, as it utilises financial rather than health opportunity costs. The EAG note that it is not uncommon for diseases to be associated with socioeconomic status, and that the use of weighting by socioeconomic deprivation to inform the decision in this evaluation would introduce inconsistency across evaluations

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10 APPENDICES

10.1 Appendix 1: Description of Simplified Economic Model

To aid understanding of the EAG's concerns regarding the company's approach to modelling mortality, the EAG has developed two simplified illustrative Excel models. The first model presented on the "EAG" sheet illustrates how mortality should be calculated, while the "company" sheet uses the company approach. The presented models are both based on a Markov structure assuming a single complication.

The models consist of three health states: i) No complications, ii) Complications and iii) Dead. All patients start without complications and may either stay in the No complications health state, develop complications in which case they move to the Complications health state, or die. Patients in the Complications health state can die but cannot move back to the No complications health state. For simplicity, the models do not consider QALYs or costs. The only model outcome is therefore life years gained.

The same inputs are used in both models and are summarised in Table 36. The input values used are made up and do not necessarily correspond with those used in the company's model. The EAG has, however, chosen plausible values to illustrate the magnitude of the issue on estimated life years.

Table 36 Summary of input parameters

Cycle length equals 1 year
Time horizon is 80 years
All patients start without complications
Patients have a 2% probability of developing complications per annum
Mortality without complications is 1% per annum
Mortality with complications is 10% per annum

On the "EAG" sheet mortality is estimated separately for patients in the No Complication and Complication health states. This means that patients with complications face a higher mortality rate than those without complications. On the "Company" sheet, a single mortality rate is calculated and applied to patients with and without complications. Mortality on the "Company" sheet is estimated exactly as in the full company model and is estimated by weighting complication-related mortality by the proportion of patients in the cohort with complications.

Results from each model show life years gained is 36.04 years in the "EAG" model and 29.14 years in the "company" model. Examination of the trace (which shows the proportion of patients in each

health state) shows that the company's modelling approach quickly overestimates the proportion of patients with complications and consequently overestimates mortality risks.

CONFIDENTIAL UNTIL PUBLISHED
External Assessment Group Report
Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia

EAG addendum: review of D120 data cut

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Nyanar Jasmine Deng, Research Fellow, CRD, University of York Mark Corbett, Research Fellow, CRD, University of York Eleonora Uphoff, Research Fellow, CRD, University of York Joseph Lord, Research Fellow, CRD, University of York Helen Fulbright, Information Specialist, CRD, University of York Susan Griffin, Professor of Health Economics, CHE, University of York Claire Rothery, Professor of Health Economics, CHE, University of York Robert Hodgson, Senior Research Fellow, CRD, University of York
Correspondence to	Robert Hodgson, Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD
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Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all depersonalised data (DPD) are highlighted in pink and underlined.

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1 DESCRIPTION AND CRITIQUE OF NEW CLINICAL EVIDENCE

1.1 EAG summary of the company's new data cut for efficacy and safety outcomes

The company reported that an analysis of efficacy and safety data had been performed at Day 120 post-marketing authorisation application (the D120 data cut) in response to a request by regulatory authorities. The analyses were therefore not pre-specified in the statistical analysis plan and the database lock for the analyses was 16th April 2023. At the D120 data cut-off, 59 patients were enrolled in CLIMB THAL-111, 54 of which had received exa-cel (this was 48 in the original submission). Updates for other data sets and stages used in the CLIMB studies are presented in Table 1.

Table 1 Patient analysis sets for the new and previous data cuts

Study stage	CS data cut (IA2) September 2022	D120 data cut April 2023
Enrolled Set	59	59
Safety Analysis Set (SAS)	59	59
Started the conditioning regimen	48	54
Full Analysis Set (FAS)	48	54
FAS beyond initial RBC transfusion washout period*	44	53
PES	27	42
Completed CLIMB THAL-111 and enrolled in CLIMB-131	8	23

Notes: Enrolled Set - all enrolled patients who signed informed consent and met eligibility criteria. SAS - all patients who started the mobilisation regiment. FAS - all patients who received exa-cel infusion. PES - all patients who had been followed least 16 months after exa-cel and for at least 14 months after completion of the RBC transfusions washout period.

1.1.1 Efficacy outcomes

The median follow-up duration after exa-cel infusion was 22.8 months (range: 2.1 to 51.1) months). Forty-two patients had at least 16 months of follow-up after exa-cel infusion and were evaluable for the PES at the D120 data cut. Following infusion with exa-cel, 92.9% of patients (39 of 42 patients, 95% CI: 80.5%, 98.5%) in the PES achieved transfusion independence at 12 months (TI12). This proportion is slightly larger than in the previous data cut (IA2: 88.9%). The same increase was observed for TI6.

All 39 subjects in the D120 PES who achieved TI12 remained transfusion independent; the mean duration of transfusion independence was 23.6 months, ranging from 13.5 to 48.1 months. Mean HbF levels and total Hb levels remained constant compared to the levels reported for the IA2 data cut.

At Month 24, mean serum ferritin levels were similar across the data-cuts. No update was provided for levels of liver iron content or cardiac iron content (T2*).

1.1.2 Safety outcomes

Table 2 summarises safety data from the TDT safety set reported in the original CS (N=48) and from the D120 data update up to M24 (N=54) and after M24 (N=23). In the data update, no new or worsening haematological disorders were reported, and no new malignancies or deaths. The SAE occurring in CLIMB-131 was influenza and was not related to the treatment.

Table 2 Safety data from exa-cel infusion to M24 and >24 M[1]

	TDT safety set		**Data update**		**TDT safety set**	**Data update**
	Exa-cel to M24 (N=48)		**Exa-cel to M24 (N=54)**		**> M24 CLIMB THAL-131 (N=9)**	**> M24 CLIMB THAL-131 (N=23)**
	Any grade	**Grade 3–5**	**Any grade**	**Grade 3-5**	**Any grade**	**Any grade**
No. of patients, n (%)						
≥ 1 AE	48 (100%)	41 (85.4%)	54 (100%)	48 (89%)		
≥ 1 SAE	17 (35.4%)		19 (35%)		1 (11.1%)	1 (4.3%)
≥ 1 AE (possibly) related to exa-cel	13 (27.1%)			14 (25.9%)	0	0
≥ 1 SAE (possibly) related to exa-cel	2 (4.2%)			2 (3.7%)	0	0
New or worsening haematological disorders	42 (87.5%)		0		0	0
Key: AE, adverse event; SAE, serious adverse event.						

1.1.3 Summary

The new D120 April 2023 data cut indicates a slightly improved rate of transfusion independence at 12 months and a continuing persistence of effect in patients who achieve TI12. Mean HbF levels and total Hb levels remained constant across the data-cuts, as did mean serum ferritin levels. The lack of an update on results for liver iron content and cardiac iron content is concerning though.

2 DESCRIPTION AND CRITIQUE OF NEW ECONOMIC EVIDENCE

2.1 Updated cost-effectiveness model parameters

The company detailed a number of parameters updated in the economic model to reflect the D120 data cut. These are detailed in Table 3 below.

Table 3 Updated model inputs

Parameter	Description of change	Previous value (IA2)	Updated value (D120)	Justification
CEA model input changes				
Age (years)	Updated mean baseline cohort age to D120	21.4	21.3	D120 data available
Weight ration	Updated weight ratio of TDT/general public to D120	0.76	0.77	D120 data available
Females (%)	Updated % of females in modelled cohort	52.1%	50.0%	D120 data available
Proportion <18 years old	Updated % of cohort < 18 years old	33.3%	35.2%	D120 data available
Annual transfusions per patient	Updated annual frequency of RBCTs per patient	16.4	16.5	D120 data available
Annualised unit of RBC transfusions	Updated annualised units of RBCTs per patient	35.3	36.4	D120 data available
Treatment withdrawal	Updated to reflect latest clinical and efficacy data (D120)	4.0%	5.3%	D120 data available
Initial engraftment success rate	Same as above	100%	100%	D120 data available
Proportion achieve TI	Same as above	92.6%	100%	D120 data available
Proportion achieve TR	Same as above	7.4%	0%	D120 data available

2.2 Health related quality of life

The company provided updated patient-reported outcome scores for the D120 data cut. The company describe how at baseline, the D120 health utility scores in CLIMB THAL-111 were 0.89 in the PES population. This contrasts to 0.87 based on the data used in the original submission. For the PES patients with 24 months of follow-up, the magnitude of gain over 24 months in health utility scores at D120 was 0.04 (n=19), less than the gain observed in patients in the original submission (0.07 (n=8). Updated patient-reported outcome scores were also provided for the other outcome measures included

in the original report. The EAG note that all patient reported outcome scores reported by the company showed numerical increases in quality of life scores, but none of these were statistically significant.

The EAG's preferred assumptions included a utility decrement associated with the condition equal to the difference in health utilities between the baseline PES score and an age-matched general population value of 0.940 reported by Ara and Brazier 2010. The EAG's preferred utility decrement in the original report was [redacted]. Using the data from the D120 data cut, the decrement used in the analysis is [redacted] and as a result, the EAG considers it appropriate to update the preferred EAG base-case assumptions to reflect this.

2.3 Treatment effectiveness and extrapolation

2.3.1 Transfusion dependence

The D120 data cut updates the proportion of the patients who achieve TI status from 92.6% to 100%. As per the original CS, TI status in the economic analysis is defined *post hoc* and is inconsistent with primary and secondary outcomes defined in CLIMB THAL-111. This definition means three patients who do not meet the TI12 criteria for transfusion independence are classified as transfusion independent in the economic analysis.

As noted in the EAR, the EAG considers the use of the *post hoc* definition of transfusion status to be inappropriate. The EAG prefers to use the TI12 primary outcome to inform the proportion of patients achieving transfusion independence. Using the data from the D120 data cut, the proportion of patients achieving transfusion independence increases from 88.9% (24/27) to 92.8% (39/42). The EAG has updated the preferred EAG base-case assumptions to reflect this new data.

2.3.2 Engraftment success and graft durability

The D120 data cut increases the number of patients who have completed 24 months follow from 8 to 23. There were no engraftment rejections (failures) and no recorded events of loss of transfusion independence. The available evidence continues to support the assumptions of a permanent treatment effect in patients achieving transfusion independence. As per the IA2 data cut, direct evidence remains limited by the small sample size and short duration of follow-up.

3 UPDATED ECONOMIC MODEL

The company updated the model to include data at the D120 cut-off based on the availability of updated CSR data and/or post-hoc analysis following the clarification stage. The company also updated DCEA inputs based on the company's clarification response to the EAG requests. The results presented in this section reflect these modifications to the base-case.

3.1 Results of the updated company base-case analysis

The cost-effectiveness results for the company's base-case analysis are presented in Table 4 and Table 5

Table 4 Base-case results with 1.5% discount rate (deterministic)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years						

Table 5 Scenario results with 3.5% discount rate (deterministic)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years						

3.2 Results inclusive of DCEA reweighting

The company base-case results and scenario analysis inclusive of severity and DCEA re-weighting are presented in

Table 6. These results are presented in NHB form as the DCEA weighting assumes that the NICE threshold represents the health opportunity cost forgone from displaced healthcare services.

Table 6 Company base case results inclusive of DCEA reweighting

Scenarios	NHB at £30,000			
	Base-case	Severity weighted	DCEA weighted	DCEA and severity weighted
Company base-case (1.5% discount rate)	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case (3.5% discount rate)	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: NHB, net health benefit; DCEA, distributional cost-effectiveness analysis				

3.3 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 7 updates scenario analysis presented in the EAR accounting for the D120 update and revised company base case.

Table 7 EAG's additional scenario analysis

Scenario	Technology	Total		Incremental		ICER	Severity weighted at ICER (1.2 multiplier)
		Costs	QALYs	Costs	QALYs		
Company base case	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Modelling no complications	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Costs and outcomes from exa-cel withdrawal	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Baseline prevalence of osteoporosis and diabetes based on CLIMB THAL-111	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Baseline iron levels based on CLIMB THAL-111	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Frequency of blood transfusions based on Shah et al., 2021	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. 3.5% Discount rate	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Align transfusion independence to the TI12 primary outcome in CLIMB THAL-111*	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8 (a). Relapse based on published values from Santarone et al. 2022	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 (b). Relapse based on US ICER report	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. Assuming 5 years to iron normalisation	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. Iron normalisation in patients with low iron levels	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11 (a). SMR of 2.5 for TD patients	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11 (b). SMR of 2 for TD patients	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12. 1.4% mortality risk for myeloablative conditioning	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13 (a). [redacted] utility decrement*	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13 (b). 0.1 utility decrement	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13 (c). 0.15 utility decrement	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14. No infertility-related decrements	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15. Use of eMIT costs	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16. No health state costs	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17. Multiplicative age-adjustment	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*Scenario has been updated following the D120 data cut							

3.4 EAG's preferred assumptions

The cumulative impact of the EAG's preferred assumptions on the base-case are presented in Table 8 and Table 9. The EAG base-case adopts the following scenarios described in the EAR:

- Scenario 1: Alternative assumptions mortality associated with complications,
- Scenario 2: Costs and outcomes from exa-cel withdrawal,
- Scenario 5: Frequency of blood transfusions based on Shah et al., 2021,

- Scenario 6: Using a 3.5% discount rate,
- Scenario 7: Aligning the definition of transfusion independence to the T12 primary outcome in CLIMB THAL-111,
- Scenario 9: Assuming 5 years to iron normalisation,
- Scenario 11: Assuming an SMR of 2.5 for TD patients,
- Scenario 13: HRQoL decrement of [redacted] relative to the general population (updated based on D120 data),
- Scenario 15: Use of eMIT costs,
- Scenario 17: Multiplicative approach to age-adjustment.

Table 8 EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY
Company base-case	5.1.1.1	[redacted]
1. Modelling no complications	4.2.2	[redacted]
2. Costs and outcomes from exa-cel withdrawal	4.2.2	[redacted]
5. Frequency of blood transfusions based on Shah et al., 2021	4.2.4	[redacted]
6. Using a 3.5% discount rate	4.2.5	[redacted]
7. Aligning transfusion independence to the T12 primary outcome in CLIMB THAL-111*	4.2.6	[redacted]
9. Assuming 5 years to iron normalisation	4.2.6	[redacted]
11. Assuming an SMR of 2.5 for TD patients	4.2.6.5	[redacted]
13. HRQoL decrement of [redacted] relative to the general population*	4.2.7	[redacted]
15. Use of eMIT costs	4.2.8	[redacted]
17. Multiplicative approach to age-adjustment	4.2.7.4	[redacted]
*Scenario has been updated following the D120 data cut		

Table 9 EAG preferred base-case

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Severity weighted ICER (1.2 multiplier)
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.4.1 Additional scenario analysis on the EAG's base case

Additional scenario analysis on the EAG's base case is presented in Table 10.

Table 10 Results of scenario analyses on the EAG alternative base case analysis

Scenario	Technology	Total		Incremental		ICER	Severity weighted at ICER (1.2 multiplier)
		Costs	QALYs	Costs	QALYs		
EAG base case	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.5% Discount rate	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse based on published values from Santarone et al. 2022	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse based on US ICER report	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.4% mortality risk for myeloablative conditioning	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4 DISTRIBUTIONAL COST-EFFECTIVENESS ANALYSIS

This section utilises the updated DCEA inputs based on the company's clarification response and the updated model at the D120 cut-off. The results presented in this section reflect these modifications to the base case. As discussed in Section 8 of the EAR, the distribution of the share of health opportunity costs was incorrectly calculated based on the distribution of the female population rather than the total population reported in the publication, therefore the EAG has implemented the correction in this section. The EAG also uses ONS data for the general population proportions, which shows that IMD quintiles should represent around 20% of the total sample population. The reasons for this are discussed in Section 8 of the EAR.

The NHB results of the DCEA scenario analyses described at a discount rate of 1.5% at £20,000 and £30,000 are presented in Table 11 and Table 12, respectively, using the EAG's preferred approach of using the equally distributed equivalent (EDE) NHB. Results with the Atkinson parameter value of 3.5 applied are also included. The results from the EAG preferred DCEA approach (Scenario 19 in the EAR) are presented in Table 13 and Table 14 at £20,000 and £30,000, respectively.

Table 11 EAG preferred DCEA inputs at a £20,000 threshold (updated model)

Scenarios	Individual level incremental NHB at £20,000 (1.5% discount rate)	
	Base-case	EDE
Company base-case	[redacted]	[redacted]
Corrected DCEA company base-case	[redacted]	[redacted]
Corrected DCEA company base-case with an inequality aversion parameter value of 3.5 applied	[redacted]	[redacted]

Table 12 EAG preferred DCEA inputs at a £30,000 threshold (updated model)

Scenarios	Individual level incremental NHB at £30,000 (1.5% discount rate)	
	Base-case	EDE
Company base-case	[redacted]	[redacted]
Corrected DCEA company base-case	[redacted]	[redacted]
Corrected DCEA company base-case with an inequality aversion parameter value of 3.5 applied	[redacted]	[redacted]

Table 13 EAG scenario 19 (updated model): summary measures of impact on health distribution at a £20,000 threshold

Social welfare index	SoC	Exa-cel
Mean health (inequality aversion = 0)	[redacted]	[redacted]
Slope index of inequality	[redacted]	[redacted]
Atkinson EDE* (inequality aversion = 11)	[redacted]	[redacted]
Atkinson EDE* (inequality aversion = 3.5)	[redacted]	[redacted]
Incremental EDE* (inequality aversion = 3.5)	[redacted]	
Change in SII* (x 1000)	[redacted]	
Individual level incremental EDE NHB	[redacted]	

Abbreviations: EDE, equally distributed equivalent health; SII, slope inequality index
*The higher the EDE the better
*As EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality
*A positive change in SII indicates an increase in inequality after the intervention

Table 14 EAG scenario 19 (updated model): summary measures of impact on health distribution at a £30,000 threshold

Social welfare index	**SoC**	**Exa-cel**
Mean health (inequality aversion = 0)	[redacted]	[redacted]
Slope index of inequality	[redacted]	[redacted]
Atkinson EDE* (inequality aversion = 11)	[redacted]	[redacted]
Atkinson EDE* (inequality aversion = 3.5)	[redacted]	[redacted]
Incremental EDE (inequality aversion = 3.5)	[redacted]	
Change in SII * 1000	[redacted]	
Individual level incremental EDE NHB	[redacted]	

Abbreviations: EDE, equally distributed equivalent health; SII, slope inequality index
*The higher the EDE the better
*As EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality
*A positive change in SII indicates an increase in inequality after the intervention

The results for scenario 19 with the updated company inputs are presented in a health equity impact plane as shown in Figure 1 and Figure 2. The equity impact plane shows the relationship between the cost-effectiveness of an intervention (shown on the vertical axis) and its impact on health inequality (shown in the horizontal axis). Both figures show that exa-cel falls in the southwest quadrant, indicating that the intervention is both cost-ineffective and inequality increasing.

Figure 1 Health equity impact plane at 1.5% discount rate (EAG analysis on updated model)

Figure 2 Health equity impact plane at 1.5% discount rate (EAG analysis on updated model)

4.1.1 EAG base case analysis

The impact of updated parameters on the EAG preferred base case (described in Sections 6.4 and 8.1 of the EAR) is presented in Table 15 and Table 16 at £20,000 and £30,000, respectively.

Note that the NHB results for the EAG preferred base-case in the equivalent tables in the main EAG report (Tables 33 and 34 of the EAR) were incorrectly derived from the base-case results sheet of the model rather than the EAG additional analysis sheet, resulting in marginally higher NHBs. The results in this section have been updated accordingly.

Table 15 EAG DCEA exploratory analysis at £20,000 (updated model)

Scenarios	NHB at £20,000	
	Base case	EDE*
Company base-case (1.5% discount rate)	[redacted]	[redacted]
Company base-case scenario (3.5% discount rate)	[redacted]	[redacted]
EAG preferred base-case (3.5% discount rate)	[redacted]	[redacted]
EAG preferred DCEA on EAG base-case	[redacted]	[redacted]
*Where EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality		

Table 16 EAG DCEA exploratory analysis at £30,000 (updated model)

Scenarios	NHB at £30,000	
	Base case	EDE*
Company base-case (1.5% discount rate)	[redacted]	[redacted]
Company base-case scenario (3.5% discount rate)	[redacted]	[redacted]
EAG preferred base-case (3.5% discount rate)	[redacted]	[redacted]
EAG preferred DCEA on EAG base-case	[redacted]	[redacted]
*Where EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality		

EAG corrections

Following the D120 update the EAG has identified errors in the implementation of Scenario 2 and 7. Results for EAG Scenario 2 were calculated incorrectly using the treatment withdrawal rate from IA2, while Scenario 7 did not recalculate the proportion of TR patient correctly. Table 1 reflects the EAG Scenario 2 results with the treatment withdrawal rate updated to the D120 data cut. Table provide results for scenario 7 updated to reflect the response rate after the TR phase following the D120 update.

Table 1 EAG additional scenario analysis, Scenario 2

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER (1.2 multiplier)
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years						

Table 2 EAG additional scenario analysis, Scenario 7

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	Severity weighted ICER (1.2 multiplier)
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years						

EAG's preferred assumptions

The results presented in Table 3 and Table 4 are equivalent to Table 8 and Table 9, respectively, in the updated efficacy and safety data cut addendum, incorporating the corrections to Scenario 2 and Scenario 7.

Table 3 EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY
Company base-case	5.1.1.1	[redacted]
1. Modelling no complications	4.2.2	[redacted]
2. Costs and outcomes from exa-cel withdrawal	4.2.2	[redacted]
5. Frequency of blood transfusions based on Shah et al., 2021	4.2.4	[redacted]

6. Using a 3.5% discount rate	4.2.5	[redacted]
7. Aligning transfusion independence to the T12 primary outcome in CLIMB THAL-111*	4.2.6	[redacted]
9. Assuming 5 years to iron normalisation	4.2.6	[redacted]
11. Assuming an SMR of 2.5 for TD patients	4.2.6.5	[redacted]
13. HRQoL decrement of [redacted] relative to the general population*	4.2.7	[redacted]
15. Use of eMIT costs	4.2.8	[redacted]
17. Multiplicative approach to age-adjustment	4.2.7.4	[redacted]
*Scenario has been updated following the D120 data cut		

Table 4 EAG preferred base-case

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Severity weighted ICER (1.2 multiplier)
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Additional scenario analysis on the EAG's base case

The results presented in Table 5 are equivalent to Table 10 in the updated efficacy and safety data cut addendum, incorporating the corrections to Scenario 2 and Scenario 7.

Table 5 Results of scenario analyses on the EAG alternative base case analysis

Scenario	Technology	Total		Incremental		ICER	Severity weighted at ICER (1.2 multiplier)
		Costs	QALYs	Costs	QALYs		
EAG base case	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.5% Discount rate	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse based on published values from Santarone et al. 2022	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapse based on US ICER report	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SoC	[redacted]	[redacted]				

1.4% mortality risk for myeloablative conditioning	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG base case DCEA analysis

The results presented in Table 6 and Table 7 are equivalent to Table 15 and Table 16, respectively, in the updated efficacy and safety data cut addendum, incorporating the corrections to Scenario 2 and Scenario 7. Note that this correction resulted in differences in the EAG base case NHBs and the respective EDE values.

Table 6 EAG DCEA exploratory analysis at £20,000 (updated model)

	NHB at £20,000	
Scenarios	**Base case**	**EDE***
Company base-case (1.5% discount rate)	[redacted]	[redacted]
Company base-case scenario (3.5% discount rate)	[redacted]	[redacted]
EAG preferred base-case (3.5% discount rate)	[redacted]	[redacted]
EAG preferred DCEA on EAG base-case	[redacted]	[redacted]
*Where EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality		

Table 7 EAG DCEA exploratory analysis at £30,000 (updated model)

	NHB at £30,000	
Scenarios	**Base case**	**EDE***
Company base-case (1.5% discount rate)	[redacted]	[redacted]
Company base-case scenario (3.5% discount rate)	[redacted]	[redacted]
EAG preferred base-case (3.5% discount rate)	[redacted]	[redacted]
EAG preferred DCEA on EAG base-case	[redacted]	[redacted]
*Where EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality		

Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 25 September** 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.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Definition of transfusion independence in CLIMB THAL-111

Description of problem	Description of proposed amendment	Justification for amendment	
In Section 3.2.1, page 37, the EAG incorrectly define TI12 as 'maintaining a weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion.'.	The EAG should correct the description to note that the evaluation of TI12 starts 60 days after the last RBC transfusion for post-transplant support or TDT disease management (referred to as the washout period).	The EAG definition of TI12 on page 37 does not take account of the 60 day RBC transfusion 'washout' period.	Text has been added as suggested.

Issue 2 Clarity on comorbidity percentages

Description of problem	Description of proposed amendment	Justification for amendment	
Section 2.2.2.1 page 26 ‘The company describe results from a UK study of patients with TDT, finding that more than 25% of these patients suffer from diabetes, hypopituitarism, and osteoporosis’	The EAG should clarify that more than 25% had diabetes, more than 25% had hypopituitarism and more than 25% had osteoporosis	Current wording implies that 25% have diabetes or hypopituitarism or osteoporosis and therefore underestimates the burden of the disease	Reworded according to proposed amendment.

Issue 3 Outcomes included in the decision problem

Description of problem	Description of proposed amendment	Justification for amendment	
Section 2.3.2 page 29 'The EAG is unsure why the outcome 'new or worsening haematologic disorders' was not included in the decision problem, given that data were available'.	Clarification of why this outcome was not included in the decision problem	'New or worsening haematologic disorders' are included in CLIMB-131 and not CLIMB THAL-111 as the aim of this outcome is to measure long term haematologic disorders e.g. aplastic anaemia, myelodysplasia, immune cytopenias which may be seen as long term complications of transplantation and myeloablation. Thrombocytopenia and neutropenia are expected and time-limited adverse events following busulfan myeloablation.	Not a factual inaccuracy. The EAG was unsure why the outcome was not included.

Issue 4 Misrepresentation of Caocci et al

Description of problem	Description of proposed amendment	Justification for amendment	
Section 3.2.1.2 page 38 'However, splenectomy can improve prognosis, since splenectomised patients may need fewer blood transfusions.'.	Caocci et al showed that despite a lower burden of annual transfusion requirement, splenectomy is associated with a higher prevalence of cardiovascular disease and diabetes. Furthermore splenectomy is most commonly performed in patients with splenomegaly and hypersplenism due to under-transfusion. Adequate transfusion (as per current guidelines) reduces the incidence of hypersplenism and splenomegaly and reduces the need for splenectomy. The EAG should provide additional context to more appropriately reflect the findings of the cited paper.	The statement does not accurately represent the findings in the quoted paper.	Text has been added about the higher prevalence of cardiovascular comorbidities and diabetes.

Issue 5 Misuse of the term mixed chimerism

Description of problem	Description of proposed amendment	Justification for amendment	
Section 3.2.2 page 41 ‘mixed chimerism’	Figure 18 of the CS shows the proportion of alleles with the intended genetic modfication (allelic editing) in the CD34+ cells of the bone marrow over time and reflects the proportion of alleles with the intended genetic modification in the exa-cel drug product (11.4.4.5 in the CSR). It is indicative of the durable engraftment of edited LT-HSCs and reflects the permanent nature of the intended edit.	Mixed chimerism refers to a state in which the lymphohaematopoeitic system of the recipient of allogeneic haematopoietic stem cells comprises a mixture of host and donor cells. As this is not an allogeneic procedure this terminology is not accurate.	This terminology was used by the EAG’s clinical adviser and appears to be the most appropriate terminology to describe the issue in question, in the absence of an alternative sugestion.

Issue 6 Critique of data extraction for clinical effectiveness SLR

Description of problem	Description of proposed amendment	Justification for amendment	
Section 3.1 page 36, the EAG notes that 'The number of studies included for data extraction but not prioritised is inconsistently reported as either 96 or 97 studies.'	The number of studies included but not prioritised is not explicitly mentioned in the CS. The updated search highlights that 100 unique studies were included, of which three studies were prioritised for data extraction. It is unclear as to how the EAG have arrived at the	Clarification regarding the number of studies included for data extraction but not prioritised	Not a factual inaccuracy. Table 66 in Appendix D (p. 63) lists 96 records.

	conclusion that 96 studies were not prioritised based on the evidence provided in the CS.		
Section 3.1, page 36, the EAG state that the 'reasons for not prioritising studies are not clearly stated'	We propose the text should be amended to the following: 'Reasons for not prioritising studies are found in Table 66 of the CS'	Clarification that reasons for not prioritising the study were summarised in the CS (Appendix D, Table 66, p. 63)	Text amended to 'Reasons for not prioritising studies were not explained, but are listed in Table 66, Appendix D (p.63).'

Issue 7 Critique of trials of the technology of interest, the company's analysis and interpretation

Description of problem	**Description of proposed amendment**	**Justification for amendment**	
Section 3.2.1.1 page 37, the EAG state that 'The company presented quality assessment results for CLIMB THAL-111 in Table 69 of the appendices document. The value of the assessment was inherently limited, given that the trial has a single-arm design. Most of the criteria which could be completed for this study design related to	It is unclear as to why the value of the quality assessment of CLIMB THAL-111 is deemed to be 'inherently limited'. The critical appraisal of CLIMB THAL-111 was performed according to the guidelines set out in the relevant chapter (2.5) of the 'STA and HST evaluation: User guide for company evidence submission template' document.	Clarification that the quality assessment for CLIMB THAL-111 was performed in accordance with the stated guidance for non-randomised and non-controlled studies.	Not a factual inaccuracy. The value of the assessment was inherently limited, given that the trial has a single-arm design. This would be the case when assessing any single-arm trial.

aspects of study reporting (which all seemed adequate).'			

Issue 8 Validity of EQ-5D-5L for capturing the impact of TDT on HRQoL

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.1, page 42, the EAG state that 'the company considered EQ-5D-5L to not be an effective tool for capturing the impact of transfusion-dependent β-thalassaemia on health related quality of life (HRQoL) and thought it may not be responsive to changes'.	Suggested to correct to 'The company considered EQ-5D-5L to not be an effective tool for capturing the impact of transfusion-dependent β-thalassaemia on health related quality of life (HRQoL) based on published data.'	Clarification that the company's position regarding the lack of responsiveness towards EQ-5D-5L for TDT is based on empirical evidence (as highlighted in the Sections B.1.3.2.2 of the CS) rather than thought alone.	Not a factual inaccuracy.

Issue 9 Studies included in the cost-effectiveness review

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.1.3, page 47, the EAG state 'Delea et al (2007) and Pepe et al. (2017) were not identified in	Both Delea et al. (2007) and Pepe et al. (2017) were identified during Ti/Ab screening but were excluded on the basis that they report cost-	Clarification that these cost-effectiveness studies were identified but were excluded on the basis that they do not	Not a factual error. The reported inclusion criteria

the review; it is unclear why they were missed.'	effectiveness analyses from a US and Italian healthcare system respectively. These are therefore not relevant to the decision problem.	report cost-effectiveness results from a UK healthcare system perspective.	do not state a geographical limit.

Issue 10 Omission of SMR calibration exercise for replication

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Secton 4.2.6.5, page 76, the EAG state that 'Full details of how the calibration of the model was undertaken are not included in the CS or executable model but it appears to have been conducted by comparing the cumulative survival in the SoC arm with that of the general population at the end of the model time horizon (last cycle of the model).'	To remove the statement or ackowledge the company's provision of cell calculations, values, and dependencies, enabling clear replication and full interpretation of the calibration for the SMR of TD patients, over the modelled time horizon.	The CS dossier submission provides a description of the equations applied to calibrate the lifetime SMR. In the CS model, several cells are provided that enable a transparent and clear replication for the calibration of the lifetime SMR for TD patients. These are cells D28:E28 of the 'Mortality inputs' sheet as well as the cell W7 in the 'Raw_mortality_UK' sheet. Both cell values are fully traceable, via the 'Trace precedents' tool in Excel, which shows raw calculations of the lifetime SMR for TD patients	Not a factual error The EAG is aware of the calculations that the company are referring to. As stated in the EAR this appears to estimate the SMR by comparing cumulative survival in the SoC arm with that of the general population. This approach will not result in an overall SMR of 5.

		within the SOC model mortality trace.	

Issue 11 Representation of transfusion burden across sources

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15, Page 64: The EAG state that 'The company base-case uses the CLIMB THAL-111 trial to inform the frequency of RBC transfusions and assumes TDT patients received 16.4 transfusions per year. The EAG notes that this frequency of RBC infusions is substantially higher than observed in the Shah et al. (UK Chart Review) where patients received an average of 13.7 transfusions per year.'	To remove the reference to substantially higher, and instead note that the range observed in CLIMB THAL-111 is at the upper end of the frequency indicated by the EAG's clinical adviser, where Shah et al is at the lower end.	The EAG's own clinical adviser 'indicated that a transfusion is normally given every three or four weeks for TDT (Pg 26)'. Every three or four weeks corresponds to a rate of 13 to 17.33 transfusions per year. As such, both the rates observed in Shah et al, and CLIMB THAL-111 fall within the range expected by the EAG's clinical adviser. In this context, representing the difference in transfusion frequency as substantial is overdone.	Not a factual error. 16.4 is substantially higher than 13.7.

Issue 12 Burden of illness study

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16, Page 67: 'The EAG highlights that	Removal of the word historic	The retrospective burden of illness study was conducted	The wording has been changed on page 16 only

literature cited in support of this assumption, is based on historic cohorts of patients who are older than those eligible to receive exa-cel and represents a restricted cohort of TDT patients which include patients otherwise ineligible for exa-cel'		with the study period 2008 – 2019 in a contemporary cohort.	to better reflect the EAG's concerns.

Issue 13 Patients with pre-existing complications

Description of problem	**Description of proposed amendment**	**Justification for amendment**	
Page 68: 'Firstly, for patients with pre-existing complications, developed as a result of TDT (e.g., cardiac or liver complications), these are unlikely to be reversable following treatment with exa-cel.'	Suggest to correct to 'Firstly, for patients with pre-existing complications, developed as a result of TDT (e.g., cardiac or liver complications), these may not be reversible following treatment with exa-cel.'	Although some of the cardiac and liver complications caused by iron overload and anaemia are not reversible, many of them are. Typographical error (reversable, reversible)	Not a factual error. The EAG recognise that this is speculative but considers this a valid point. Typo corrected

Issue 14 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout the EAG report, the EAG confuse transfusion and infusion when describing the exa-cel administration process.	Throughout, where referring to the exa-cel procedure, exa-cel is administered via an infusion, not a transfusion.	Technical error	Change accepted.
Page 10: the EAG states ‘The EAG prefers to use simplified model structure which remove iron overload related complications’.	Suggest to correct to ‘The EAG prefers to use a simplified model structure which removes iron overload related complications’.	Typographical error	Change accepted.
Page 11: the EAG states ‘The EAG prefers use a UK Chart Review (Shah et al.) to inform the frequency of blood transfusions in transfusion dependent patients’.	Suggest to correct to ‘The EAG prefers to use a UK Chart Review (Shah et al.) to inform the frequency of blood transfusions in transfusion dependent patients’.	Typographical error	Change accepted.
Page 11: the EAG states 'The EAG prefers to use the T12 definition of transfusion independence..'	Suggest to correct to ' The EAG prefers to use the TI12 definition of transfusion independence..	Typographical error	Change accepted.

Page 11: the EAG states ‘The EAG prefers to assume 5-year iron normalisation period’.	Suggest to correct to ‘The EAG prefers to assume a 5-year iron normalisation period’.	Typographical error	Change accepted.
Page 11: the EAG states ‘The EAG prefers to apply standardised mortality rate of 2.5 to transfusion dependent patients’.	Suggest to correct to ‘The EAG prefers to apply a standardised mortality rate of 2.5 to transfusion dependent patients’.	Typographical error	Change accepted.
Page 11: the EAG states ‘The EAG prefers to use multiplicative approach to age adjustment’.	Suggest to correct to ‘The EAG prefers to use a multiplicative approach to age adjustment’.	Typographical error	Change accepted.
Page 12: the EAG states ‘The EAG explores two alternative rates of relapse of 2.19% based on values reported by Santarone et al 2022 and 10% based on values from the Betibeglogene US ICER report’.	Suggest to correct to ‘The EAG explores two alternative rates of relapse of 2.19% based on values reported by Santarone et al 2022 and 10% based on values from the betibeglogene US ICER report’.	Typographical error (betibeglogene is the international non-proprietary name of the technology)	Change accepted.
Page 13: the EAG states 'Using the T12 definition of TI to inform the economic analysis'.	Suggest to correct to 'Using the TI12 definition of TI to inform the economic analysis'.	Double-spacing and typographical error	Change accepted.

Page 14: the EAG states ' This imposes several structural assumptions which impact significant on model outcomes.'	Suggest to correct to 'This imposes several structural assumptions which impact significantly on model outcomes.'	Typographical error	Change accepted.
Page 15: the EAG states 'The company stated that it typically takes 5-6 months from the cell cycle collection (apheresis) to patients being infused exa-cel.'	Suggest to correct to 'The company stated that it typically takes 5-6 months from the cell cycle collection (apheresis) to patients being infused with exa-cel.'	Typographical error	Change accepted.
Page 15: the EAG states 'This represents significant period of time which is not explicitly accounted for in the economic analysis	Suggest to correct to "This represents a significant period of time which is not explicitly accounted for in the economic analysis'	Typographical error	Change accepted.
Page 15: the EAG states 'otherwise become ineligible for treatment after gene editing has been performed but prior transfusion.'	Suggest to correct to "otherwise become ineligible for treatment after gene editing has been performed but prior to infusion.'	Typographical error, confusion of transfusion and infusion.	Change accepted.
Page 15: the EAG states ‘The EAG notes that it is common to utilise a decision tree framework in the	Suggest to correct to ‘The EAG notes that it is common to utilise a decision tree framework in the modelling of gene therapies to capture the	Typographical errors	Change accepted.

modelling of gene-therapies to capture the alternative outcomes of patients who unable or unwilling to proceed to transfusion’.	alternative outcomes of patients who are unable or unwilling to proceed to infusion’.		
Page 16: the EAG states 'The EAG notes the availability of updated data cut of the CLIMB THAL-11 trial'	Suggest to correct to "The EAG notes the availability an updated data cut of the CLIMB THAL-111 trial'	Typographical errors	Change accepted.
Page 16: the EAG states ‘Ongoing data collection in the CLIMB THAL-131 trial wil also be useful in resolving this uncertainty’.	Suggest to correct to ‘Ongoing data collection in the CLIMB-131 trial will also be useful in resolving this uncertainty’.	Typographical error	Change accepted.
Page 17, the EAG states 'To capture disease related mortality not attributable to cardiac or diabetes complications an standardised mortality ratio..'	Suggest to correct to 'To capture disease related mortality not attributable to cardiac or diabetes complications a standardised mortality ratio..'	Typographical error	Change accepted.
Page 17: the EAG states ‘Such advances are likely to have resulted in improved survival outcomes for TDT patients and such these	Suggest to correct to ‘Such advances are likely to have resulted in improved survival outcomes for TDT patients and as such these studies are likely	Typographical error	Change accepted.

studies are likely to significantly overestimate disease related mortality'.	to significantly overestimate disease related mortality'.		
Page 17: the EAG states 'In addition to the SMR described above the economic analysis applies an additional mortality rate of 13% per annum to patient with cardiac complications'.	Suggest to correct to 'In addition to the SMR described above the economic analysis applies an additional mortality rate of 13% per annum to patients with cardiac complications'.	Typographical error	Change accepted.
Page 17: the EAG states 'The EAG has been unable to identify alternative source of cardiac mortality rates.'	Suggest to correct to ' The EAG has been unable to identify alternative sources of cardiac mortality rates.' or 'an alternative source' depending on the EAG's intention.	Typographical error	Change accepted.
Page 18, the EAG states 'This approach was justified on the basis that EQ-5D is unsuitable to capture the HRQoL burden of TDT due issue of adaptation, ceiling effects and the lack of a 'fatigue' domain.'	Suggest to correct to 'This approach was justified on the basis that EQ-5D is unsuitable to capture the HRQoL burden of TDT due to issues of adaptation, ceiling effects and the lack of a 'fatigue' domain.'	Typographical errors	Change accepted.
Page 18, the EAG states 'The EAG considers that EQ-5D available from the CLIMB	Suggest to correct to 'The EAG considers that EQ-5D available from the CLIMB THAL-111 trial should be	Typographical error	Change accepted.

THAL-11 trial should be appropriately analysed and used to inform the model.'	appropriately analysed and used to inform the model.'		
Page 18: the EAG states 'Despite requests from the EAG at points for clarification (PFC 12b, PFC 13)'	Suggest to consistently use PfC, as this is the abbreviation specified in the List of Abbreviations	Typographical error	Change accepted.
Page 18: the EAG states 'Appropriate EQ-5D data is available from the CLIMB THAL-111'	Suggest to correct to 'Appropriate EQ-5D data is available from the CLIMB THAL-111'	Double-spacing	Change accepted.
Page 19: the EAG states ' Issue 10 eMIT costs'	Suggest to correct to 'Issue 11 eMIT costs'	Typographical error	Change accepted.
Page 23: the EAG states 'Issue 15 Discounting and Severity modifier ad distributional cost-effectiveness analysis'	Suggest to correct to 'Issue 15 Discounting and Severity modifier and distributional cost-effectiveness analysis'	Typographical error	Change accepted.
Page 23: the EAG states ‘The EAG, however, considers it likely that here is no precedent for such a situation’.	Suggest to correct to ‘The EAG, however, considers it likely that there is no precedent for such a situation’.	Typographical error	Change accepted.

Page 25: the EAG states 'including the mechanism of action and the treatment process, in section 1.2 of the CS.'	Suggest to correct to 'including the mechanism of action and the treatment process, in Section B.1.2 of the CS	Incorrect format of citation.	Change accepted.
Page 25: the EAG states 'in which the BCL11A gene is edited ex-vivo to reactivate the production of HbF'	Latin words should be printed in italics. Suggested to correct to 'in which the BCL11A gene is edited *ex-vivo* to reactivate the production of HbF	Typographical error	Change accepted.
Page 25: the EAG states 'Successful treatment is indicated by trilineage engraftment; the growth of the stem cells and production of healthy RBCs.'	Suggest to correct to 'Successful treatment is indicated by trilineage engraftment; the growth of stem cells and production of healthy RBCs.'	Typographical error	Change accepted.
Page 26: the EAG states 'Beta-thalassaemia patients carry a genetic mutation'	Suggest to correct to 'β-thalassaemia patients carry a genetic mutation'	Typographical error	Change accepted.
Page 26: the EAG states 'but there is variation between patients depending on severity of the condition.'	Suggest to correct to 'but there is variation between patients depending on the severity of the condition.'	Typographical error	Change accepted.

Page 26: the EAG states 'Another 25% of patients show signs of prediabetes or insulin resistance, and other physical and mental health problems are common (CS Table 3, p. 27).'	Incorrect page citation. Table 3 is located on p. 28 of the CS.	Referencing error	No change made. Referencing appears to be correct
Page 27: the EAG states 'the proposed position of exa-cel in the clinical pathway is shown in Figure 9 of the CS (p. 42).'	Incorrect page citation. Figure 9 is located on p. 43 of the CS.	Referencing error	No change made. Referencing appears to be correct
Page 27: the EAG states 'allogeneic stem cell therapy'	Suggest to refer to as 'allogeneic stem cell transplantation (allo-SCT)'	Typographical error	Change accepted.
Page 28: the EAG states ‘Although no upper age limit is specified in the expected license’	Suggest to correct to ‘Although no upper age limit is specified in the expected licence’	Typographical error	Change accepted.
Page 28: allogeneic-SCT is referenced three times, despite the abbreviation provided on the previous page	Suggest to provide the full-term and abbreviation once, followed by allo-SCT throughout	Typographical error	Change accepted.

Page 28: the EAG states 'become a suitable treatment option for more older children and young adults'	Suggest to correct to 'become a suitable treatment option for more adolescents and young adults'.	Typographical error	No change made.
Page 28: the EAG states ''reduction in the use of iron chelating agents' was not stated a priori as an endpoint'	Suggested to correct to "reduction in the use of iron chelating agents' was not stated *a priori* as an endpoint'	Latin words should be printed in italics.	Change accepted.
Page 29: the EAG states 'experienced adverse events relating to this outcome after tranfusion'	Suggest to correct to 'experienced adverse events relating to this outcome after transfusion'	Typographical error	Change accepted.
Page 33: the EAG states 'Table 2 in Appendix D (p. 58-59) states that the update was performed'	Inaccurate table citation. Correct reference should cite Table 63 in Appendix D.	Referencing error	Change accepted.
Page 34: the EAG states 'The company did not comment on why they did not search dedicated trials registries'.	Suggest to correct to 'The company did not comment on why they did not search dedicated trial registries'.	Typographical error	Change accepted.
Page 34: the EAG states 'The company stated that [redacted] patients in the FAS had an IVS-I-5 mutation, adding that	Suggest to correct to 'The company stated that [redacted]patients in the FAS had an IVS-I-5 mutation, adding that exa-cel treatment resulted in transfusion	Consistency error	Change accepted.

exa-cel treatment resulted in transfusion independence in all three subjects past the transfusion washout period’	independence in all three patients past the transfusion washout period’		
Page 36: the EAG states ' Reasons for not prioritising studies are not clearly statedT'	Suggest to correct to 'Reasons for not prioritising studies are not clearly stated'	Typographical error	Change accepted.
Page 37: the EAG states ' the company’s economic model uses the Shah Chart Teview cohort'	Suggest to correct to 'the company's economic model uses the Shah Chart Review cohort'	Typographical error	Change accepted.
Page 38: the EAG states ‘The longer-term data available so far for the outcome ‘new or worsening hematologic disorders’ from the CLIMB THAL-131 long-term follow up study are presented in Table 8’.	Suggest to correct to ‘The longer-term data available so far for the outcome ‘new or worsening haematologic disorders’ from the CLIMB-131 long-term follow up study are presented in Table 8’.	Typographical and nomenclature errors	Change accepted.
Page 43: ‘(CLIMB THAL-11 CSR)’	Suggest to correct to ‘(CLIMB THAL-111 CSR)’	Typographical error	Change accepted.
Pages 43, pages 79-82: further references to ‘CLIMB THAL-131’.	Suggest to correct to ‘CLIMB-131’	Typographical/nomenclature error	Change accepted.

Page 48: the EAG states ‘Although the betibeglogene NICE appraisal and US ICER assessments for betibeglogene…’	Suggest to correct to ‘Although the betibeglogene NICE appraisal and US ICER assessment for betibeglogene…’	Typographical error	Change accepted.

Page 51: the EAG states ‘The NICE appraisal of betibeglogene autotemcel was terminated following withdrawal of the technology by the company’.	Suggest to correct to ‘The NICE appraisal of betibeglogene autotemcel was discontinued following withdrawal of the technology by the company’.	Nomenclature error (termination and discontinuation are different mechanisms of not proceeding with a NICE appraisal)	Change accepted.
Page 51: the EAG states 'The company response indicated that the appraisal of betibeglogene concerned a different technology, with different mode of action and under different NICE guidance'	Suggest to correct to "The company response indicated that the appraisal of betibeglogene concerned a different technology, with a different mode of action and under different NICE guidance'	Typographical error	Change accepted.
Page 52: the EAG states ‘Although the EAG considers the company’s model to provide the most relevant evidence for the cost-effectiveness of Exa-cel…’	Suggest to correct to ‘Although the EAG considers the company’s model to provide the most relevant evidence for the cost-effectiveness of exa-cel…’	Typographical error	Change accepted.
Page 53: the EAG states 'Heath effects from both patients and carers were included.'	Suggest to correct to 'Health effects from both patients and carers were included.'	Typographical error	Change accepted.
Page 58: the EAG states ' This not an error.'	Suggest to correct to 'This is not an error.'	Typographical error	Change accepted.

Page 63: the EAG states 'As explained in Section **Error! Reference source not found.**, exa-cel is a gene therapy and involves the transplantation of autologous CD34+ haematopoietic stem cells which have been transduced using CRISPR gene-editing to encode the BCL11A gene'.	Suggest to correct to 'As explained in Section **Error! Reference source not found.**, exa-cel is a gene therapy and involves the transplantation of autologous CD34+ haematopoietic stem cells which have been transduced using CRISPR-Cas9 gene-editing to encode the BCL11A gene'.	Nomenclature error	Change accepted.
Page 64: the EAG states 'The base case analysis also includes the costs of perixafor (0.24 mg/kg/day for 3 days) administered as part of the mobilisation procedure'.	Suggest to correct to 'The base case analysis also includes the costs of plerixafor (0.24 mg/kg/day for 3 days) administered as part of the mobilisation procedure'.	Typographical error	Change accepted.
Page 71: the EAG states 'The EAG notes that there is precedent for cure in TDT, allogeneic HSCT is accepted as being a curative treatment but it is rarely used in older patients due to high mortality rates.	Suggest to correct to 'The EAG notes that there is precedent for cure in TDT. Allogeneic HSCT is accepted as being a curative treatment but it is rarely used in older patients due to high mortality rates'.	Typographical errors	Change accepted.
Page 72: repetition of a table cross-reference ('Table 14Table 14').	Correct to 'Table 14'	Typographical error	Change accepted.

Page 79: the EAG states ‘at different points on the RBC cycle’	Suggest to correct to ‘RBCT cycle’ to maintain consistency throughout document	Typographical error	Change accepted. “RBC transfusion cycle”
Page 99: the EAG states 'The EAG reviewed the model in detail and applied the TECHnical VERification (TECH-VER) checklis.'	Suggest to correct to 'The EAG reviewed the model in detail and applied the TECHnical VERification (TECH-VER) checklist.'	Typographical error	Change accepted.
Page 103: the EAG states 'A consequence, patient 002 from the trial is classified as transfusion independent despite not meeting the requirements of the TI12 primary outcome.'	Suggest to correct to ' As a consequence, patient 002 from the trial is classified as transfusion independent despite not meeting the requirements of the TI12 primary outcome.'	Typographical error	Change accepted.
Page 104: the EAG states 'The mortality risk associated with myeoblative conditioning is assumed to be 0% in the company’s base case.'	Suggest to correct to 'The mortality risk associated with myeloablative conditioning is assumed to be 0% in the company’s base case.'	Typographical error	Change accepted.
Page 105: the EAG states 'The EAG also concerned that the TD health state costs double count some care costs'	Suggested to correct to "The EAG is also concerned that the TD health state costs double count some care costs'	Typographical error	Change accepted.
Page 108: the EAG states 'The selection of changes made to the EEG base-case	Suggest to correct to 'The selection of changes made to the EAG base-case analysis were driven by the available	Typographical error	Change accepted.

analysis were driven by the available evidence; however, a number of important uncertainties remain. To address the remaining uncertainty, the EEG conducted a number of scenarios on their alternative base-case analysis.'	evidence; however, a number of important uncertainties remain. To address the remaining uncertainty, the EAG conducted a number of scenarios on their alternative base-case analysis.'		
Page 109: the EAG states: 'In terms of there likely impact on the ICER the most of important of these issues centered on the modelling approach adopted by the company. While superficially similar to the model consider in ID968'	Suggest to correct to 'In terms of their likely impact on the ICER the most important of these issues centered on the modelling approach adopted by the company. While superficially similar to the model considered in ID968…'	Typographical errors	Change accepted.
Page 114, the EAG states 'but opted not to in the27pdatee.'	Suggest to correct to 'but opted not to in the update'	Typographical error	Changed to “but opted not to in the 2022 methods update”
Page 114: the EAG states 'The company applied an aggregate approach to DCEA, Ih relies on aggregate data, Including the summary results from a cost-effectiveness analysis'	Suggest the EAG amends this passage of text to reflect to their intention.	Typographical errors	Changed to “The company applied an aggregate approach to DCEA, which relies on aggregate data, including the summary results from a cost-effectiveness analysis,

			without explicitly considering variation in cost-effectiveness analysis inputs across specific subgroups”
Page 118: the EAG states 'The company also judged the availa”le e’hnicity data for patients identified in the BoI study as inadequate for analysis based on ethnicity in the TDT population'	Suggest to correct to 'The company also judged the available ethnicity data for patients identified in the BoI study as inadequate for analysis based on ethnicity in the TDT population'	Typographical error	Change accepted.

Unmarked confidential data

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
Section 4.2.3, Page 63	‘With regards to diabetes, the company considers the omission an error and confirms that 3/48 patients had baseline diabetes’.	‘With regards to diabetes, the company considers the omission an error and confirms that 3/48 patients had baseline diabetes’.	Change accepted.

Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 25 September** 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.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Serum ferritin levels

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.1. The EAG report serum ferritin levels in D120, and contrast these with IA2 in a negative light. The serum ferritin figure reported for IA2 is not correct.	At Month 24, (n=23) patients had a mean serum ferritin of 2,221 pmol/L in the D120 data cut compared to a baseline of 3,785 pmol/L, (n=42). This was slightly higher than seen in the IA2 data cut (mean at month 24 was 2,094 pmol/L, n=8, compared to a baseline of 3,705 pmol/L). No update was provided for levels of liver iron content or cardiac iron content (T2*). Removal of the reference to serum ferritin in the following statement: ' However, an increase in serum ferritin levels, coupled with the lack of an update on liver iron content and cardiac iron content, is concerning.'	The serum ferritin figure for the IA2 data cut at Month 24 (n=8) is 2,094 pmol/L, as presented in Table 14.2.13.2 of the CLIMB THAL-111 CSR. Whilst the company acknowledge the figure for d120 is a very slight increase relative to IA2, it could also be noted that the baseline value was slightly higher for the PES population at D120. As such, alongside correcting the reported figure, we propose a softening of the language to reflect the difference in values reported.	The text has been changed to state that mean serum ferritin levels were similar across the data-cuts. The EAG originally quoted the figure at the top of p85 of the CS and therefore assumes this was an error in the original submission.

Issue 2 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3.2. The EAG state 'As per the IA1 data cut, direct evidence remains limited by the small sample size and short duration of follow-up.'	Propose to replace IA1 with IA2.	Typographical error.	Change accepted
Section 1.1. The EAG state ‘Updates for other data sets and stages used in the two CLIMB THAL studies are presented in Table 1’.	Propose to amend as follows: ‘Updates for other data sets and stages used in the two CLIMB THAL studies are presented in Table 1’.	Typographical/nomenclature error (there is only one ‘CLIMB THAL’ study; CLIMB-131 is a long-term follow-up study of patients with β-thalassaemia or sickle cell disease).	Change accepted
Section 2.3.1. The EAG state ‘The EAG has update the preferred EAG base-case assumptions to reflect this new data’.	Propose to amend as follows: ‘The EAG has updated the preferred EAG base-case assumptions to reflect this new data’.	Typographical error	Change accepted
Section 3.3 (Table 7), Section 3.4 (EAG Scenario 7). Repeated references to T12.	Propose to replace T12 with TI12.	Typographical/nomenclature error	Change accepted

Section 4. The EAG state 'The results from the EAG preferred DCEA approach (Scenario 19 in the EAR) are presented in Table 13 and Table 14 at £20,000 and £30,000, respectively'.	Propose to amend as follows: 'The results from the EAG preferred DCEA approach (Scenario 19 in the EAR) are presented in Table 13 and Table 14 at £20,000 and £30,000, respectively'.	Typographical error (extra space between words).	Change accepted
Section 3.2. 'The company base-case results and scenario analysis inclusive of severity and DCEA re-weighting are presented in Table 6.These results are presented in NHB form…'	Propose to amend as follows: 'The company base-case results and scenario analysis inclusive of severity and DCEA re-weighting are presented in Table 6. These results are presented in NHB form…'	Typographical error (insert space after full-stop).	Change accepted

Issue 3 Patient numbers

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Section 1.1, Table 1. States that 56 patients had started conditioning.	Change 56 to 54 patients	The day 120 results state that 54 patients had started conditioning, not 56 as stated here. We note that 56 patients had started mobilisation.	Change accepted

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **Monday 6 November 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Vertex Pharmaceuticals
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Not applicable**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**Not applicable**

Introduction

Vertex would like to thank the NICE technical team for reviewing the company submission for exa-cel in TDT, preparing the technical report, and for providing us with the opportunity to engage in the technical engagement process.

Our response is split into three separate parts:

1) Our response to the key issues for engagement
2) Our brief response to additional issues, including issues for which we have accepted the EAG's preferred assumption
3) Details of the revised company base case

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Issue impacting decision making:	Description:	Does this response contain new evidence, data or analyses?	Response
EAG issue 1	Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile	**No**	Although the EAG considers that the base case assumption of a permanent treatment effect with exa-cel is reasonable given the evidence from CLIMB THAL-111 used to inform it, they believe there is uncertainty in the permanence of transfusion independence. Given this stated uncertainty, the EAG proposes two alternative sources for relapse rate. **Santarone *et al.* (2022) is specific to allo-SCT, a modality with key differences to CRISPR gene editing.** The EAG's initial proposed source is Santarone *et al.* (2022), which reports the long-term outcomes of allogeneic stem cell transplant (allo-SCT) in thalassaemia major (1). As described in our company submission (CS), allo-SCT differs in significant ways to CRISPR gene editing, which is an autologous process, and as such avoids the risk of issues such as graft-versus-host disease (GvHD). For exa-cel, there is no clonal advantage of the patient's own cells versus the edited ones as they are all autologous. Late graft failures due to endogenous immune reconstitution/human leukocyte antigen (HLA) incompatibilities between donor and recipient due to the change in the immune profile of the patients (i.e., due to

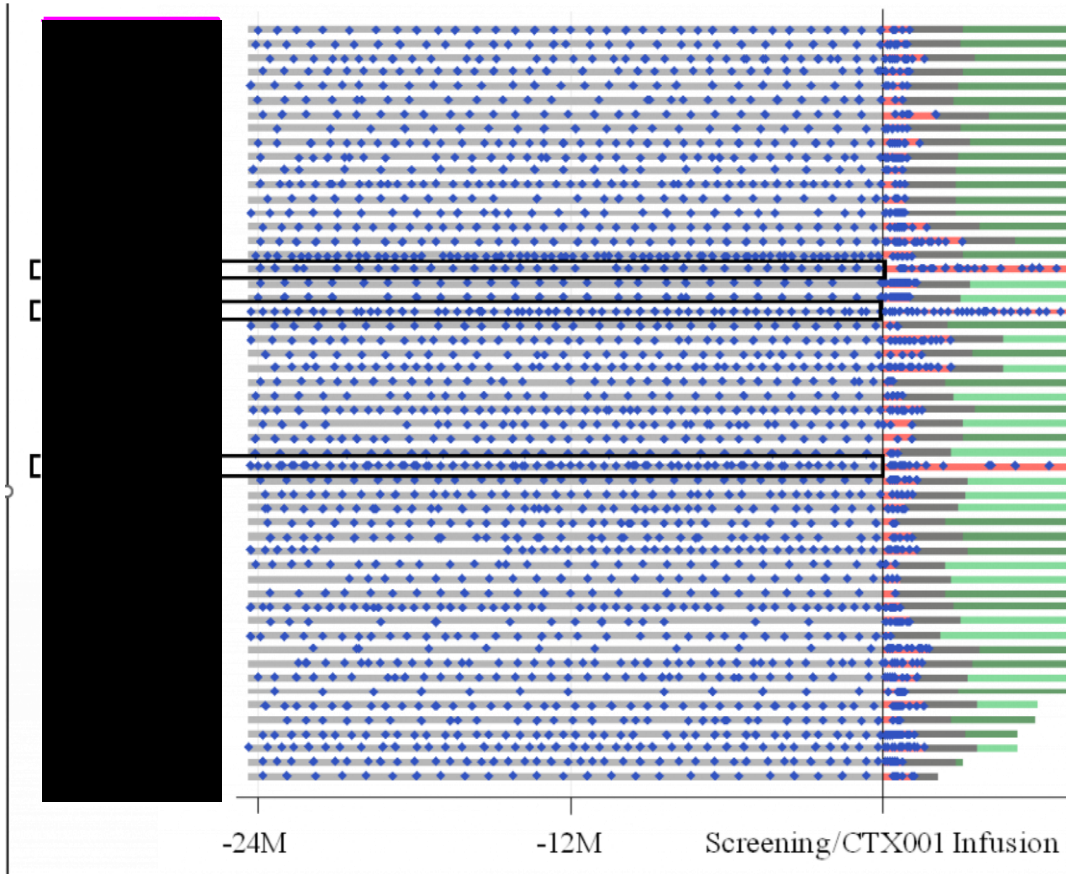
			issues with the allograft) would not be expected with an autologous procedure. As such, any late clonal advantage that may be seen with allo-SCT and the associated late graft failure, as in Santarone *et al.* (2022), is not expected to be seen with exa-cel. Furthermore, whilst the EAG cites Santarone *et al*. (2022), there are other publications reporting long-term outcomes after allo-SCT in thalassaemia with contrasting findings. For instance, Rahal *et al.* (2018) reported on patients with β-thalassaemia major transplanted between 1984 and 2012. After a median post-transplant follow-up of 12 years (range: 7-19 years), there were no instances of delayed graft failure with thalassaemia recurrence (2, 3). To conclude, whilst Vertex firmly refutes any attempt to use long-term outcomes with allo-SCT as predictive of long-term outcomes with autologous CRISPR gene editing, we note that there are inconsistent findings even within the long-term allo-SCT studies, and therefore, the EAG's position is not reasonable. **The beti-cel ICER report relies on an estimate made by a single gene therapy expert, with other ICER expert opinion suggesting 0% reversion rate is more appropriate.** The EAG's second proposed scenario is a 10% rate of relapse based on the betibeglogene autotemcel (beti-cel) ICER report (4). The authors of the ICER report sought expert opinion on the potential long-term relapse rates with gene therapy. The chosen figure of 10% is based on a single expert, who stated that it would be theoretically possible for patients to revert to transfusion dependent (TD) status; this expert then made an estimate of 10%. Further expert opinion obtained during the development of the ICER report suggested an assumption of a 0% rate of relapse would be appropriate. The theoretical basis for the estimate of 10% was the possibility that the population of infused stem cells that were not genetically modified could become dominant. Clonal haematopoiesis (CH) has been studied in the allo-SCT setting and the presence of donor CH was not reported as a risk factor for poor graft function or leukaemic transformation. In addition, recipients of allogeneic donors

			with CH do not see accelerated CH expansion post-transplant (5). Thus, mutational background does not seem to alter clonal expansion post-transplant. Therefore, clonal outgrowth post-transplant, at least in the allo-SCT setting, is not associated with increased risk. In summary, in Vertex's interpretation of the available patient-level data, CH/clonal evolution is not likely to have affected the trajectory of HbF responses or led to the differences in allelic editing in the blood compared to bone marrow CD34+ cells. In CLIMB THAL-111, haemoglobin levels increased to normal or near normal levels in all patients and were stable over the duration of follow-up. The assumption of a 10% relapse rate is not underpinned by any evidence beyond the view of a single gene therapy expert. Furthermore, as already discussed, another expert consulted by ICER suggested assuming 0% reversion, and it is not clear why preference was given to the opinion of one expert over another. As such, Vertex does not consider it appropriate to base a relapse rate assumption on the opinion of one anonymous gene therapy expert providing advice in the context of a beti-cel review when there is data from 54 patients treated with exa-cel in CLIMB THAL-111, with median follow-up of 22.8 months (6). **There is no biological plausibility that the exa-cel genetic edit is reversible.** Biologically there is no reason the introduced CRISPR/Cas9 gene edit will not be permanent in TDT. There is no known mechanism by which an edited haematopoietic stem cell (HSC) could convert back to a wild-type sequence. Edits to HSCs are permanent and durable. Support for this comes from the latest data from CLIMB THAL-111. The stable proportion of alleles with the intended genetic modification (allelic editing) in peripheral blood and in the CD34+ cells of the bone marrow over time are indicative of the durable engraftment of edited long-term HSCs and reflect the permanent nature of the intended edit. Additional support for the permanence comes from UK clinical experts from UK transplant centres consulted by Vertex, who stated that if the haemoglobin level is sustained at 11.5-12g/dL or more over a 2-year period, they would expect long-term stability (7).

			In summary, the EAG state in their own report that they '*consider the assumption of 0% relapse reasonable given the evidence from the trial*'. In exploring uncertainty, the EAG present two alternative assumptions. Vertex firmly believes that neither assumption is relevant to exa-cel, and that the relapse rate observed in CLIMB THAL-111 is most appropriate. Allelic editing remains stable at the time of the D120 data cut, and there is no biologically plausible reason that genetic editing with exa-cel is reversible. In addition, Vertex has proposed a managed access agreement to better characterise the long-term durability of exa-cel in TDT. This aligns with the EAG's view, as stated on page 71 of their report that uncertainty relating to durability may be resolved by an appropriately implemented managed access arrangement.
EAG issue 2	Definition of transfusion independence	**No**	As described in the EAG report, the time point at which transfusion independence is determined in the economic model is defined as 60 days after the last RBC transfusion for post-transplant support or TDT disease management. All patients had achieved this outcome at D120, whereas 92.9% (39 of 42 patients) had achieved TI12 (6). **The 60-day washout period is a suitable timepoint for evaluation of TI, in the context of transfusion frequency at baseline** By the end of the 60-day washout period stipulated in CLIMB THAL-111, it is expected that the majority of transfused cells will have been destroyed and the haemoglobin level will be maintained only by the patient's production of their own cells. As depicted in Figure 1, patients enrolled in CLIMB THAL-111 experienced a considerable transfusion burden at baseline. Patients received a mean of 17.0 transfusions per year in the Primary Efficacy Set (PES), and 16.5 per year in the Full Analysis Set (FAS), equivalent to a transfusion every 21-22 days. Figure 1 highlights the three patients not to achieve TI12 (outlined with a black box). These patients had received 33, 57, and 70 transfusions in the 2 years prior to exa-cel infusion, or an annualised rate of 16.5, 28.5, and 35 transfusions per

year for the two years prior to exa-cel infusion. This equates to a transfusion every 22, 13, and 10 days at baseline. In this context, a period of 60 days free from transfusion is considered clinically meaningful, demonstrative of the clear impact of exa-cel treatment, and likely to translate into long-term durability.

Figure 1: Transfusion frequency at baseline (D120, FAS)

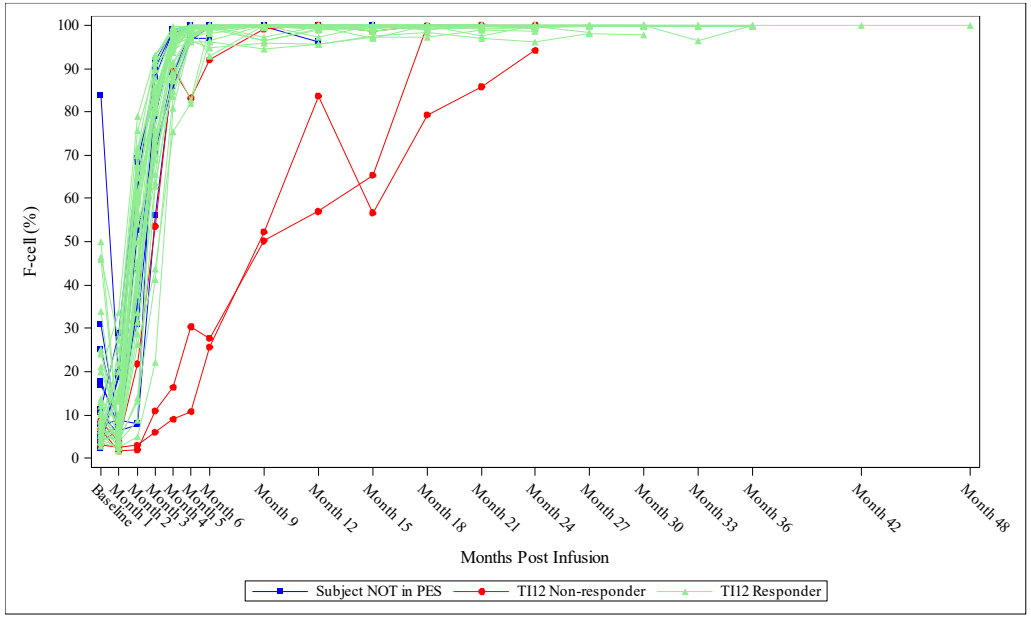


			Notes: blue diamonds indicate a TDT-related RBC transfusion. CTX001 now referred to as exa-cel. Patients highlighted with a black outline are those not to achieve TI12. **Source:** D120 report (6). **Most recent data from CLIMB THAL-111 shows that the 3 patients not to achieve TI12 yet are transfusion free for up to 12.3 months (including washout period)** The 3 patients who had not achieved the primary endpoint of TI12 at the time of the most recent data cut (D120) have demonstrated clinical benefit, with reductions in annualised RBC transfusion volume at this latest analysis of 83.4%, 98.5%, and 86.9% from baseline and in annualised RBC transfusion frequency of 82.4%, 96.0%, and 73.4% from baseline. Furthermore, all 3 of these patients have stopped receiving RBC transfusions 14.5 months, 12.2 months, and 21.6 months after exa-cel infusion and have been transfusion free through the time of this data cutoff date for 10.3 months, 7.0 months, and 2.8 months (starting 60 days after the last RBC transfusion). The below bullet points provide additional context on the 3 patients not to achieve TI12, that further supports the substantial and durable impact of exa-cel: • [redacted] has been TI for over a year (12.3 months including washout period). At baseline, this patient was receiving 16.5 transfusions per year, or a transfusion every 22 days. • [redacted] has been TI for 4.8 months including the washout period. At baseline, this patient was receiving 28.5 transfusions per year, or a transfusion every 13 days. • [redacted] has been TI for 9.0 months including the washout period. At baseline, this patient was receiving 35 transfusions per year, or a transfusion every 10 days. Further support for the expected long-term benefit and durability of exa-cel in the 3 patients not to achieve TI12 comes from analysis of the change in proportion of F-cells over time. As presented in Figure 2, there is a clear trend of increasing F-

cell % for the 3 patients not to achieve TI12. For these patients, although it takes longer to achieve ~100% distribution of HbF across the RBCs in circulation, all have achieved it now. The high percentage of F-cells observed after exa-cel infusion (≥90%) is consistent with a pancellular distribution of HbF, indicating that almost all RBCs in circulation are derived from exa-cel. Previous natural history studies of patients with β-thalassaemia-HPFH demonstrate that high levels of F-cells (pancellularity) contribute to transfusion independence (8).

Notably, the time periods taken to achieve ~100% F-cell distribution are roughly aligned with time taken to achieve transfusion independence in CLIMB THAL-111.

Figure 2: Individual F-cells (%) Over Time (Studies 111 and 131 [TDT] FAS)

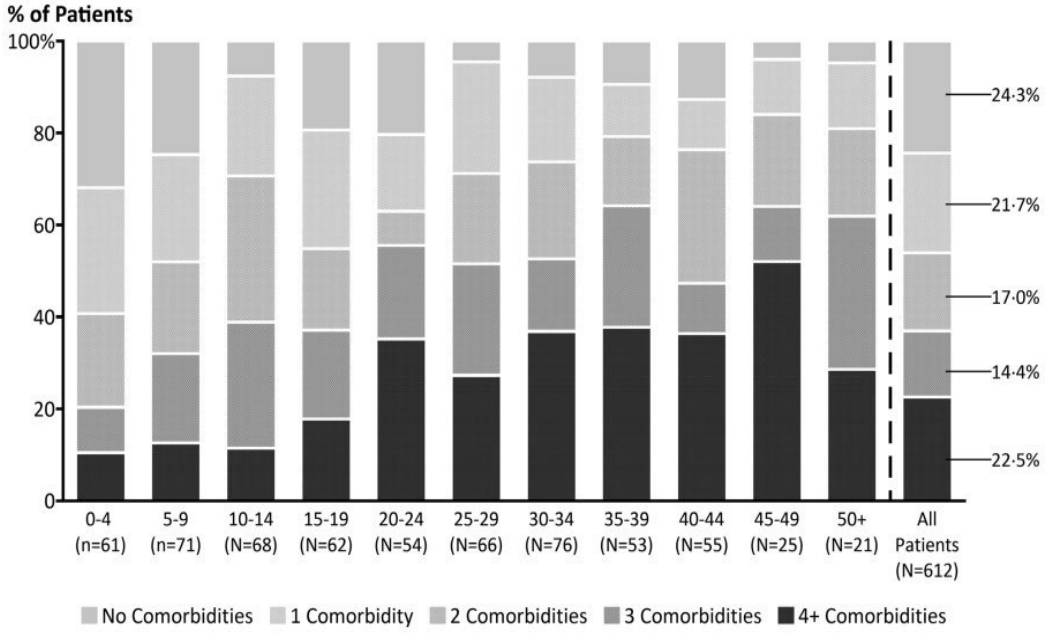


Notes: for ease of viewing, blue lines are subjects not in PES, red lines are TI12 nonresponders.

Source: D120 report (6).

			The percent allelic editing for each of these 3 patients was within the range of those in the FAS, including those in the PES who achieved TI12, and was stable for the duration of follow-up (see Figure 9 of D120 report). All 3 patients have progressive increases in HbF from baseline, however, they have lower levels of HbF compared to other patients in the PES who achieved TI12 at each time point after exa-cel infusion. There are no unique features identified for the 3 patients in terms of patients' baseline characteristics. Importantly, the allelic editing in these patients is consistent with the patients in the PES who achieved TI12 and is stable over time which means that lower levels of HbF are not due to insufficient editing or secondary graft failure. Given that these patients have stable engraftment of edited HSCs with progressive improvement in HbF production over time, it is expected that they will continue to experience clinical benefit from exa-cel treatment. All 3 patients have stopped receiving RBC transfusions and have remained transfusion free for 10.3, 7.0, and 2.8 months, starting 60 days after last RBC transfusion, respectively. The overall clinical data supports the expectation that all 3 patents will remain transfusion independent over time. In summary, the 60-day time period to define transfusion independence is appropriate. This is supported by clinical principles (lifespan of RBCs), as well as the frequency of transfusions required by patients in CLIMB THAL-111 at baseline. The three patients yet to achieve TI12 have been transfusion-free for 4.9-12.3 months, despite requiring a transfusion on average every 10-22 days at baseline. All three have achieved ~100% F-cell distribution at the time of D120, and their allelic editing is consistent with those to achieve TI12. As such, Vertex believe that an assumption of transfusion independence aligned to the 60-day time period currently adopted in the economic model is appropriate.
EAG issue 3, 4	Uncertain relationship between transfusion status and final outcomes	**No**	The EAG argues that the model incurs a systematic over-accumulation of patients with complications, which, in turn leads to a progressive overestimation of mortality. The EAG have suggested alternative approaches to modelling, including redesigning the model as a Patient-Level Simulation Model (PLS) or simplifying

	Modelling approach and how mortality risks are attributed to modelled patients		the current conceptual model to reduce the number of complications modelled. However, there is substantial contrary evidence and rationale to consider in relation to these points of critique. **The evidence that TDT leads to complications is irrefutable. The model predicts clinically realistic proportions of patients with comorbidities, therefore the model structure underpinning these predictions is suitable for decision-making.** The EAG stated that evidence should be provided demonstrating the plausibility and reliability of surrogate relationships used to infer HRQoL and survival benefits in the model. Firstly, it should be noted that the iron level thresholds defined in TDT monitoring guidelines worldwide are derived from the substantial body of evidence on the surrogate relationship between iron levels and comorbidities. The company has already provided this evidence in the form of a pragmatic literature review, including a comprehensive Excel spreadsheet with all studies identified and reasons for exclusion of studies not selected for the model. We note that despite their concerns regarding uncertainty, the EAG did not request any scenario analyses using alternative sources from this review, instead preferring to remove comorbidities from the model altogether. The fact that TDT leads to comorbidities is irrefutable and a blanket removal of these would generate a clinically unrealistic model that does not capture the costs, health-related quality of life (HRQoL) and mortality associated with TDT. A high prevalence of complications was observed in two contemporary burden of illness (BoI) studies. In Vertex's BoI study 14.35% of participants had cardiac and cardiopulmonary complications, 58.23% had endocrine complications and bone disorders, 28.69% had diabetes, and 13.50% had liver complications (9). High prevalence of comorbidities was similarly observed in Jobanputra *et al* (2020) (10). For instance (see Figure 3 below, from the same source), in patients aged 5-9 at the start of the 10-year observation, ~16% of patients had at least ≥4 comorbidities, ~20% of patients had at least 3 comorbidities, and ~20% of patients had at least 2 comorbidities at the end of the 2009-2018 observation period. Note

			that these proportions of accruing comorbidities are observed in a subgroup of patients who have only been treated with contemporary ICT and TDT protocols. **Figure 3: Comorbidity rates by age from Jobanputra et al**  Fig 2. Ten-year (2009–2018) co-morbidity rates by age range in 2009. Given the above, removing comorbidity-related costs and health outcomes underestimates the true costs and impact on health outcomes of these significant events in TDT patients. **Differing clinical specialities require independent resource use.**

			Moreover, differing clinical specialities, for example cardiovascular, hepatic, and diabetology, are managed by separate NHS specialties. Since the comorbidities in our model concern distinct clinical specialities, the comorbidities are - and always ought to be in an economic model - costed and calculated independently and there would be no risk of double-counting of comorbidities managed by the same NHS service. Maintaining costs and disutilities of comorbidities in the model thus provides a fair assessment of the true costs and benefits accrued to the NHS and patients, respectively. **The model is unlikely to overestimate the impact of multiple morbidities on TDT patient quality of life (QoL).** There is also a negative relationship between an increasing number of comorbidities and HRQoL. The multiplicative method of combining the disutility of multiple comorbidities has been shown to be relatively accurate, particularly at health-state values above 0.5, therefore it is unlikely that our model results in double-counting of disutilities for those patients who have multiple comorbidities (11). Moreover, there is evidence to suggest that there is additional utility decrement in instances of multiple, chronic morbidities, which the submitted model did not include. Several papers indicate that this is especially relevant in disease areas with increased synergy, such as heart disease and diabetes. When synergetic conditions are experienced simultaneously there is a further interaction effect reducing overall patient health-related quality of life in addition to the individual condition health effects (12-14). **NICE suggested, via the Early Scientific Advice programme, that the use of a Markov model would be appropriate.** Based on consultation with NICE through Early Scientific Advice, Vertex were advised that a Markov model was preferable and that the existing plan to use a PLS would be overly complex. We also previously validated model assumptions in the CS, comparing clinical outcomes to contemporary literature on TDT in Appendix J. Updated predictions (following removal of mortality from comorbidities in our new base case, see later), are presented in the Table 1 below. In general,

the model underpredicts the presence of comorbidities when compared with the UK TDT population (in particular for osteoporosis and cardiac morbidities), suggesting that results are likely biased against exa-cel.

Table 1: Predicted cumulative % of comorbidities

Source	***New base case (SoC)***	***Previous model (SoC)***	***Jobanputra et al 2020 (SoC)***
Complications: % at 49 years of age			
Cardiac (%)	27.28	23.39	64.0
Liver (%)	15.60	14.29	16.0
Diabetes (%)	42.26	34.18	48.0
Osteoporosis (%)	32.08	26.01	80.0

We thus emphasise that a Markov model is still sufficient for decision making if it predicts clinically valid proportions of patients with comorbidities, which the Vertex submitted model does. Furthermore, the EAG themselves stated that use of an alternative model structure such an individual simulation model would not address the uncertainty of predicting development of comorbidities.

Excess mortality persists in the contemporary TDT population, which demonstrates that simplifying a model by removing complications would significantly underestimate mortality.

The persistence of excess mortality in contemporary TDT patients is supported by the Vertex BoI study and Jobanputra *et al.* (2020) (specifically, please see the 10-year crude mortality and comorbidities for age group 5-9, who were born well after

			the introduction of modern ICT) (9, 10). Notably, the submitted model predicted mean survival aligned with the average age at death of 55 years in the Vertex BoI study, an age substantially higher than the average age at death in patients with TDT observed in Greece both before 2005 (36 years) and after 2005 (47 years) (15) suggesting that the average age of death in the BoI already reflects improved management and mortality of TDT patients. In an update of the Greek analysis, the authors reported that the majority of deaths in the 2010-2015 cohort were observed among patients with TDT between 46 and 50 years of age followed by the 41–45 age group (16). Another recent study in Greek Cypriots with TDT reported that "*during recent decades, there have been no overall differences in mortality rate, but causes of death have changed due to a downward trend in cardiac and an increasing trend in liver, malignancy and infection- related deaths*" (17). This was also supported by the Greek analysis which reported that heart-related deaths were significantly reduced during 2000-2006 and remained stable thereafter, whereas liver-related deaths rose steadily from 2000 to 2015 (16). In the BoI study, the overall mortality rate for patients with TDT was 1.19 deaths compared to 0.2 for controls, per 100 person-years. The majority of participants were less than 36 years old, with approximately 39% of patients being 17 years or younger. This is further strengthened by the fact that the analysis of the UK BoI cohort followed from 2008-2018 demonstrates excess mortality for TDT patients aged 0-11, indicating that despite modern ICT, excess mortality persists. Our study clearly demonstrates that even for children who have been on optimal care over the last ~5 years, there is still a high risk of death due to TDT. Jobanputra *et al.* (2020) also shows a considerably higher 10-year crude mortality over 2009–2018 for TDT patients aged 0-9 years compared to the general population (see Table IV of the study). Jobanputra *et al.* reported a crude mortality rate of 6.2% over the period 2009-2018 in a population with TDT, which was slightly lower than observed in our BoI study (7.17%) (9, 10).

			Therefore, Vertex propose an alternative approach that appropriately captures the true disease state, but considers some of the EAG's recommendations. Given the above, our modelling approach is justified, and it is not reasonable to remove complications, especially the costs and the health outcomes of the patients experiencing these comorbidities. To respond to the EAG's comments, we are open to removing comorbidity-related mortality given their concern regarding the progressive overestimation of mortality. This removes the interaction between complications and mortality. But, since excess mortality clearly persists in contemporary TDT patients despite improved treatment protocols, this necessitates that the base case SMR for transfusion dependent patients [redacted] to align with the contemporary BoI studies. [redacted] transfusion dependent patients is necessary to capture the excess mortality risk that is evident in the contemporary TDT population. This value is based on data from Vertex's BoI study (please see our response to EAG issue 7 for further details) (9). Even after increasing the SMR, it is important to note that mean age at death now predicted by the model is 65, substantially older than the mean age of death of 55 in the Vertex BoI. Furthermore, in the 2000-2018 cohort of the previously mentioned Greek Cypriot study (17) overall survival was 94% at age 30 and 89% at age 40. This compares with 98% survival and 95% survival at age 30 and 40, respectively, in our updated model that removes the comorbidity- specific mortality. Therefore, while the updated model reduces the complexity of capturing multiple causes of mortality, it fails to capture early mortality in TDT (which importantly reduces discounted QALY shortfall and achievement of the severity modifier). While Vertex is amenable to using the SMR alone to capture increased mortality, maintaining the costs and health outcomes of comorbidities in the model provides a fair and more accurate assessment of the true costs and benefits accrued to the NHS and patients.

<table>
<tr><td></td><td></td><td></td><td>We have tabulated the scenario of removing comorbidity related mortality while maintaining comorbidity costs and utilities below.

Table 2: Updated economic results after removing comorbidity-related mortality

<table>
<tr><th>Scenario</th><th>Base case incremental QALYs</th><th>Base case incremental Costs</th><th>Base case ICER</th><th>DCEA Weighted ICER</th></tr>
<tr><td>Base case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Remove comorbidity-related mortality [redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td></tr>
<tr><td>EAG issue 5</td><td>Omission of withdrawals from exa-cel treatment in the economic analysis</td><td>No</td><td>[redacted]</td></tr>
<tr><td>EAG issue 6</td><td>Frequency of red blood cell transfusions</td><td>No</td><td>The EAG notes the higher transfusion frequency in CLIMB THAL-111 compared to Shah et al. (2021) and considers the modelled number of transfusions to be uncertain and potentially higher than would be expected in UK patients eligible for treatment with exa-cel (18).

CLIMB THAL-111 is the most appropriate source for transfusion frequency data.

At the time of the latest data cut (D120), the mean annual frequency of transfusions in the FAS is 16.5 per year, compared to 13.7 per year in Shah et al. (2021) publication. In general, more severely affected patients with higher transfusion burden are more likely to opt for gene therapy, so it is unsurprising that patients in</td></tr>
</table>

			the CLIMB THAL-111 study had higher transfusion burden at baseline than the Shah cohort. Existence of a more severe cohort is evident in the Shah publication, in which 23% of patients received >16 blood transfusion per year (see Shah Figure S1). There are further reasons why the transfusion frequency from CLIMB THAL-111 is more likely to be generalisable to the population eligible for exa-cel than the Shah *et al.* cohort: • The genotype proportions are not reported in Shah *et a.l* (2021). The CLIMB THAL-111 study had a low proportion of milder genotypes and there are likely to be larger proportions with milder genotypes and consequently reduced transfusion requirements within the general TDT population. • In Shah *et al.* (2021), 20% were >40 years old; this population in particular may have had increased numbers of milder genotypes who were needing transfusions as they aged. • 25% of patients in Shah *et al.* (2021) were less than 12 years old and would not have been eligible for CLIMB THAL-111 Clinical expert feedback received by Vertex was that more severely affected patients are more likely to take up gene therapy treatment (7). As such, the frequency reported in CLIMB THAL-111 is likely to be the most generalisable to patients receiving exa-cel in UK clinical practice. Furthermore, the EAG's own clinical adviser indicated that a transfusion is normally given every three or four weeks for TDT. The frequency reported in Shah *et al* (2021) is at the bottom of that range, whilst the figure from CLIMB THAL-111 is at the top end. As described, there are a range of reasons that patients treated with exa-cel in UK clinical practice are likely to be those more severely impacted by TDT, and as such towards the higher end of the transfusion frequency range as estimated by the EAG's clinical adviser. **Managed access would provide further certainty relating to this issue.** The managed access protocol proposed is expected to collect 1 year of retrospective data for patients treated with exa-cel, which will include prior RBC

			use. As such, the proposed managed access agreement is expected to directly address this issue. In summary, Vertex strongly believe that CLIMB THAL-111 provides the most relevant source of prior transfusion rate data for exa-cel, and that this data is expected to be highly generalisable to clinical practice. Additionally, Vertex's proposed managed access agreement provides an opportunity to confirm this assumption with data on patients treated in UK clinical practice.
EAG issue 7	Non-reference discount rate	**Yes**	The EAG has concerns regarding the application of the non-reference discount rate. We note a cautious acceptance of the criterion relating to permanence of exa-cel engraftment, and the EAG's belief this can be addressed through further data collection in CLIMB-131, as well as through managed access. As such, and given this is addressed in part in our response to key issue 1, we do not focus on this criterion here. Further, the criterion relating to irrecoverable costs in the event of a non-permanent effect is the subject of ongoing commercial discussions, and also addressed as part of key issue #1. On that basis we do not focus on this issue in our response either. The EAG's chief concern relates to the criterion '*Exa-cel restores people who would otherwise die or have a very severely impaired life to full or near- full health'.* **Contemporary sources support the substantial reduction in life expectancy experienced by patients with TDT in the UK** Without treatment with exa-cel, patients would otherwise die many decades early when compared to the UK general population, due to complications relating to TDT. As reported in a retrospective burden of illness (BoI) study of 237 TDT patients in the UK, the mean age at death is 55 years old (n=17, 7.17% of patients), and the crude mortality rate is more than 5 times the matched general population (1.38 v 0.26 per person-year) (9). We note the mean age at death is 25-30 years lower than the mean age at death for the UK general population.

			Additionally, the mortality rate was in fact higher for those indexed between 2014-2018 (n=71 (1.38 per 100 person-years) than it was for those indexed between 2008-2013 (n=166) (1.15 per 100 person-years). This runs counter to the idea that outcomes are improving through time. This increase appears to be primarily driven by the youngest age group (0-11 years, n=[redacted]), for whom the mortality rate was [redacted] per 100 person-years for those indexed between 2014-2018, compared to [redacted] for those indexed between 2008-2013. Notably, the mortality rate in the retrospective BoI study is likely underestimated, given the continuous enrolment criterion. Another recent study reported decreased survival in patients with TDT in England, reporting a crude 10-year mortality rate that was 5 times higher in patients with TDT than in the general population of England and a mean age of death of 44 years in patients with TDT (10). As explained in our response to EAG issues 3 and 4, an number of studies in southern Mediterranean populations have examined the evolution of mortality in TDT over time (15-17). These studies have concluded that, although there was a significant reduction in cardiac- related mortality in the period 2000-2006, this has plateaued and been replaced with liver, infection and malignancy- related mortality. Similarly, the mean age at death has increased significantly since 2000, but appears to have reached a plateau over the past decade**.** Again, we reiterate that the study period for Vertex's BoI study was 2008-2018 and that the BoI study is thus highly generalisable to current UK clinical practice. **Analysis of a contemporary UK BoI cohort followed from 2008-2018 demonstrates the burden of TDT, irrespective of age.** The mortality rate for TDT patients is substantially higher than matched controls, irrespective of age (Figure 3). These rates being [redacted] higher than matched controls in the subgroup of patients aged <18 years counteract the notion that well monitored and chelated young individuals with TDT will have a near normal life expectancy (9).

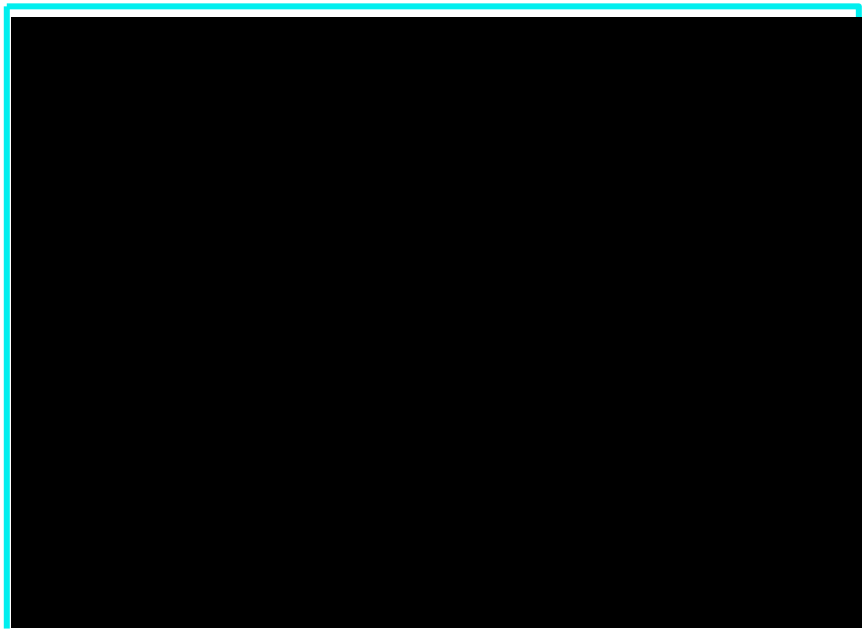
			Figure 4: Mortality rates for Patients with TDT and Matched Controls Stratified by Age Group  **Source**: Vertex BoI study (9) During the BoI study period (2008-2018), with mean (SD) follow-up of 6.0 (3.3) years, the most commonly experienced chronic complications included endocrine complications and bone disorders (58.2%), mental health problems (14.8%), cardiovascular complications (14.4%), liver complications (13.5%), and splenomegaly (10.55%), demonstrating the truly multi-organ impact of TDT. Rates of complications were substantially higher for patients with TDT across all age subgroups compared to matched controls (Table 2).

Table 3: Chronic Complications in Patients with TDT Stratified by Age Group

	Age Group			
	<18 Years		≥18 Years	
	TDT (n = 93)	Matched controls (n = 466)	TDT (n = 144)	Matched controls (n = 718)
Rate (Per 100 Person-Years)				
Cardiopulmonary complications	0.69	0	1.90	0.20
Heart failure	0.68	0	0.91	0.20
Pulmonary hypertension	0.17	0	0.99	0.02
Endocrine complications and bone disorders	2.72	0.26	13.86	1.77
Osteoporosis	0.51	0	7.18	0.22
Infertility	0.69	0	2.60	0.23
Hypopituitarism	1.09	0	4.85	0
Hypogonadotropic hypogonadism	0.35	0	2.52	0
Hypothyroidism	0.34	0.18	1.90	0.35
Diabetes mellitus	1.05	0.04	3.12	0.75

Liver complications	0.38	0	1.37	0.10		
Malignancy	0	0.04	0.25	0.15		
Mental health complications	0.69	0.63	1.05	1.35		
Renal complications	0.17	0	0.66	0.25		
Splenomegaly	0.53	0	1.05	0		
Urinary tract complications	2.90	0.18	1.46	0.61		

Source: Vertex BoI study (9)

The frequent and consistent need for time-consuming transfusions every 2-3 weeks poses a substantial burden on TDT patients

Aside from the array of acute and chronic complications of TDT already described the requirement to receive blood transfusions every few weeks poses a considerable burden on TDT patients. As noted by Anthony Nolan in their submission as part of this appraisal, each transfusion can take 3-4 hours (for 2-3 units) which unless administered very early in the day, or later in the evening (which is unlikely), results in the patient's day being dominated by the transfusion, and the associated requirement for a day off from work or school especially, particularly when factoring in travel time to the hospital and return journey. In addition, patients are often required to come in 1-2 days in advance for pre-transfusion blood testing.

As observed in a contemporary UK cohort of TDT patients, TDT patients require ~35 secondary care visits or hospitalisations per year.

Table 4: HCRU and Treatment Use in Patients with TDT Stratified by Age Group

Mean Rate PPPY	TDT (N = 237) Mean (SD)	Matched Controls (N = 1,184) Mean (SD)
HCRU		
Primary care visits[a,b]	6.98[c]	4.19[c]
To a GP*	3.99 (5.48)	2.96 (3.80)
To a nurse*	2.99 (8.14)	1.23 (2.07)
Prescriptions*	24.09 (58.67)	8.61 (26.62)
Secondary care visits or hospitalizations	34.78 (13.92)	1.94 (3.50)
A&E visits*	0.67 (1.02)	0.39 (0.90)
Outpatient visits*	16.69 (10.66)	1.31 (2.63)
Inpatient hospitalizations*	17.41 (7.71)	0.24 (0.85)
<1 day*	16.62 (7.51)	0.14 (0.65)
≥1 day*	0.79 (1.81)	0.10 (0.37)

A&E, accident and emergency; GP, general practitioner; HCRU, healthcare resource utilization; NSAID, non-steroidal anti-inflammatory drug; PPPY, per patient per year; SD, standard deviation; TDT, transfusion-dependent β-thalassaemia.
[a]Statistical testing not conducted for primary care visits;[b]SD not available
*p≤0.05 between patients with TDT and matched controls (Z-test for proportions)

			There is an updated UKTS Standards being published imminently, that supports the burden of TDT in the UK In support of their argument against the claim that patients would "otherwise die" the EAG cites the UKTS 2016 Standards statement that patients are expected to "*live a normal or near normal lifespan*". We note that the EAG omits the next sentence "*Unfortunately, this outcome is still not universal throughout the UK. Premature deaths still occasionally occur and children still develop complications such as growth failure and hypogonadism due to endocrine damage*.". The reason for this is stated as iron overload and non-adherence to iron chelation. As established in Shah *et al.* (2021) the issue of non-adherence to ICT persists (18). Vertex is aware that an update to the UKTS standards 2016 is currently in press. We understand that this is expected to be published in early December 2023. This includes updated information and the patient view on increased mortality and the high clinical burden and reduced quality of life of patients with TDT. In addition, the updated Standards includes a previously unpublished survey run by the UKTS in 2021/22 which concludes that over 85% of those with TDT have an impaired quality of life. The availability of this more contemporary version of the UKTS standards will supersede version 3 published in 2016, and provide an up-to-date reflection of the severe burden faced by TDT patients in the UK. **Exa-cel will restore patients to full or near-full health, with the majority of complications reversible following treatment with exa-cel.** The majority of co-morbidities in TDT patients are secondary to iron overload (e.g., cardiac, liver, endocrine complications). Patients with severe cardiac damage (reduced ejection fraction) or severe liver disease (bridging fibrosis or cirrhosis) will not be eligible for treatment. Untreated patients have the potential to develop cardiac and liver damage due to iron overload in later life. Once treated and iron removal is complete, patients would not be expected to have any

			ongoing risk of iron overload-related cardiac or liver damage (i.e., they will return to normal health). Patients with iron-related endocrinopathies (e.g., diabetes, hypothyroidism, hypopituitarism) may be eligible to receive exa-cel treatment. These conditions will not be reversed by exa-cel therapy, and these pre-existing conditions would need ongoing treatment post exa-cel. However, the risk of worsening iron related endocrinopathies is removed by receiving exa-cel therapy. If they do not have iron related endocrinopathies at the time of treatment, they would not be expected to have any ongoing risk of iron related endocrinopathies. Some of the co-morbidities in TDT are multi-factorial and not only due to iron overload (e.g., osteoporosis). Patients may have osteoporosis at the time of therapy. This is treatable post exa-cel therapy and once treated it would not be expected to recur at a higher rate than the normal age-related risk. If patients do not have osteoporosis at the time of exa-cel, once treated they would return to having the normal population risk of osteoporosis. The risk of other complications such as leg ulcers would return to the normal population level post exa-cel therapy. In summary, contemporary UK-specific data supports the substantial impact of TDT on patients' life expectancy and quality of life. Patients with TDT have a life expectancy that is reduced by decades relative to the general population. Mortality rates for TDT patients are increased by over fivefold relative to matched controls. Importantly, this increase is even higher in those <18 years of age, who are at an over [redacted] risk of mortality relative to matched controls. This runs counter to the EAG's position that well monitored and chelated young individuals with TDT will have a near normal life expectancy. The majority of TDT symptoms are secondary to iron overload. Following exa-cel treatment and subsequent iron removal, patients are expected to return to full or near-full health. Vertex re-affirms our belief that the application of the non-reference discount rate is appropriate for exa-cel in TDT.

EAG issue 8	Mortality in transfusion dependent patients and associated with complications	**No**	Please see our response to EAG issues 3 and 4. Based on our proposed alternative approach to the model in EAG issues 3 and 4, this issue is no longer relevant.
EAG issue 9	HRQoL in transfusion independent patients	**No**	The EAG states that appropriate EQ-5D data is available from the CLIMB THAL-111 and should be used to inform the modelled value set. The EAG bases this on critique on the argument that we have not presented sufficient evidence from CLIMB THAL-111 and CLIMB-131 to demonstrate the inappropriateness of the EQ-5D measure to adaptation and ceiling effects. The EAG further states that the finding of high baseline EQ-5D values in the TDT population is consistent with the beti-cel trials and other studies that have reported EQ-5D values in this population. Based on these arguments, the EAG applies a decrement of ~0.05 to transfusion dependent patients based on an assumption related to the trial utilities. **The EQ-5D-5L does not capture the burden of the disease and its fluctuating symptoms over time.** We believe that there is clear evidence indicating that derived utility index scores from the EQ-5D-5L do not fully represent and underestimate the burden of TDT in affected patients. For instance, a study of 30 patients with TDT from the UK, France, and the US found that EQ-5D-5L does not fully capture important symptoms/functional impacts and therefore lacks face validity in a TDT population given that these patients undergo frequent RBC transfusions and require treatment with ICT, which is associated with poor tolerability. Specifically, the study states that the EQ-5D-5L descriptive system (DS) lacks the capacity to capture fluctuating symptoms over time (i.e., given the recall period of “today”) and that responses are highly dependent on where patients are in their RBC transfusion cycle. Given that these patients have an inherited condition and have experienced chronic symptoms of TDT with associated treatment since early childhood, the high baseline utility values can be explained by adaptation, fluctuating haemoglobin levels at the time of response and absence of a fatigue domain in the EQ-5D. This is further supported by the observation that patients in

			CLIMB THAL-111 saw substantial improvements on other disease-specific HRQoL instruments such as the FACT-BMT. Specifically, fatigue related scores indicated improvements in energy and reduction in tiredness after exa-cel infusion, as well as improvements in physical and emotional well-being subscales that were sustained through follow-up. To support the above, we have analysed individual patients' baseline EQ-5D responses (mapped from 5L to 3L utility) in the FAS and PES. Over [redacted] of patients in the FAS and over [redacted] of patients in the PES reported an EQ-5D value of 1, perfect health, at baseline (19). This clearly lacks face validity, given the risks associated with transplantation with an experimental treatment that these apparently perfectly healthy patients were willing to undertake. Furthermore, it means that the observed increase in utility of [redacted] observed by 24 months in the PES is driven by only a proportion of the evaluable cohort being able to experience an improvement. That is, there is a clear rationale for a ceiling effect in the reported increase in EQ-5D. We therefore contend that it is inappropriate to base assumptions on the highly uncertain trial data that may inaccurately reflect the true burden of TDT. Given the substantial uncertainty associated with the EQ-5D-5L instrument's ability to accurately reflect TDT patient HRQoL, we believe, currently, until further analyses have been conducted, that the most robust source of utilities to use in the model is the Matza *et al.* (2020) vignette (20). **The decrement value for transfusion dependent patients proposed by the EAG is lower than the precedent value applied in the beti-cel appraisal.** Regardless of the above, we would like to highlight that the value proposed by the EAG, i.e., a decrement value of 0.05, is lower than the precedent value applied in the beti-cel appraisal [GID-TA10334], in which a decrement value of ~0.1 was applied, by the EAG, to transfusion independent patients.

EAG issue 12	Reweighting of benefits and costs through use of non-reference DCEA	**No**	The EAG considers that if DCEA methodology is to be applied, NICE should first develop suitable reference case guidance. **Submission of the DCEA was based on prior discussions with NICE.** Prior to submission, Vertex had several productive conversations with the NICE team about our intention to submit this additional evidence with a view to supporting principle 9 of NICE's charter. Vertex was pleased to hear that NICE would consider the DCEA, once submitted, in support of this objective. Vertex therefore seeks to not only highlight the health inequalities experienced by patients with TDT through qualitative evidence, but also to bring quantitative evidence to bear and make clear the inequalities experienced by these underserved patients, especially via quantitative metrics such as the Slope Index of Inequality (SII).
EAG issue 13	Approach to distributional cost-effectiveness analysis	**No**	The EAG considers that in the absence of evidence as to how input values vary by subgroup, an aggregate DCEA approach will produce similar results to a full DCEA. However, the EAG go on to state that the justification given for the aggregate approach to DCEA may conflict with arguments presented by the company in respect to ethnicity concerns. The EAG argues that Vertex's approach to DCEA is non-standard and, moreover, that the equity- weighted financial opportunity costs presented in the submission are not a function of the cost-effectiveness threshold. We strongly disagree with these statements. **Socio-economic deprivation is a key determinant of health status in the UK.** In the UK, TDT predominantly affects individuals of Pakistani and South Asian origin as evidenced by the National Haemoglobinopathy Registry (NHR) 2021 data and the BoI study respectively (9, 21). TDT patients are also more likely to live in a more deprived area of the UK, with 56.2% of TDT patients identified in the Vertex BoI study living in the two most deprived quintiles according to the Index for Multiple Deprivation (IMD). The relationship between deprivation and ethnicity, within the context of TDT, is evident especially when reflecting on the fact that, for

			example, people from the Pakistani and Bangladeshi ethnic groups are over 3 times as likely as White British people to live in the most income-deprived 10% of neighbourhoods (22). It is thus apparent that there is a disproportionate distribution of TDT prevalence across ethnic minorities whom, in turn, are also most likely to be disproportionately affected by socio-economic deprivation. Supported by external expert consultation, we therefore considered socio-economic deprivation to be an adequate proxy which reflects and is sufficiently correlated with ethnicity. **Our approach was informed by consultation with an external DCEA expert.** Although the EAG considers use of indirect equity weights non-standard to DCEA, our approach was based on consultation with an external expert, Professor Richard Cookson. Our approach, as agreed by the EAG, still provides an indication of the priority placed on QALY gains across different deprivation groups. **Our approach maintains the relationship between health opportunity costs and the cost-effectiveness threshold.** Our approach proportionally weights financial opportunity costs (i.e., incremental costs) and incremental QALYs, within each IMD group, according to the health opportunity cost shares attributed to each IMD quintile. This means that the financial opportunity cost shares are apportioned to each IMD quintile according to the specified distribution of health opportunity costs shares for each quintile. In other words, the greater the proportion of individuals within an IMD group, the greater the financial opportunity costs are accrued to that quintile. These values are then further weighted by the aversion parameter – the higher the aversion to inequality, the higher the weight applied to the opportunity costs in each IMD quintile. Note that the aversion weighting is also dependent upon pre-existing health inequalities, represented by the general population QALE distribution.

			For example, if there is a majority proportion of individuals within the most deprived quintile who also incur the largest proportion of health opportunity cost shares, the resulting financial opportunity costs will implicitly reflect higher health opportunity costs incurred within the most deprived quintiles. Thus, financial opportunity costs are weighted by the health opportunity costs shares *and* the aversion weights. This also implies that the health opportunity costs within more deprived quintiles are implicitly considered to have greater value than the least deprived group – i.e., in such scenarios, the worse-off 'have more to lose'. At the aggregate level, our approach, therefore, still provides a proportional weighting of the costs and incremental benefits that are accrued to the overall target population. Thus, a direct relationship with net health benefit and the decision threshold is preserved. **Regardless, our approach maintains ordinal utility and provides the decision-maker with the same optimal decision as the Equally Distributed Equivalent (EDE) function.** In the exercise spreadsheet related to chapter 13, Indirect equity weights, from Cookson *et al.* (2020), found in the online supporting supplementary materials, it is noted that our approach is the simpler, unabbreviated form of the EDE function. In terms of decision theory, the approaches are ordinally equivalent and would not provide a contradictory optimal decision. The approach is consistent within the framework of utility theory. We therefore expect that the committee would find the presentation of our DCEA results useful in quantitatively valuing and demonstrating the potential impact that exa-cel will have on health inequalities.
EAG issue 14	Input parameters used in the distributional cost-effectiveness analysis	**No**	As per the EAG recommendation, we have aligned our base case with the EAG inputs for scenarios 18 and 20, as we had previously agreed to align our base case with the EAG during clarification.

EAG issue 15	Discounting and severity modifier and distributional cost-effectiveness analysis	**No**	The EAG notes the lack of precedent for application of a severity modifier, non-reference discount rate, and DCEA, and lack of clear direction on appropriate approach to this in the NICE methods manual. In addition, the EAG considers that should both the severity modifier and DCEA be applied simultaneously, the QALY shortfall input into the severity modifier should be calculated between the quality-adjusted life expectancy (QALE) in the target patient population and QALE in an age, sex and IMD matched general population. **The three modifiers applied are described independently in the NICE methods manual, and there is no reason to believe they are mutually exclusive.** As described in our clarification response, all of these factors have their own dedicated but independent sections in the NICE methods manual: **Severity** Severity is presented as a 'decision modifier'; that is, a factor that has not been included in the estimated QALY because it cannot be. The severity modifier captures the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS. An important feature of the severity modifier is that it is determined by the shortfall in discounted QALYs. This performs extremely well in situations where near-term mortality risk is high and/or HRQoL is extremely low at baseline. However, progressive diseases in which mortality increases or HRQoL deteriorates substantially over time are penalised by the discounted QALY approach and the only way that these diseases would be eligible for a modifier is by decreasing the QALY discount rate. It notable how, in this respect, the modifier differs between STA and HST, modifiers in the HST appraisal route being underpinned by undiscounted QALYs. Indeed, it is evident that a number of HSTs would never have been awarded a modifier had it been reliant on discounted QALYs (23). **Discount rate** The 1.5% discount rate considers satisfaction of 3 criteria:

			• The technology is for people who would otherwise die or have a very severely impaired life. • It is likely to restore them to full or near-full health. • The benefits are likely to be sustained over a very long period. Only the first criterion overlaps with disease severity; the other two criteria are entirely unrelated. The overall objective of the 1.5% discount rate is to avoid penalising those treatments with high upfront (undiscounted) costs but where the QALY gain and cost savings accrue over a long time period and are subject to discounting. In summary, severe diseases may achieve the severity modifier, but only curative therapies, which are generally advanced cell and gene therapies with high upfront costs, are likely to be eligible for a 1.5% discount rate. **Health inequalities** Health inequalities are addressed in section 2.2.24 of the NICE methods guide, a section dedicated to 'Other issues likely to affect the evaluation'. While NICE makes it clear that they will consider whether the technology could address inequality or unfairness in the distribution of health across society, there is no explicit description of how it will be used in committee decision-making from a quantitative perspective. This lack of transparency could be considered a weakness of existing deliberation processes. We have simply applied published methods of quantifying the impact of exa-cel on health inequalities and applied the associated, published, weightings to incremental costs and QALYs. A severe disease on its own would not generate a DCEA weighting; the DCEA weighting is *only* generated if the disease is disproportionately experienced by people living in the most deprived population quintiles. This population-level criterion is completely unrelated to either the severity modifier or the 1.5% discount criteria. In summary, the absence of precedent for this particular situation does not preclude its application. Instead, an absence of precedent relates more to the relative recency of the introduction of the severity modifier, as well as Vertex's novel

approach to quantifying the health inequalities that NICE often consider deliberatively, in a qualitative manner. The three factors are independently described in the NICE methods manual, and application of one should not prejudice against application of another.

Nevertheless, the EAG state in their report that if the severity modifier is to be applied in combination with a DCEA that accounts for health inequalities between IMD quintiles, it would be appropriate to calculate the QALY shortfall between QALE in the target patient population and QALE in an age, sex and IMD matched general population.

The DCEA has been updated to remove any influence of the IMD distribution on the QALE shortfall calculations.

To consider EAG's recommendation, we have provided an updated shortfall calculation using an age, gender, and IMD matched population distribution of general population shares for IMD. Vertex's updated base case results have already been provided in our response to EAG issue 3 and 4. Vertex have updated the general population shares distribution (see row C in the table below) to reflect data from the control cohort IMD distribution from Vertex's BoI study. To demonstrate that IMD now negligibly influences the years of the QALY shortfall for individuals with TDT, we have tabulated a like-for-like comparison of the EAG's calculations, found in Table 35 of the EAG report, in Table 5 below.

Table 5: QALE shortfall calculation based on age, gender, and IMD matched general population shares

	IMD 1	IMD 2	IMD 3	IMD 4	IMD 5
A. QALE	62.17	65.28	69.55	71.59	73.42
B. TDT population share	0.26	0.30	0.20	0.14	0.10

<table>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>C. General population share</td><td>0.235</td><td>0.203</td><td>0.203</td><td>0.185</td><td>0.174</td></tr>
<tr><td>Sum Product A and B</td><td></td><td></td><td></td><td></td><td>67.0228</td></tr>
<tr><td>Sum Product A and C</td><td></td><td></td><td></td><td></td><td>67.1986</td></tr>
</table>

These changes now indicate that only 0.17 years of the QALY shortfall for individuals with TDT may be explained by the association of IMD with QALE. This is negligible and should not negate the consideration for the clear evidence of health inequalities that are present within the TDT population.
</td></tr>
<tr><td colspan="4">EAG issues accepted by Vertex</td></tr>
<tr><td>EAG issue 10</td><td>Multiplicative age-adjustment</td><td>No</td><td>We accept the EAG’s proposal for a multiplicative age adjustment.</td></tr>
<tr><td>EAG issue 11</td><td>Use of eMIT costs</td><td>No</td><td>We accept the EAG’s proposal for use of eMIT costs.</td></tr>
</table>

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 16: **Baseline iron levels based on CLIMB THAL-111**	Section 4.2.3.1 Section 6.1 Point 4	No	The EAG considers the distribution of iron loading, derived from the Chart Review, to be broadly appropriate (18). However, the EAG state that any apparent relationship in the Chart Review population is likely to be confounded by changes in the management of iron overload complications over time. On the basis described in key issue 7, we reiterate that baseline iron-level data from CLIMB THAL-111 fail to capture the transition of TD patients to higher iron levels over their lifetime and consider these data as unrepresentative of contemporary TDT populations.
Additional issue (not in key issues table): **Iron normalisation in patients with low iron levels**	Section 6.1 Point 10	Yes: see issue 7	The EAG state 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. Please see our response to key issue 7, where we describe how the majority of TDT-related complications are secondary to iron overload, and would be reversible following treatment with exa-cel. Based on our response to key issue 7, we re-state our position that exa-cel will restore patients to full or near-full health.

Additional issue (not in key issues table): **1.4% mortality risk for myeloablative conditioning**	Section 6.1 Point 12	No	**Late mortality effects associated with the transplantation procedure are already captured by an SMR of 1.25 applied to functionally cured patients** While it is possible to apply an instantaneous event rate due to busulfan conditioning in the model, this was intended to capture any mortality observed during the CLIMB THAL-111 trial observation period. As no mortality has been observed thus far, we have not included any in the model. Furthermore, late mortality effects associated with the transplantation procedure are already captured by an SMR of 1.25 applied to functionally cured patients, in line with that applied during the beti-cel appraisal (ID968). There are no relevant sources of near-term mortality rate that can be taken from the literature, as we have not been able to identify any evidence for the mortality impact of busulfan monotherapy in the TDT population. The majority of regimens in the literature being utilised within the context of allogeneic stem-cell transplant and comprising combinations of busulfan, cyclophosphamide, fludarabine, treosulfan and anti-thymocyte globulin have low or zero rates of transplant related mortality. It would therefore be impossible to separate out the relative contribution to mortality of busulfan monotherapy within these very different transplantation settings.
Additional issue 23: **Removal of health state costs**	Section 4.2.8 Section 6.1 Point 16	Yes: micro-costing spreadsheet provided	We accept the EAG's proposal for removing health-state costs on the basis that Shah *et al*. (2021) does not separate out costs related to management of comorbidities already included in the model.

			Removing these costs altogether does, however, bias against exa-cel as the model will fail to capture other costs associated with TDT that are not explicitly captured by the model. These will include the routine monitoring of patients and their iron levels, as well as hospitalisations for conditions caused by TDT not captured in the model such as infection. Therefore, we have incorporated monitoring costs only via a micro costing approach, which includes blood tests, echocardiogram (echo) and MRI costs. These costs total £107.64 per month and are applied to TD and TR patients, replacing the original health state costs. No costs have been applied to the TI health state, as the model already includes additional monitoring costs over the iron normalisation period. Following iron normalisation, it is anticipated that patients will either no longer incur these monitoring costs, or they will be so infrequent as to have limited impact on the ICER. Frequencies for MRI and echo assessments were based on a weighted average of the frequencies cited in the Shah *et al* appendix (2021) (18). All other frequencies for monitoring tests were obtained from the UKTS guidelines. All unit costs were obtained from NHS reference costs. Details of the micro costing have been provided in an Excel spreadsheet (24) .
Additional issue 6: **Assuming 5 years to iron normalisation**	Section 6.1 Point 9	Yes: additional literature only	Whilst acknowledging a lack of clear data relating to this issue, our assumption of 4 years is supported by the literature. Aloobacker *et al.* (2021) provide a useful summary of the data, such that it is. They

			observed a median duration of 47 months (n=149) of iron reduction treatment in patients treated with allo-SCT between 2001 and 2012. We note that these patients were highly iron overloaded at baseline (25). Angelucci *et al* looked at 48 patients treated with phlebotomy post-transplant; these patients had a median duration of 35 months (+/- 18months) to iron normalisation (26) In summary – the literature on this shows median rates of 14-17 months, 35 months and 47 months to iron normalisation. The paper with the longest time to iron normalisation still only gives 4 years and in this study patients were very iron loaded. In this context, we propose that 4 years to iron normalisation is a conservative estimate.
Additional EAG issues accepted by Vertex			
Additional issue 1: **Baseline prevalence of osteoporosis and diabetes based on CLIMB THAL-111**	Section 4.2.3.1 Section 6.1 Point 3	No	We accept the EAG's proposal for using baseline prevalence of osteoporosis and diabetes based on CLIMB THAL-111.
Additional issue 22: **No infertility-related decrements**	Section 4.2.7.3 Section 6.1 Point 14	No	We accept the EAG's proposal for no infertility-related decrements.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
EAG Issue 3, 4	Comorbidity-related mortality, costs, and health outcomes are incorporated into the model	Removed comorbidity-related mortality to address the EAG's concern of potential progressive overestimation of mortality	Updated co-base case (no DCEA): [redacted] Updated DCEA co-base case: [redacted] Original co-base case (no DCEA): [redacted] Original DCEA co-base case: [redacted]
EAG Issue 10	Drug costs based on BNF drug tariff prices	Drug costs based on eMIT drug tariff prices	Updated co-base case (no DCEA): [redacted] Updated DCEA co-base case: [redacted] Original co-base case (no DCEA): [redacted] Original DCEA co-base case: [redacted]

EAG Issue 11	Applied additive utility age-adjustment to utility	Applied multiplicative utility age-adjustment	Updated co-base case (no DCEA): [redacted] Updated DCEA co-base case: [redacted] Original co-base case (no DCEA): [redacted] Original DCEA co-base case: [redacted]
EAG Issue 15	General population shares based on external source	Applied age, gender, and IMD matched general population shares in response to EAG's critique that a proportion of the QALY shortfall for individuals with TDT may be explained by the association of IMD with QALE	Updated DCEA co-base case: [redacted] Original DCEA co-base case: [redacted]
Additional Issue 1	Assumed 0% baseline prevalence of osteoporosis and diabetes	Baseline prevalence of osteoporosis and diabetes based on CLIMB THAL-111	Updated co-base case (no DCEA): [redacted] Updated DCEA co-base case: [redacted] Original co-base case (no DCEA): [redacted] Original DCEA co-base case: [redacted]
Additional Issue 5	Included lump sum health state costs	Changed lump sum health state costs to only include monitoring costs for patients treated with RBCTs and ICT	Updated co-base case (no DCEA): [redacted] Updated DCEA co-base case: [redacted] Original co-base case (no DCEA): [redacted]

			Original DCEA co-base case: [redacted]
Additional issue 22	Included disutility of osteoporosis	Excludes disutility of osteoporosis	Updated co-base case (no DCEA): [redacted] Updated DCEA co-base case: [redacted] Original co-base case (no DCEA): [redacted] Original DCEA co-base case: [redacted]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: 13.22	Incremental costs: £1,048,626	Updated co-base case (1.5% discount rate no DCEA, with 1.2 severity modifier): [redacted] Updated DCEA co-base case, 1.5% discount rate and 1.2 severity modifier: [redacted]

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel (exa-cel) for treating transfusion-dependent beta-thalassaemia [ID4015]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing 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. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1, Table 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. 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.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Monday 6 November 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

NICE National Institute for Health and Care Excellence

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.

Part 1: Treating transfusion-dependent beta-thalassaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Ben Carpenter
2. Name of organisation	UCLH NHS 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 transfusion-dependent beta-thalassaemia? ☐ A specialist in the clinical evidence base for transfusion-dependent beta-thalassaemia or technology? ☒ Other (please specify): Transplant physician who has delivered this treatment (Exacel) in the context of the study, and alloHSCT for haemoglobinopathies.
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 did not submit one, I do not 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. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

8. What is the main aim of treatment for transfusion-dependent beta-thalassaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	With Exacel the intent is curative.
9. 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)	Removal for the need of ongoing transfusions Significant reduction in transfusion requirement leading to reduced increased quality of life and reduced iron burden/exposure.
10. In your view, is there an unmet need for patients and healthcare professionals in transfusion-dependent beta-thalassaemia?	Yes, currently regular transfusions leads to significant morbidity, poorer quality of life and increased risk of mortality. A curative treatment is highly desirable.
11. How is transfusion-dependent beta-thalassaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	I am not an expert in this area. But the delivery of regular transfusion, chelation therapy and supportive care is systematically delivered by the NHS and subject to a number of guidelines on how it should be delivered. This therapy being organised through HCCs. Exacel would likely remove the need for ongoing transfusion, improving quality of life and likely significantly reduce morbidity and mortality.
12. 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? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Exacel would need to be delivered in a different way to current therapy- with red cell and transplant teams delivering this therapy. It should be delivered in specialist centres with input from Thalassaemia and transplant teams. Required infrastructure would predominantly be staff- for instance joint red cell/transplant clinical nurse specialists, psychological support appropriate to these therapies and the decision making around them. Ensuring appropriate capacity in red cell and transplant teams to take this work on. A suitable tariff

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	would be needed to support this work, proportional to the increased complexity and length of stay, say compared to a standard autologous transplant.
13. 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? • Do you expect the technology to increase health-related quality of life more than current care?	Yes I do- based on the current study data, showing high levels of efficacy in achieving transfusion independence. I would expect the therapy to improve quality of life and health related outcomes- as supported by the CLIMB Thal-111 study. This is highly likely to translate into reduction in morbidity and mortality due to the cessation of transfusion the therapy should provide.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As long as the population treated with this technology is reflective of the CLIMB Thal-111populaton- Beta TDT including β^0/β^0 patients I would expect it to be equally effective.
15. 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 initial mobilisation and transplant procedure will be more intensive than standard therapy. There will be a higher risk of adverse events during particularly the transplant procedure, but then post engraftment and recovery from the transplant procedures (short months) I would expect the technology to significantly improve patients' quality of life and health status. This short period of difficulty for patients I believe will be quickly balanced out if transfusion independence is achieved. Supportive care would need to be delivered through this treatment including fertility preservation, treatment of transplant complications and psychological support throughout the whole process.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The patients should be physically (as defined by screening tests as per CLIMB Thal-111) and psychology screened before proceeding further with this treatment. I think this is key to ensuring medically unfit patients are not put forward, and that psychologically patients are ready and supported to navigate this treatment.

17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The treatment should mean that patient move from frequent healthcare interactions and management of complications, to very infrequent follow up monitoring.
18. 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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	I do, the treatment is potentially transformative in its ability to deliver a cure, providing transfusion independence and likely associated reduction in morbidity and mortality. The treatment is attractive in that it should be a 'once off' treatment that requires very occasional subsequent follow up.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In the short-term, during the transplant period, adverse effects will be higher. But within 2-3 months the majority of patients will recover from this procedure. From this point accrual of complications should reduce rapidly, and with this quality of life improve significantly.
20. Do the clinical trials on the technology reflect current UK 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? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	I think primary and secondary endpoints were reflective of the key considerations- particularly transfusion independence and patient report outcomes. The clinical trial was not reflective of standard technology usage, as this is a new technology, but the patient inclusion criteria were appropriate for the population in question.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	No other 'real-world' experience is available to the best of my knowledge.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	The technology is predominantly appropriate for patients from ethnic backgrounds that have been overlooked and disproportionally suffer from socio-economic deprivation. These factors often lead to poorer health outcomes, and thus this technology could address these for the patient group.

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue impacting decision making:	Description:	
EAG issue 1	**Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile:** **Permanence of transfusion independence: after successful exa-cel treatment (defined as achievement of transfusion independence) how likely is:** • **the risk of thalassaemia recurrence** • **a 0% rate of thalassaemia recurrence** **Safety: the company notes that exa-cel's mechanism of action eliminates any risk of treatment-related**	I agree persistence of transfusion independence is highly probably- -given the stability of allelic editing out to 24 months in bone marrow CD34+ stem cells and further in peripheral blood, post Exacel infusion seen in CLIMB Thal-111. This should also mean the engraftment of edited haematopoietic stem cells should persist into the long term. This should translate to a very low risk of Thalassaemia recurrence. Currently no patient that has become transfusion independent has reverted to requiring transfusion. Therefore this is the only guide we have currently. Stability of a graft at 24 months would be highly

	cancer (risk of mutagenesis and transcriptional deregulation) • **Do you agree?** • **Do you have any further comments on exa-cel's safety?**	predictive of success in the alloHSCT setting, a situation in which graft stability is more problematic given allogenic stem cells are transferred (and maybe immunologically rejected). With regards to the second question, the data we have to date reports no malignancies secondary to the use of Exacel. I believe it is difficult to say this risk is definitely eliminated, however other approaches e.g. alloHSCT are not without the risk of secondary malignancies and we would accept these, in the presence of a matched sibling donor, as a viable option. Therefore, I believe the lack of malignant events to date does support this technology having reached a threshold of safety to allow its implementation.
EAG issue 2	**Definition of transfusion independence** **Do you have any comments on the most appropriate definition, and/or advantages and disadvantages of the definitions below:** • **maintaining a weighted average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months any time after exa-cel infusion (CLIMB THAL-111 primary outcome – 'TI12')** • **as people who are transfusion-free starting 60 days after the last blood transfusion for post-transplant support or disease management**	Just to note patients that became transfusion independent maintained this to the extent of current follow up.
EAG issue 3	**Uncertain relationship between transfusion status and final outcomes**	This is not my area of expertise, but dependent on the health status and end organ damage at the time of intervention removing the need for ongoing transfusion is

	• **Can you comment on how transfusion status (transfusion independent, reduced, dependent) is related to iron levels, risk of chronic complication, mortality rates and quality of life?** • **What are some of the advantages and disadvantages of assuming a link between transfusion status and these outcomes without direct evidence?** • **Are there any evidence sources that can be used to help inform the link between transfusions status and the outcomes listed above?**	likely to achieve improved final outcomes. Given, by definition, patients undertaking this treatment have no problematic end organ damage they are likely to derive the most benefit from achieving transfusion independence.
EAG issue 5	**Omission of withdrawals from exa-cel treatment in the economic analysis** • **What proportion of people would you expect will withdraw/be unwilling to proceed after cell collection, but before the exa-cel infusion?**	I think this is likely to be very low as indicated. However, I have personal experience of a patient withdrawing from the gene therapy/editing process and I believe the appropriate assessment and support of a psychology team with relevant experience is necessary to minimise patient withdrawal post mobilisation.
EAG issue 6	**Frequency of red blood cell transfusions** • **A UK chart review reported that people with transfusion dependent beta-thalassaemia on average will have 13.7 transfusions per year** • **Do you agree with this estimate?** • **What is the range you would expect to see in clinical practice?**	I am not best placed to comment on this
EAG issue 7	**Non-reference discount rate** **According to the NICE manual for a non-reference discount rate to be applicable a set of criteria need to**	Yes TDT patients are more likely to experience morbidity and earlier mortality than the general population. As stated above if patients without established end organ failure are

	be met. The questions below have been tailored to the criteria. **Are people with transfusion dependent beta-thalassaemia on current standard care more likely to die or have a very severely impaired life compared with the general population?** • **What is the life-expectancy of people being offered current standard care with this condition?** • **How different is the mortality rate compared with the general population? (for example is 5 times higher a reasonable approximation?)** • **How different is the quality of life of people with this condition?** **Is treatment with exa-cel likely to restore people with the condition to full or near-full health:** • **Does this condition already cause permanent damage from pre-existing complications (for example cardiac or liver complications) that cannot be reversed by exa-cel treatment?** • **If yes, what proportion of people are likely to experience this?** **The benefits of exa-cel are likely to be sustained over a very long period.** • **Do you expect the benefits of exa-cel observed during a maximum of 42 months of follow-up to be sustained over time?**	treated with this therapy- as per CLIMB Thal-111, then they are likely to experience near-full health. As also stated above extrapolating from the alloHSCT setting, and in view of the allelic editing data I think it is highly likely Exacel will deliver long term benefits of transfusion independence and the associated health benefits.

	• **If no, why not?**	
EAG issue 8	**Mortality for people with transfusion dependent beta-thalassaemia, and mortality associated with complications** • **What would you expect the mortality rate or standardised mortality rate* to be for people with this condition who have cardiac or diabetic complications?** ***Standardised mortality rate = the number of deaths observed in a population over a given period divided by the number that would be expected over the same period if the study population had the same age-specific rates as the standard population**	I believe my thalassaemia colleagues would be best placed to answer this
EAG issue 9	**Health related quality of life in people who are transfusion dependent** • **Since the condition is inherited/ starts from early childhood. How likely is it that people with this condition get used to the symptoms over time?** • **Do you have any other comments about the quality of life of people living with this condition?**	I think it is highly unlikely patients will adapt to the symptoms- given the symptoms of anaemia are not those you 'get used to' across all disease subtypes. The complications of transfusion and iron loading again are not ones you can adapt to e.g. severe cardiac and endocrine dysfunction. CLIMB Thal-111 demonstrated reduced patient reported health outcomes at baseline, that improve post treatment.
EAG issue 12-14	**Would the introduction of exa-cel have any impact on health inequalities? If so, how?**	As above the technology is predominantly appropriate for patients from ethnic backgrounds that have been overlooked and disproportionally suffer from socio-economic deprivation. These factors often lead to poorer health outcomes, and thus this technology could address these for the patient group.

	Economic modelling specific issues **(Focus of issues are less clinical and more methodological/conceptual please refer to section 1 of EAR to more details)**	
EAG issue 11	**Using eMIT costs instead of national tariff**	
	Other issues that need clinical expert opinion:	
	Baseline osteoporosis and diabetes complication rates: **Do you agree with the following statement:** • **The pathogenesis of beta-thalassaemia-related osteoporosis is not well understood but it is theorised to be a result of many factors such as inherent genetic factors, ineffective erythropoiesis, high iron levels, and low levels of vitamin D. Exa-cel treatment may impact some of these factors.** **Do you expect exa-cel treatment would reverse osteoporosis symptoms or complications?**	I believe my thalassaemia colleagues would be best placed to answer this
	Risk of initial graft failure: **The CLIMB THAL-111 trial showed there were no engraftment rejections (failures). But 6.9% initial engraftment failure have been reported in haematopoietic stem cell transplant.** • **Is it reasonable to assume 100% initial engraftment success in clinical practice?** • **If not, what is the range of initial engraftment failures seen in clinical practice?**	The risk of graft failure does appear to be very low across the use of Exacel and busulfan based gene therapy/editing for haemoglobinopathies. I do not believe the comparison of alloHSCT is a fair one, given the use of allogeneic rather than autologous haematopoietic stem cells (HSCs) with the attended risk of immunological graft rejects in the former setting. Practically we do not see graft rejection in autologous transplantation if suitable numbers of HSCs are infused. In our practice we are confident this is ≥2 x10^6/Kg or with checking of appropriate viability ≥1 x10^6/Kg infused

		HSCs is sufficient for robust engraftment. Therefore, with the planned dose of ≥3 x10^6/Kg I do not anticipate graft failures.
	Iron normalisation period: **How long does it take for people with transfusion-independent beta-thalassaemia to achieve normalised iron levels in all organ systems:** • **Four years (company assumption)** • **Five years (EAG assumption)** • **Other?**	I believe my thalassaemia colleagues would be best placed to answer this
	Severity modifier: **Please refer to Table 2a below to help answer this question. Table 2a presents the utility values and undiscounted life years (LYs) split by health state from the EAG and company models. Life years are the amount of time someone spends in that state in the model in years.** **Considering both the EAG and company values, can you comment on the utility values per health state? (for example, are the differences in utility values between the health states too high, too low or reasonable)?** **Considering both the EAG and company values, can you comment on the undiscounted life years for a person living with transfusion-dependent beta thalassemia who is accessing standard of care? (for example, are the figures too high, too low or reasonable)?**	This is not my area of expertise.

	Do you have any further comments on the other issues not included within this list?	No
	Are there any important issues that have been missed in EAR?	

Table 2a. Company and EAG estimates for utility values and undiscounted life years (LYs)

Health state	Utility value	Undiscounted LYs for standard of care
Company estimates		
Transfusion independent	**0.93**	[redacted]
Transfusion reduction	**0.75**	[redacted]
Transfusion dependent	**0.73**	[redacted]
EAG estimates		
Transfusion independent	**0.93**	[redacted]
Transfusion reduction	[redacted]	[redacted]
Transfusion dependent	[redacted]	[redacted]

Estimates based on the IA2 clinical trial data cut.

[redacted]

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1) This is a curative treatment for a condition that's currently causes multi-organ morbidity and early mortality
2) Patients predominantly come from ethnic groups that have been historically overlooked, with often poorer socio-economic backgrounds reducing health outcomes, potentiating the unmet need.
3) This therapy will give much wider access to curative treatment, which currently is matched sibling alloHSCT, that 80%+ will not have access to.
4) The therapy does have risks; however, study data indicates these are manageable, with no mortality or malignancy reported, and once past the transplant procedure, patient reported health outcome improve significantly.
5) Engraftment was 100% and graft stability was maintained to clinically meaningful timepoints, resulting in stable transfusion independence for the majority of patients.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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

Single Technology Appraisal

Exagamglogene autotemcel (exa-cel) for treating transfusion-dependent beta-thalassaemia [ID4015]

Patient expert statement and technical engagement response form

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

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with transfusion-dependent beta-thalassaemia or caring for a patient with transfusion-dependent beta-thalassaemia. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1, Table 1).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

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Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Patient expert statement

The deadline for your response is **5pm** on **Monday 6 November 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

Part 1: Living with this condition or caring for a patient with transfusion-dependent beta-thalassaemia

Table 1 About you, transfusion-dependent beta-thalassaemia, current treatments and equality

1. Your name	Roanna Maharaj
2. Are you (please tick all that apply)	☒ A patient with transfusion-dependent beta-thalassaemia? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with transfusion-dependent beta-thalassaemia? ☒ A patient organisation employee or **volunteer**? ☐ Other (please specify):
3. Name of your nominating organisation	United Kingdom Thalassaemia Society (UKTS)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with transfusion-dependent beta-thalassaemia? **If you are a carer (for someone with transfusion-dependent beta-thalassaemia) please share your experience of caring for them**	I received a diagnosis of beta thalassaemia major when I was just 5 months old, after my parents had received a misdiagnosis for months. The day after my diagnosis, I had my first blood transfusion, and from then until the age of 21, I needed transfusions every three weeks. When I turned one year old, I received my first pump to start a lifelong subcutaneous treatment with Desferal, a powerful iron chelator. Managing severe iron overload and undergoing iron chelation therapy was one of the most challenging aspects of my condition as I grew up. It was difficult for me to keep up with my medication, and I did everything I could to avoid it. The nightly injections, which took 8-10 hours, were incredibly painful. Despite trying different injection sites, I experienced redness, swelling, lumps, and increased pain. Every night, as I watched the sunset, I would cry in anticipation of the pain I knew was coming. My parents had to hold me down as I squirmed and tried to escape. It was a traumatic experience. During my school years, I made a conscious effort to live my life as normally as possible. I was an active and well-liked student, involved in various activities. However, there were moments when I faced derogatory comments from some individuals, who referred to me as a mosquito, vampire, or even evil, all because of my need for transfusions. Thankfully, my parents played a crucial role in helping me brush off these hurtful labels. They were open about my condition and did their best to normalise it. I vividly recall an incident when one of my friends was forbidden from playing with me anymore. Their parents were afraid that if we both got injured and bled, their child might contract HIV or some other illness from me. As I grew older, I began to

	understand why many families felt compelled to hide their conditions, as the stigmas associated with them were incredibly intense. At the age of 12, I was prescribed an oral chelator in addition to my Desferal infusions due to severe iron overload. While it seemed like it would be easier to manage in theory, I struggled with the side effects of both treatments. At that age, I didn't fully understand the impact iron overload was having on my body, so I would often skip medication or pretend that I had taken it, unknowingly reducing my life expectancy. By the time I was 14, I was on the verge of developing cardiac failure due to severe iron loading in my heart and liver. I also experienced moderate joint pain, but I didn't fully comprehend the damage caused by iron overload. I would compare my bedtime routine to that of my friends and cousins, and I noticed that they had an easier time while mine was always difficult for my parents and me. As I entered my later teens, I became more serious about taking my medication despite the side effects. My growth, height, and weight were significantly affected compared to someone without the condition at my age. I looked much younger than my peers, which had an impact on my self-esteem. At the age of 17/18, I was diagnosed with hypothyroidism, hypotropic hypogonadism, and severe osteoporosis. Due to my bones being comparable to those of an 80-year-old, I immediately started intravenous bisphosphonates. However, being treated with bisphosphonates at such a young age resulted in severe complications and reactions that affected my overall health, daily life, education, and social activities. I lived with constant bone pain, vomiting, poorly treated thrombophlebitis, and the need to stay on medication because my bones required it. When I turned 21, I started experiencing severe reactions to my blood transfusions. These reactions were so severe that my blood requirements increased from receiving two units of blood every three weeks to three units of blood every week. These reactions caused me to lose my twenties and half of my thirties, as they prevented me from pursuing my doctorate studies, working, and enjoying the things I once loved.

	To address the reactions, my blood had to be processed differently. Initially, it was washed, then washed and HLA matched, and finally washed and irradiated because it was discovered that I had developed GVHD-associated transfusion reactions. Since May 2011, each transfusion I've had has resulted in increasingly inflamed skin, burning rashes, oedema in my face, abdomen, hands, and legs, severe and debilitating bone pain affecting my mobility, vision disturbances, and severe urinary retention, among other symptoms. Initially, I believed my case was an exception, which is why I never spoke about it. However, we are now hearing about more people reacting to transfusions and experiencing severe bone pain afterwards. Unfortunately, there is little knowledge on how to treat this, as transfusion reactions in multi-transfused patients are becoming more common due to longer lifespans. Throughout my life, I have always struggled with cannulation, often requiring over 24 attempts to find a viable vein. Even routine blood work became a challenge. This caused distress not just for me, but also for healthcare professionals who would express their anxiety and lack of sleep over the thought of trying to cannulate me. Hearing this was never easy, and I always felt guilty for putting them through that. As a result, I agreed to have central lines inserted at an early stage to improve the experience, but they came with their own issues, such as sepsis over 10 times, thrombosis, and on occasion, one of my portacaths protruding through my skin and being visible. In addition to all these challenges, I have also developed diabetes, gallstones, and other complications. I made every effort to actively participate in sports and other activities until I reached a point where my physical abilities limited me, which happened at a much earlier age compared to peers my age. As time has passed, I have witnessed the progression of my condition and the significant impact it has had on my aging process, which is a challenging concept to fully grasp. Adjusting to this reality is something I find difficult and uncertain if I will ever truly adapt to it.

	Another difficult aspect that I face now is witnessing the impact of my condition on my family, friends, and community. The guilt, fear, and uncertainty they experience after every transfusion, infection, complication, and the constant adjustments they make to accommodate my needs weigh heavily on me. As I have grown older, I can see how their feelings have deepened. I observe the toll it takes on my parents and my partner, who often must take time off work to accompany me for treatment or provide care. This has led them having to change jobs or even relocate to be more accessible to me. Despite their willingness to do so, the guilt I feel is overwhelming. It is important to recognise that thalassaemia does not solely impact the individual, but it affects the entire support system. Enduring the challenges of living with thalassaemia has never been a simple task, and I genuinely wish that no one else would have to experience it. Whilst I would not be eligible for this treatment, my heartfelt hope that is that the younger generation and those who qualify will be spared from the difficulties I and others have faced.
7a. What do you think of the current treatments and care available for transfusion-dependent beta-thalassaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Thalassaemia care in the UK lacks standardisation across the country. While I appreciate the care I receive in London, which includes regular transfusions, medication, and specialised monitoring, this level of care is not consistent in other parts of England. Many trusts provide subpar care, leading to fragmented services requiring patients to visit multiple venues on different days for blood tests, transfusions, scans, specialist care, and medications. This situation is far from satisfactory. It is important to acknowledge that the care we receive addresses the symptoms of anaemia and iron overload but does not offer a cure. The use of generic forms of oral iron chelation medication in many trusts has resulted in increased side effects for myself and others. Moreover, we lack access to essential services such as dieticians, physiotherapists, and psychological and wellbeing support within thalassaemia

	services and unfortunately prioritisation of thalassaemia care and improving services have declined in recent years. There is a lack of education, staffing levels and time needed to adequately treat patients as they deserve. Regarding curative options, less than 10 percent of individuals have access to HSCT (hematopoietic stem cell transplantation), and the community does not believe that current treatments are sufficient.
8. If there are disadvantages for patients of current NHS treatments for transfusion-dependent beta-thalassaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Blood transfusion reactions which are beyond allo-immunisations are not paid enough attention and there are no clear pathways to treat those who suffer with painful transfusion reactions or those that patients like I encounter. Pain on the whole in thalassaemia is not appropriately acknowledged, prioritised and treated in the UK and this negatively affects the quality of life of our thalassaemia community. Based on research and feedback from the thalassaemia community side effects of medication are not properly addressed or acknowledged and often only picked up when things are extremely serious.
9a. If there are advantages of exagamglogene autotemcel (exa-cel) over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does exa-cel help to overcome or address any of the listed disadvantages of current treatment that you**	With regards to the thalassaemia community who are eligible for this treatment, being transfusion independent has been described as freedom. Freedom from being tied to the hospital for regular transfusions, freedom from iron chelation medication and a sense of freedom from stopping or reducing the progression of the condition. This will directly improve their quality of life as not only will it stop iron over related complications from developing and cease transfusion reactions, it will help decrease time spent in hospital and needed for treatment which they could invest in whatever lifestyle they would like.

have described in question 8? If so, please describe these	With even missing school, work for at least 61 days per year for treatment and monitoring, this has a profound impact in opportunities and support not just for the patients but their families. The curative option exacel is offering reduces risks associated with HSCT like gvhd and organ rejection.
10. If there are disadvantages of exa-cel over current treatments on the NHS please describe these. For example, are there any risks with exa-cel? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The risks associated with the myeloablative agents with regards to cancer development and sepsis/ infection is my concern however, it is no greater than the risk with these agents being used in HSCT. Patients will need to be kept in a sterile environment until it is safe to be integrate into society.
11. Are there any groups of patients who might benefit more from exa-cel or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I think all patients should have access to this if they choose to stop the need for transfusions, decrease time spent in hospital, iron overload side effects, organ damage etc to improve their QoI and life expectancy as soon as possible. However, those with long term blood transfusions, reactions and serious comorbidities etc would also benefit. Additionally, one of the key concerns is access to treatment and its affordability. In some cases, certain groups face disadvantages when it comes to accessing treatment. For example, individuals from low-income backgrounds struggle with the financial burden associated with ongoing transfusions, prescriptions and overheads.
12. Are there any potential equality issues that should be taken into account when considering transfusion-dependent beta-thalassaemia and exa-cel? Please	With regards to TDT, there are potential equality issues that should be taken into account. Such as;

explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Individuals from lower socioeconomic backgrounds may face barriers in accessing appropriate healthcare, including regular transfusions, medication, and specialist monitoring. Limited financial resources can hinder their ability to afford transportation costs, time off work, and necessary medical expenses. People living in rural or remote areas may face difficulties in accessing specialised thalassaemia care. Limited availability of healthcare facilities and specialists in these regions can result in delayed diagnosis, inadequate treatment, and increased travel burdens to reach appropriate medical centres. Thalassaemia is more commonly found in certain ethnic groups, such as people of Mediterranean, Middle Eastern, Asian and South Asian descent. These communities may face additional challenges due to language barriers, cultural differences, and limited awareness about the condition, leading to delays in diagnosis and inadequate support. Children and adolescents with tdt require ongoing specialised care and support. However, they may face difficulties in accessing appropriate educational resources, social integration, and psychological support. Transitioning to adult healthcare services can also be challenging for young adults with thalassaemia. Living with a chronic condition like tdt can have a significant impact on mental health and overall wellbeing. Some individuals may face stigmatisation, social isolation, and emotional distress. Access to psychological support and wellbeing services may be limited, exacerbating these challenges.
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue impacting decision making:	Description:	
EAG issue 1	**Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile:** **Permanence of transfusion independence: after successful exa-cel treatment (defined as achievement of transfusion independence) how likely is:** • **the risk of thalassaemia recurrence** • **a 0% rate of thalassaemia recurrence**	

Patient expert statement

	Safety: the company notes that exa-cel's mechanism of action eliminates any risk of treatment-related cancer (risk of mutagenesis and transcriptional deregulation) • **Do you agree?** • **Do you have any further comments on exa-cel's safety?**	
EAG issue 2	**Definition of transfusion independence** **Do you have any comments on the most appropriate definition and/or advantages and disadvantages of the definitions below:** • **maintaining a weighted average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months any time after exa-cel infusion (CLIMB THAL-111 primary outcome – 'TI12')** • **as people who are transfusion-free starting 60 days after the last blood transfusion for post-transplant support or disease management** **We consider patient perspectives may particularly help to address this issue**	
EAG issue 3	**Uncertain relationship between transfusion status and final outcomes** • **Can you comment on how transfusion status (transfusion independent, reduced, dependent) is related to iron levels, risk of chronic**	

	complication, mortality rates and quality of life? • **What are some of the advantages and disadvantages of assuming a link between transfusion status and these outcomes without direct evidence?** • **Are there any evidence sources that can be used to help inform the link between transfusions status and the outcomes listed above?** **We consider patient perspectives may particularly help to address this issue**	
EAG issue 5	**Omission of withdrawals from exa-cel treatment in the economic analysis** • **What proportion of people would you expect will withdraw/be unwilling to proceed after cell collection, but before the exa-cel infusion?** **We consider patient perspectives may particularly help to address this issue**	
EAG issue 6	**Frequency of red blood cell transfusions** • **A UK chart review reported that people with transfusion dependent beta-thalassaemia on average will have 13.7 transfusions per year** • **Do you agree with this estimate?** • **What is the range you would expect to see in clinical practice?**	

Patient expert statement

	We consider patient perspectives may particularly help to address this issue	
EAG issue 7	**Non-reference discount rate** **According to the NICE manual for a non-reference discount rate to be applicable a set of criteria need to be met. The questions below have been tailored to the criteria.** **Are people with transfusion dependent beta-thalassaemia on current standard care more likely to die or have a very severely impaired life compared with the general population?** • **What is the life-expectancy of people being offered current standard care with this condition?** • **How different is the mortality rate compared with the general population? (for example is 5 times higher a reasonable approximation?)** • **How different is the quality of life of people with this condition?** **Is treatment with exa-cel likely to restore people with the condition to full or near-full health:** • **Does this condition already cause permanent damage from pre-existing complications (for example cardiac or liver complications) that cannot be reversed by exa-cel treatment?** • **If yes, what proportion of people are likely to experience this?**	

Patient expert statement

	The benefits of exa-cel are likely to be sustained over a very long period. • **Do you expect the benefits of exa-cel observed during a maximum of 42 months of follow-up to be sustained over time?** • **If no, why not?** **We consider patient perspectives may particularly help to address this issue**	
EAG issue 8	**Mortality for people with transfusion dependent beta-thalassaemia, and mortality associated with complications** • **What would you expect the mortality rate or standardised mortality rate* to be for people with this condition who have cardiac or diabetic complications?** ***Standardised mortality rate = the number of deaths observed in a population over a given period divided by the number that would be expected over the same period if the study population had the same age-specific rates as the standard population**	
EAG issue 9	**Health related quality of life in people who are transfusion dependent** • **Since the condition is inherited/ starts from early childhood. How likely is it that people with this condition get used to the symptoms over time?**	

	• **Do you have any other comments about the quality of life of people living with this condition?** **We consider patient perspectives may particularly help to address this issue**	
EAG issue 12-14	**Would the introduction of exa-cel have any impact on health inequalities? If so, how?** **We consider patient perspectives may particularly help to address this issue**	
	Economic modelling specific issues **(Focus of issues are less clinical and more methodological/conceptual please refer to section 1 of EAR to more details)**	
EAG issue 11	**Using eMIT costs instead of national tariff**	
	Other issues that need patient expert opinion:	
	Baseline osteoporosis and diabetes complication rates: **Do you agree with the following statement:** • **The pathogenesis of beta-thalassaemia-related osteoporosis is not well understood but it is theorised to be a result of many factors such as inherent genetic factors, ineffective erythropoiesis, high iron levels, and low levels of vitamin D. Exa-cel treatment may impact some of these factors.**	

Patient expert statement

	Do you expect exa-cel treatment would reverse osteoporosis symptoms or complications? **We consider patient perspectives may particularly help to address this issue**	
	Risk of initial graft failure: **The CLIMB THAL-111 trial showed there were no engraftment rejections (failures). But 6.9% initial engraftment failure have been reported in haematopoietic stem cell transplant.** • **Is it reasonable to assume 100% initial engraftment success in clinical practice?** • **If not, what is the range of initial engraftment failures seen in clinical practice?** **We consider patient perspectives may particularly help to address this issue**	
	Iron normalisation period: **How long does it take for people with transfusion-independent beta-thalassaemia to achieve normalised iron levels in all organ systems:** • **Four years (company assumption)** • **Five years (EAG assumption)** • **Other?** **We consider patient perspectives may particularly help to address this issue**	
	Severity modifier:	

Patient expert statement

	Please refer to Table 2a below to help answer this question. Table 2a presents the utility values and undiscounted life years (LYs) split by health state from the EAG and company models. Life years are the amount of time someone spends in that state in the model in years. **Considering both the EAG and company values, can you comment on the utility values per health state? (for example, are the differences in utility values between the health states too high, too low or reasonable)?** **Considering both the EAG and company values, can you comment on the undiscounted life years for a person living with transfusion-dependent beta thalassemia who is accessing standard of care? (for example, are the figures too high, too low or reasonable)?** **We consider patient perspectives may particularly help to address this issue**	
	Do you have any further comments on the other issues not included within this list?	
	Are there any important issues that have been missed in EAR?	

Table 2a. Company and EAG estimates for utility values and undiscounted life years (LYs)

Health state	Utility value	Undiscounted LYs for standard of care
Company estimates		
Transfusion independent	**0.93**	[redacted]
Transfusion reduction	**0.75**	[redacted]
Transfusion dependent	**0.73**	[redacted]
EAG estimates		
Transfusion independent	**0.93**	[redacted]
Transfusion reduction	[redacted]	[redacted]
Transfusion dependent	[redacted]	[redacted]

Estimates based on the IA2 clinical trial data cut.

[redacted]

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Individuals with tdt have a reduced QoL and Life expectancy
- Life with thalassaemia is challenging and patients need treatment options.
- There is not enough ethnicity data or research on secondary complications and long term effects on thalassaemia with regards to aging and life expectancy.
- Treatment for thalassaemia is difficult for all and sub par throughout the country.
- Exacel offers a curative option and a chance to ring the bell to end transfusions

Thank you for your time.

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 NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel (exa-cel) for treating transfusion-dependent beta-thalassaemia [ID4015]

Patient expert statement and technical engagement response form

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

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with transfusion-dependent beta-thalassaemia or caring for a patient with transfusion-dependent beta-thalassaemia. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1, Table 1).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Patient expert statement

The deadline for your response is **5pm** on **Monday 6 November 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

Part 1: Living with this condition or caring for a patient with transfusion-dependent beta-thalassaemia

Table 1 About you, transfusion-dependent beta-thalassaemia, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☒ A patient with transfusion-dependent beta-thalassaemia? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with transfusion-dependent beta-thalassaemia? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	United Kingdom Thalassaemia Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with transfusion-dependent beta-thalassaemia? **If you are a carer (for someone with transfusion-dependent beta-thalassaemia) please share your experience of caring for them**	Living with a chronic blood condition such as thalassaemia major has been and continues to be extremely challenging for me and for others who are also transfusion dependent. Some of the challenges faced include: • Delayed growth • Bone problems • Liver and gall bladder problems. • Enlarged spleen and kidneys. • Diabetes • Hypothyroidism • Eyesight and hearing problems • Dental problems. • Living and coping with pain • Restriction in activities • Problems with job access • Extreme fatigue
7a. What do you think of the current treatments and care available for transfusion-dependent beta-thalassaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be**	To date, the treatment options focussed on keeping patients alive. The care for patients vary dependent on location and services offered. Most patients only receive the bare necessities to keep them alive and little or no notice is given to the quality of life and other important aspects of coping with a severe lifelong condition. Since the pandemic the level of care has also deteriorated for most of the patients

aware of?	throughout the UK. In the UK, we do not have access to any curative treatments for older patients like myself. Gene therapy has been available to patients in the US and parts of Europe for a number of years and have been achieving excellent results to date. Current treatments for thalassaemia, including beta thalassaemia major, vary based on location. Some may find the current treatments, such as regular blood transfusions and iron chelation therapy, to be effective in managing their condition and improving their quality of life. These treatments can help prevent complications associated with thalassaemia, such as anaemia and iron overload. It is also important to acknowledge that living with thalassaemia and undergoing regular treatments can be challenging for many individuals like myself. Most people also experience physical discomfort or side effects from treatments, such as transfusion reactions or the burden of frequent medical appointments and medication administration. Additionally, the need for lifelong treatment and management impacts various aspects of life, including emotional well-being, relationships, and career choices.
8. If there are disadvantages for patients of current NHS treatments for transfusion-dependent beta-thalassaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Transfusion-dependent beta-thalassaemia major requires lifelong treatment with blood transfusions and medication. While these treatments are essential for managing the condition, there are some disadvantages for patients like myself. Here are a few: Iron Overload: Regular blood transfusions can lead to an excess buildup of iron in the body, known as iron overload . This can be harmful to organs and tissues and may require additional treatment to remove the excess iron. Chelation therapy is used to remove excess iron caused by transfusions . However, chelation therapy itself can have its own challenges, such as the need for frequent infusions or multiple daily doses of medication.

	Chelation Therapy: Chelation therapy is necessary to remove excess iron from the body, but it brings its own challenges. The current available chelating agents include desferrioxamine (DFO), deferiprone (DFP), and deferasirox (DFX) . These medications may require frequent infusions, multiple daily doses, or long-term use, which can be inconvenient and impact the patient's quality of life. They also cause severe side effects as the medication is given in doses which could be toxic to be effective. Limited Treatment Options: While blood transfusions and chelation therapy are the standard treatments for transfusion-dependent beta-thalassaemia, there are limited alternative treatment options available. A very small portion of the thalassaemia population have access to stem cell transplantation which is curative but for the majority there is currently no hope. Long-Term Commitment: Transfusion-dependent beta-thalassaemia requires lifelong treatment, including regular blood transfusions and medication. This long-term commitment can be physically and emotionally challenging for patients and their families.
9a. If there are advantages of exagamglogene autotemcel (exa-cel) over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	Personally, living with thalassaemia major has affected my life immensely. It has affected my education, having to be away from school and university for treatment and hospital appointments. It has affected my working life as I am now struggling with bone problems, extreme fatigue and other secondary conditions. Having access to exagamglogene autotemcel (exa-cel) would potentially mean that the younger patients would have better options, improved quality of life and a brighter outlook on life.

9c. Does exa-cel help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	Being hospital and pain free would drastically improve my quality of life. Elimination of Lifelong Treatment: A cure for thalassaemia would mean that patients would no longer require lifelong treatment with blood transfusions and chelation therapy This would greatly reduce the burden on patients and improve their quality of life. Improved Health Outcomes: With a cure, individuals with thalassaemia, like myself, would no longer experience the complications associated with the condition, such as iron overload, alloimmunization, and anaemia . They would have a normal blood count and would not require regular transfusions or iron chelation therapy. Reduced Risk of Infections and Complications: Transfusions and chelation therapy can put individuals at risk for infections and other complications A cure would eliminate the need for these treatments, reducing the risk of associated complications. Improved Life Expectancy: While individuals with mild thalassaemia have a normal life expectancy if they follow their treatment program, a cure would eliminate the need for ongoing treatment and further improve life expectancy. It would also provide the freedom for holiday, travel and job selections.
10. If there are disadvantages of exa-cel over current treatments on the NHS please describe these. For example, are there any risks with exa-cel? If you are	None identified to date

concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from exa-cel or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Having an option for a curative treatment at an earlier age would be beneficial for patients for several reasons. Some of these are: 1. less organ damage 2. fewer secondary conditions 3. less hospital and medical appointments 4. freedom to choose career pathway rather than to be treated as a burden Although I am older than the group currently being considered for the exa-cel I would support the application for others to have a chance of a "normal "life.
12. Are there any potential equality issues that should be taken into account when considering transfusion-dependent beta-thalassaemia and exa-cel? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	We are aware that there is a huge disparity in treatment and care for people living with thalassaemia major based on community and location. Some of our members have been facing discrimination and hardship based on their location. Covid has been extremely difficult for people living with thalassaemia major, as most of the older patients like myself had their spleens removed at an early age and were forced to shield as we were listed as extremely vulnerable. This impacted on our ability to hold on to jobs, interact with friends and family, even after the initial restrictions were lifted. Despite the need, the majority of patients have not been able to access any help or mental support. Some patients faced racial discrimination whenever they tried to speak out about the challenges being faced. Based on this we continue to lose patients at much younger ages in the main areas of concern. Some patients have been refusing to continue with their treatment, choosing to die rather than to continue being treated as second class citizens. This has been raised as a matter of concern but continues to be ignored.

	Being able to have access to a curative option would provide hope and opportunity for most of the patients in areas highlighted to become independent and treatment free.
13. Are there any other issues that you would like the committee to consider?	Thalassaemia major is a very difficult condition to live with and while we understand that most decisions are made based on the financial impact, this therapy would provide our patients with a chance of life, being able to also have dreams, aspire to be productive citizens. It is very important to also mention that thalassaemia major does not only affect the person born with the condition, it changes the life of the parents, siblings, relatives and friends. It could potentially change the outcomes for the families having to struggle through life, with the endless hospital visits, having to watch their child suffer through the many obstacles and experiences they currently face.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue impacting decision making:	Description:	
EAG issue 1	**Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile:** **Permanence of transfusion independence: after successful exa-cel treatment (defined as achievement of transfusion independence) how likely is:** • **the risk of thalassaemia recurrence** • **a 0% rate of thalassaemia recurrence**	

Patient expert statement

	Safety: the company notes that exa-cel's mechanism of action eliminates any risk of treatment-related cancer (risk of mutagenesis and transcriptional deregulation) • **Do you agree?** • **Do you have any further comments on exa-cel's safety?**	
EAG issue 2	**Definition of transfusion independence** **Do you have any comments on the most appropriate definition and/or advantages and disadvantages of the definitions below:** • **maintaining a weighted average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months any time after exa-cel infusion (CLIMB THAL-111 primary outcome – 'TI12')** • **as people who are transfusion-free starting 60 days after the last blood transfusion for post-transplant support or disease management** **We consider patient perspectives may particularly help to address this issue**	
EAG issue 3	**Uncertain relationship between transfusion status and final outcomes** • **Can you comment on how transfusion status (transfusion independent, reduced, dependent) is related to iron levels, risk of chronic complication, mortality rates and quality of**	

Patient expert statement

	life? • **What are some of the advantages and disadvantages of assuming a link between transfusion status and these outcomes without direct evidence?** • **Are there any evidence sources that can be used to help inform the link between transfusions status and the outcomes listed above?** **We consider patient perspectives may particularly help to address this issue**	
EAG issue 5	**Omission of withdrawals from exa-cel treatment in the economic analysis** • **What proportion of people would you expect will withdraw/be unwilling to proceed after cell collection, but before the exa-cel infusion?** **We consider patient perspectives may particularly help to address this issue**	
EAG issue 6	**Frequency of red blood cell transfusions** • **A UK chart review reported that people with transfusion dependent beta-thalassaemia on average will have 13.7 transfusions per year** • **Do you agree with this estimate?** • **What is the range you would expect to see in clinical practice?** **We consider patient perspectives may particularly**	

Patient expert statement

	help to address this issue	
EAG issue 7	**Non-reference discount rate** **According to the NICE manual for a non-reference discount rate to be applicable a set of criteria need to be met. The questions below have been tailored to the criteria.** **Are people with transfusion dependent beta-thalassaemia on current standard care more likely to die or have a very severely impaired life compared with the general population?** • **What is the life-expectancy of people being offered current standard care with this condition?** • **How different is the mortality rate compared with the general population? (for example is 5 times higher a reasonable approximation?)** • **How different is the quality of life of people with this condition?** **Is treatment with exa-cel likely to restore people with the condition to full or near-full health:** • **Does this condition already cause permanent damage from pre-existing complications (for example cardiac or liver complications) that cannot be reversed by exa-cel treatment?** • **If yes, what proportion of people are likely to experience this?**	

Patient expert statement

	The benefits of exa-cel are likely to be sustained over a very long period. • **Do you expect the benefits of exa-cel observed during a maximum of 42 months of follow-up to be sustained over time?** • **If no, why not?** **We consider patient perspectives may particularly help to address this issue**	
EAG issue 8	**Mortality for people with transfusion dependent beta-thalassaemia, and mortality associated with complications** • **What would you expect the mortality rate or standardised mortality rate* to be for people with this condition who have cardiac or diabetic complications?** ***Standardised mortality rate = the number of deaths observed in a population over a given period divided by the number that would be expected over the same period if the study population had the same age-specific rates as the standard population**	
EAG issue 9	**Health related quality of life in people who are transfusion dependent** • **Since the condition is inherited/ starts from early childhood. How likely is it that people with this condition get used to the symptoms over time?** • **Do you have any other comments about the quality of life of people living with this**	

Patient expert statement

	condition? **We consider patient perspectives may particularly help to address this issue**	
EAG issue 12-14	**Would the introduction of exa-cel have any impact on health inequalities? If so, how?** **We consider patient perspectives may particularly help to address this issue**	
	Economic modelling specific issues **(Focus of issues are less clinical and more methodological/conceptual please refer to section 1 of EAR to more details)**	
EAG issue 11	**Using eMIT costs instead of national tariff**	
	Other issues that need patient expert opinion:	
	Baseline osteoporosis and diabetes complication rates: **Do you agree with the following statement:** • **The pathogenesis of beta-thalassaemia-related osteoporosis is not well understood but it is theorised to be a result of many factors such as inherent genetic factors, ineffective erythropoiesis, high iron levels, and low levels of vitamin D. Exa-cel treatment may impact some of these factors.** **Do you expect exa-cel treatment would reverse osteoporosis symptoms or complications?**	

Patient expert statement

	We consider patient perspectives may particularly help to address this issue	
	Risk of initial graft failure: **The CLIMB THAL-111 trial showed there were no engraftment rejections (failures). But 6.9% initial engraftment failure have been reported in haematopoietic stem cell transplant.** • **Is it reasonable to assume 100% initial engraftment success in clinical practice?** • **If not, what is the range of initial engraftment failures seen in clinical practice?** **We consider patient perspectives may particularly help to address this issue**	
	Iron normalisation period: **How long does it take for people with transfusion-independent beta-thalassaemia to achieve normalised iron levels in all organ systems:** • **Four years (company assumption)** • **Five years (EAG assumption)** • **Other?** **We consider patient perspectives may particularly help to address this issue**	
	Severity modifier: **Please refer to Table 2a below to help answer this question. Table 2a presents the utility values and undiscounted life years (LYs) split by health state**	

Patient expert statement

	from the EAG and company models. Life years are the amount of time someone spends in that state in the model in years. **Considering both the EAG and company values, can you comment on the utility values per health state? (for example, are the differences in utility values between the health states too high, too low or reasonable)?** **Considering both the EAG and company values, can you comment on the undiscounted life years for a person living with transfusion-dependent beta thalassemia who is accessing standard of care? (for example, are the figures too high, too low or reasonable)?** **We consider patient perspectives may particularly help to address this issue**	
	Do you have any further comments on the other issues not included within this list?	
	Are there any important issues that have been missed in EAR?	

Table 2a. Company and EAG estimates for utility values and undiscounted life years (LYs)

Health state	Utility value	Undiscounted LYs for standard of care
Company estimates		
Transfusion independent	**0.93**	[redacted]
Transfusion reduction	**0.75**	[redacted]
Transfusion dependent	**0.73**	[redacted]
EAG estimates		
Transfusion independent	**0.93**	[redacted]
Transfusion reduction	[redacted]	[redacted]
Transfusion dependent	[redacted]	[redacted]

Estimates based on the IA2 clinical trial data cut.

[redacted]

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel (exa-cel) for treating transfusion-dependent beta-thalassaemia [ID4015]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing 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. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1, Table 1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. 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.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Monday 6 November 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

NICE National Institute for Health and Care Excellence

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.

Part 1: Treating transfusion-dependent beta-thalassaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Emma Drasar
2. Name of organisation	Whittington Health
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 transfusion-dependent beta-thalassaemia? ☐ A specialist in the clinical evidence base for transfusion-dependent beta-thalassaemia 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 did not submit one, I do not 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. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for transfusion-dependent beta-thalassaemia?	The current treatment is to keep alive

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. 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)	Patient having a normal life – ie minimal hospital attendances as per age related controls, able to achieve life goals such as education, work and travel and to be on limited amounts of medication
10. In your view, is there an unmet need for patients and healthcare professionals in transfusion-dependent beta-thalassaemia?	Yes – limited curative options available
11. How is transfusion-dependent beta-thalassaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	1) Transfusion – 2 hospital appointments every 3 weeks average 2) Chelation – usually daily minimum x3 a week and sometimes combination 3) Extensive monitoring – minimum annual MRIs for iron loading, 18/12 DEXA scans 4) Well defined pathways improved with formation of HCCs
12. 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? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Decision for gene therapy will be discussed in the HCCs and then referred onto the NHP. It will occur in existing transplant centres but may require formation of specific clinics to see and assess appropriate patients. The technology will be used in IP setting.

13. 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? • Do you expect the technology to increase health-related quality of life more than current care?	I have had 3 patients undergo this treatment in the trial and they remain transfusion independent and well. I have a significant proportion of young patients with critical iron overload and psychological harm from their condition. The burden of having to attend a hospital as a minimum twice every 3 weeks on average plus other appointments is MASSIVE however as this is all patients know it is “normal” for them. I have young patients who will die under the age of 40 due to complications from their thalassaemia
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The trial treated patients under the age of 35 so this should be the initial group
15. 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)	Requires specialist location and team to administer the therapy. Oddly requires no more monitoring even in the early phases than current treatment and will eventually lessen healthcare interactions
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	NHP and HCC discussion. Sibling donor testing as is exclusion criteria in trial
17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	As I explained to NICE in the initial meeting when all you have known is regular hospital attendances that is your normal. This is a chronic condition present from birth. Having to attend hospital, be dependant on transfusions for survival limits people quality of life

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. 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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	I think that is is a "step change" in the management of thalassaemia. Patients have limited curative options and this would add another one
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Potentially but massive impacts of standard treatment
20. Do the clinical trials on the technology reflect current UK 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? • 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?	Yes. Transfusion independence most important outcome. Agree with the long term outcome measures used.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	No comment on this as not in existence in real world. My patients have massively benefited from this treatment
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any	SIGNIFICANT EQUALITY ISSUES. Younger thalassaemia patients who might be eligible for this treatment are likely to be of Asian origin and therefore subject

potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	to racism. Large proportion of these patients also from lower income backgrounds and impacted by deprivation.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue impacting decision making:	Description:	
EAG issue 1	**Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile:** **Permanence of transfusion independence: after successful exa-cel treatment (defined as achievement of transfusion independence) how likely is:** • **the risk of thalassaemia recurrence** • **a 0% rate of thalassaemia recurrence** **Safety: the company notes that exa-cel's mechanism of action eliminates any risk of treatment-related**	I agree with the company data – it is an autologous transplant so rejection risk is absent. I think this is a safe treatment given inherent chemotherapy risks

	cancer (risk of mutagenesis and transcriptional deregulation) • **Do you agree?** • **Do you have any further comments on exa-cel's safety?**	
EAG issue 2	**Definition of transfusion independence** **Do you have any comments on the most appropriate definition, and/or advantages and disadvantages of the definitions below:** • **maintaining a weighted average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months any time after exa-cel infusion (CLIMB THAL-111 primary outcome – 'TI12')** • **as people who are transfusion-free starting 60 days after the last blood transfusion for post-transplant support or disease management**	I think this is a fair statement. In my experience patients have significantly higher Hbs usually over 120-130
EAG issue 3	**Uncertain relationship between transfusion status and final outcomes** • **Can you comment on how transfusion status (transfusion independent, reduced, dependent) is related to iron levels, risk of chronic complication, mortality rates and quality of life?** • **What are some of the advantages and disadvantages of assuming a link between transfusion status and these outcomes without direct evidence?** • **Are there any evidence sources that can be used to help inform the link between**	If you are transfusion free then you are highly likely not to iron loading. Iron impacts all causes of mortality in this patient group – cardiac and liver disease, endocrinopathies, bone density and infection risk. I have no idea how there isn't evidence for this. It is clear from over 50 years of clinical practice in this area. How about all published data on thalassaemia and chelation trials? That all patients in pre chelation era died and that

	transfusions status and the outcomes listed above?	the oldest transfusion dependant patient in UK is around 65 years of age???!!!!
EAG issue 5	**Omission of withdrawals from exa-cel treatment in the economic analysis** • **What proportion of people would you expect will withdraw/be unwilling to proceed after cell collection, but before the exa-cel infusion?**	A minimal proportion – I would be surprised if any
EAG issue 6	**Frequency of red blood cell transfusions** • **A UK chart review reported that people with transfusion dependent beta-thalassaemia on average will have 13.7 transfusions per year** • **Do you agree with this estimate?** • **What is the range you would expect to see in clinical practice?**	No – in my clinical practice patients are transfused far more frequently than this. I would be interested to know what these patients trough Hbs are and how many units they receive. Outside of my unit the majority of patients are transfused on mixed units and the white cell patients are prioritised so this should also be considered as to why these patients are on lower transfusion frequency. However more units and a bigger gap does not suppress the patients erythropoiesis and therefore risk of extra medullary haematopoesis and yo-yoing of Hbs
EAG issue 7	**Non-reference discount rate** **According to the NICE manual for a non-reference discount rate to be applicable a set of criteria need to be met. The questions below have been tailored to the criteria.** **Are people with transfusion dependent beta-thalassaemia on current standard care more likely to die or have a very severely impaired life compared with the general population?**	Yes they are more likely to die and have severely impaired life. My oldest patient is 65 years old and we usually lose about 2 patients a year from my cohort under the age of 50. These patients have to attend hospital twice every 3 weeks as a minimum and have multiple other hospital appointments. Psychological, physically this is massively impactful. How many employers will facilitate this? How

	• **What is the life-expectancy of people being offered current standard care with this condition?** • **How different is the mortality rate compared with the general population? (for example is 5 times higher a reasonable approximation?)** • **How different is the quality of life of people with this condition?** **Is treatment with exa-cel likely to restore people with the condition to full or near-full health:** • **Does this condition already cause permanent damage from pre-existing complications (for example cardiac or liver complications) that cannot be reversed by exa-cel treatment?** • **If yes, what proportion of people are likely to experience this?** **The benefits of exa-cel are likely to be sustained over a very long period.** • **Do you expect the benefits of exa-cel observed during a maximum of 42 months of follow-up to be sustained over time?** • **If no, why not?**	much school will children miss? How can people travel for more than 2 weeks at a time?? Everything has to be planned around transfusions and ability to chelate. My older patients have significant damage from previous iron overload but these are not the target population. Damage from iron overload is dependant on the "area under the curve" and therefore longer pt transfused higher the risks even with good chelation and iron control. I expect the benefit to be long term.
EAG issue 8	**Mortality for people with transfusion dependent beta-thalassaemia, and mortality associated with complications** • **What would you expect the mortality rate or standardised mortality rate* to be for people**	I would expect them to be far more likely to die

	with this condition who have cardiac or diabetic complications? ***Standardised mortality rate = the number of deaths observed in a population over a given period divided by the number that would be expected over the same period if the study population had the same age-specific rates as the standard population**	
EAG issue 9	**Health related quality of life in people who are transfusion dependent** • **Since the condition is inherited/ starts from early childhood. How likely is it that people with this condition get used to the symptoms over time?** • **Do you have any other comments about the quality of life of people living with this condition?**	Yes – they have only ever known this situation and therefore this is their normal. However it is an evolving condition. Getting used to a situation is not a reason to deny treatment. Thalassaemia has ruined many of my patients lives and limited their options and choices
EAG issue 12-14	**Would the introduction of exa-cel have any impact on health inequalities? If so, how?**	SIGNIFICANT EQUALITY ISSUES. Younger thalassaemia patients who might be eligible for this treatment are likely to be of Asian origin and therefore subject to racism. Large proportion of these patients also from lower income backgrounds and impacted by deprivation.
	Economic modelling specific issues **(Focus of issues are less clinical and more methodological/conceptual please refer to section 1 of EAR to more details)**	
EAG issue 11	**Using eMIT costs instead of national tariff**	
	Other issues that need clinical expert opinion:	

	Baseline osteoporosis and diabetes complication rates: **Do you agree with the following statement:** • **The pathogenesis of beta-thalassaemia-related osteoporosis is not well understood but it is theorised to be a result of many factors such as inherent genetic factors, ineffective erythropoiesis, high iron levels, and low levels of vitamin D. Exa-cel treatment may impact some of these factors.** **Do you expect exa-cel treatment would reverse osteoporosis symptoms or complications?**	Yes – chelation also causes a calcium leak as does chronic anaemia. I would expect reversal
	Risk of initial graft failure: **The CLIMB THAL-111 trial showed there were no engraftment rejections (failures). But 6.9% initial engraftment failure have been reported in haematopoietic stem cell transplant.** • **Is it reasonable to assume 100% initial engraftment success in clinical practice?** • **If not, what is the range of initial engraftment failures seen in clinical practice?**	That is a haplo transplant rather than autologous transplant so completely irrelevant. I would expect 100% engraftment
	Iron normalisation period: **How long does it take for people with transfusion-independent beta-thalassaemia to achieve normalised iron levels in all organ systems:** • **Four years (company assumption)** • **Five years (EAG assumption)** • **Other?**	4 years should be sufficient possibly less with combination chelation and venesection

	Severity modifier: **Please refer to Table 2a below to help answer this question. Table 2a presents the utility values and undiscounted life years (LYs) split by health state from the EAG and company models. Life years are the amount of time someone spends in that state in the model in years.** **Considering both the EAG and company values, can you comment on the utility values per health state? (for example, are the differences in utility values between the health states too high, too low or reasonable)?** **Considering both the EAG and company values, can you comment on the undiscounted life years for a person living with transfusion-dependent beta thalassemia who is accessing standard of care? (for example, are the figures too high, too low or reasonable)?**	
	Do you have any further comments on the other issues not included within this list?	
	Are there any important issues that have been missed in EAR?	

Table 2a. Company and EAG estimates for utility values and undiscounted life years (LYs)

Health state	Utility value	Undiscounted LYs for standard of care
Company estimates		
Transfusion independent	**0.93**	[redacted]
Transfusion reduction	**0.75**	[redacted]
Transfusion dependent	**0.73**	[redacted]
EAG estimates		
Transfusion independent	**0.93**	[redacted]
Transfusion reduction	[redacted]	[redacted]
Transfusion dependent	[redacted]	[redacted]

Estimates based on the IA2 clinical trial data cut.

[redacted]

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Massive need for curative option in thalassaemia

If your only experience significant treatment episodes and health issues then that is your normal quality of life. You have nothing to compare it to unlike in acquired conditions

This condition impacts minioritised populations which are already suffer due to systemic racism in society and the NHS

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel (exa-cel) for treating transfusion-dependent beta-thalassaemia [ID4015]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

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A clinical perspective could help either:

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NICE National Institute for Health and Care Excellence

Part 1: Treating transfusion-dependent beta-thalassaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Subarna Chakravorty
2. Name of organisation	King's College Hospital NHS Trust , Clinical Reference Group Haemoglobinopathy, NHS England
3. Job title or position	Consultant Paediatric Haematologist, National Speciality Adviser Haemoglobinopathy
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 transfusion-dependent beta-thalassaemia? ☐ A specialist in the clinical evidence base for transfusion-dependent beta-thalassaemia 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 did not submit one, I do not 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. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for transfusion-dependent beta-thalassaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of treatment for transfusion dependent beta thalassaemia is to provide adequate numbers of functional red blood cells in the circulation to allow oxygen supply to vital organs, thereby supporting life, growth, and activity.
9. 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)	A clinically significant treatment response is when the patient can have a good quality of life, minimum adverse effect of disease or treatment and minimum disruption to education and employment.
10. In your view, is there an unmet need for patients and healthcare professionals in transfusion-dependent beta-thalassaemia?	Yes- I believe there is an unmet need for both patients and healthcare professionals
11. How is transfusion-dependent beta-thalassaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	Current treatment of beta thalassaemia: 1. Regular red cell transfusions. This is given in 2-4 weekly intervals 2. Iron chelation to prevent organ iron overload 3. Other supportive therapies as needed- for example hormonal replacement, bisphosphonates for osteoporosis, management of fertility, painkillers, pubertal induction agents, etc. 4. Referral to bone marrow transplantation for curative treatment if HLA identical donor is available The current guidelines are: 1. UK Thalassaemia Society Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK 2. British Society for Haematology Guidelines for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias 3. British Society for Haematology Guidelines Significant haemoglobinopathies: A guideline for screening and diagnosis

	4. British Society for Haematology Guideline: Red blood cell specifications for patients with hemoglobinopathies: a systematic review and guideline The pathway of care is well defined following establishment of diagnosis. However, diagnostic delays occur as beta thalassaemia is not routinely screened in the new-born screening programme, although may be picked up as a by-product of the sickle cell screening programme. Once diagnosed with a homozygous beta thalassaemia condition, and patients are identified as transfusion dependent, patients then attend a clinical unit to receive red cell transfusion. Transfusion intervals is decided based on clinical need but can be between 2-4 weeks. Patients are referred to their Specialist Haemoglobinopathy Team for annual reviews. Complex cases are discussed in the Haemoglobinopathy Coordinating Centre multi-disciplinary team meeting or in the National Haemoglobinopathy Panel MDT. If HLA identical sibling donor is available, the patient is referred for a sibling donor stem cell transplant
12. 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? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The current technology is expected to be expensive. However, it is also expected to be a one- off treatment, providing a lifetime freedom from transfusion and chelation needs. This technology should only be used in designated tertiary specialist centres where JACIE- accredited cellular therapies are currently being provided to NHS patients Investment needed for this technology: No specific investment is needed for new estates. Existing JACIE- accredited cell collection units will undertake apheresis procedure and the existing cellular processing laboratories attached to the Stem Cell Unit will undertake cellular processing, which includes storage, labelling and shipping to the commercial company (Vertex) for genetic manipulation. There is significant training needs for this programme, which will include training of all aspects of management. Robust governance structures should be in place as per JACIE requirements.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, my expectation is that there will be clinically meaningful benefit from this technology. Patients will achieve freedom from transfusions – this will mean that

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	they will avoid two visits per transfusion episode- which could be as often as 2-3 weekly. This means that they will not need to adjust their working hours to attend their hospital appointments and will be able to plan their work and recreation with more certainty. This will result in significant improvement in quality of life once the gene-edited stem cells are fully engrafted. The patient will no longer need iron chelation. Their energy levels will not fluctuate according to their transfusion cycle. Their bone health, including osteopenia and osteoporosis is likely to improve and will certainly not worsen with time more than expected in a healthy ageing population. Intravenous access issues will no longer be a problem. Repeated scans for iron overload monitoring will not be needed. Once fully-de-ironed, patients will not be at an increased risk of cardiac complications associated with poorly- chelated thalassaemia.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology is for transfusion dependent beta thalassaemia. This will therefore not be effective for patients with other types of transfusion dependent anaemias.
15. 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 treatment will require the patient to be referred to a designated cellular therapy unit The treatment will be difficult for the patient to begin with, due to the need for stem cell mobilisation and myeloablation. However, this difficulty is short lived and will be perceived as an easy trade-off for long term freedom from transfusion and iron chelation
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients with available HLA identical donors should be treated with stem cell transplant and not exa-cel . Hence HLA screening for patient and siblings will be necessary

17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	I am not a health economist. However, I feel that it is important to ensure that while traditional QALY measurements are very important in cost effectiveness analysis, the importance of deprivation and health inequality in this patient group needs to be considered when the economic evaluation is made. Beta thalassaemia affects UK patients from some of the most deprived areas and minoritised populations, such as those from South Asia. Their access to high standard treatment has also been very poor compared to their white counterparts
18. 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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	I believe we are in the era of gene therapy in the treatment of haemoglobin disorders such as transfusion dependent beta thalassaemia. This technology is a step change in the management of this condition- as patients without suitable stem cell donors can now expect to achieve transfusion independence with a step cell therapy. The unmet need of this population is the severe lack to therapies available for this disease group – currently only two- namely blood transfusion or stem cell transplant, the latter not suitable for all.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The adverse side effects immediately after the procedure are no different from other diseases using similar myeloablative agents- it is expected that patients will remain neutropaenic for a short period of time. There is no risk of graft versus host disease. These adverse effects are short lived and not expected to affect the overall quality of life
20. Do the clinical trials on the technology reflect current UK 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? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Current UK practice is to offer stem cell transplant to patients with suitable stem cell donor. UK patients were recruited to the pivotal study that underpins this application. All the procedures involved in this technology is highly suitable for use in the current NHS clinical practice, including the presence of a National Haemoglobinopathy panel of experts who will provide clinical approval. The trials assessed the length of time spent by patients when they were free from transfusions. The follow up period is short but there is no concern that the transfusion free status will not continue for the patient's life.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Real world data are not available for this technology
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	Beta thalassaemia affects some of the most deprived people in the UK. Lack of research funding has led to very poor availability of effective treatment for this condition. Patients frequently face racial discrimination in healthcare setting and clinical service improvements, including staffing and technical support are frequently overlooked. This technology will help address historical inequality in availability of effective treatment for this deprived population

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue impacting decision making:	Description:	
EAG issue 1	**Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile:** **Permanence of transfusion independence: after successful exa-cel treatment (defined as achievement of transfusion independence) how likely is:** • **the risk of thalassaemia recurrence** • **a 0% rate of thalassaemia recurrence** **Safety: the company notes that exa-cel's mechanism of action eliminates any risk of treatment-related**	The risk of thalassaemia recurrence is very low to zero. This is because the edited engrafted stem cells are expected to continue to function and produce HbF for as long as the patient is alive I would suggests that the risk of thalassaemia recurrence is virtually nil Exa-cel uses CRISPR technology, which provides much less chance of developing off target effects. However,

	cancer (risk of mutagenesis and transcriptional deregulation) • **Do you agree?** • **Do you have any further comments on exa-cel's safety?**	CRISPR induces a double stranded break in the desired area of the genome (in this case the regulatory area of the gene BCL11A) which then has to be repaired using the inbuilt biological processes
EAG issue 2	**Definition of transfusion independence** **Do you have any comments on the most appropriate definition, and/or advantages and disadvantages of the definitions below:** • **maintaining a weighted average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months any time after exa-cel infusion (CLIMB THAL-111 primary outcome – 'TI12')** • **as people who are transfusion-free starting 60 days after the last blood transfusion for post-transplant support or disease management**	No further comments. Transfusion independence with Hb >90g/l is an appropriate outcome to improve quality of life
EAG issue 3	**Uncertain relationship between transfusion status and final outcomes** • **Can you comment on how transfusion status (transfusion independent, reduced, dependent) is related to iron levels, risk of chronic complication, mortality rates and quality of life?** • **What are some of the advantages and disadvantages of assuming a link between transfusion status and these outcomes without direct evidence?** • **Are there any evidence sources that can be used to help inform the link between**	Freedom from transfusions lead to the following: 1. No need to come to hospital every 2-4 weeks, twice per transfusion 2. No need to receive iron chelation- which can mean receiving subcutaneous infusions 10-24 hours per day 3. Inability to comply with iron chelation can lead to early death due to heart failure 4. Regular iron overload monitoring with scans will not be needed

	transfusions status and the outcomes listed above?	5. Iron overload can lead to endocrine disease, including diabetes, hypothyroidism, etc. These can be avoided with transfusion independence
EAG issue 5	**Omission of withdrawals from exa-cel treatment in the economic analysis** • **What proportion of people would you expect will withdraw/be unwilling to proceed after cell collection, but before the exa-cel infusion?**	<10%
EAG issue 6	**Frequency of red blood cell transfusions** • **A UK chart review reported that people with transfusion dependent beta-thalassaemia on average will have 13.7 transfusions per year** • **Do you agree with this estimate?** • **What is the range you would expect to see in clinical practice?**	People receive transfusions at a rate of 2-4 weekly in clinical practice So patients may be transfused 12 (lowest) and 24 (highest) times a year. In practice more people are in the 3-4 weekly transfused category, so may be more like 17 episodes per year. This will vary with individual patients, spleen size, etc.
EAG issue 7	**Non-reference discount rate** **According to the NICE manual for a non-reference discount rate to be applicable a set of criteria need to be met. The questions below have been tailored to the criteria.** **Are people with transfusion dependent beta-thalassaemia on current standard care more likely to die or have a very severely impaired life compared with the general population?** • **What is the life-expectancy of people being offered current standard care with this condition?**	Median age of death is 34 years in the last 10 years in the UK (NHR data) – however, the death rates may be under reported Life expectancy is much less than normal population (I do not have a value). Mortality rates are very high compared to normal population – 5x is reasonable Quality of life in these patients are very poor. They are in frequent pain, often tired, particularly towards the end of a transfusion cycle. They have a heavy burden of treatment-leading to loss of days at work and education. They have chronic pain and severe mobility issues.

	• **How different is the mortality rate compared with the general population? (for example is 5 times higher a reasonable approximation?)** • **How different is the quality of life of people with this condition?** **Is treatment with exa-cel likely to restore people with the condition to full or near-full health:** • **Does this condition already cause permanent damage from pre-existing complications (for example cardiac or liver complications) that cannot be reversed by exa-cel treatment?** • **If yes, what proportion of people are likely to experience this?** **The benefits of exa-cel are likely to be sustained over a very long period.** • **Do you expect the benefits of exa-cel observed during a maximum of 42 months of follow-up to be sustained over time?** • **If no, why not?**	Exa-cel is likely to restore people with TDT to full or near full health. Cardiac and liver complication due to iron overload are reversible in most people. I would expect the effect of exa- cel to be sustained in the long term. This is because the edited stem cells will be permanently engrafted with no reason for graft rejection later in life as it is an autologous procedure
EAG issue 8	**Mortality for people with transfusion dependent beta-thalassaemia, and mortality associated with complications** • **What would you expect the mortality rate or standardised mortality rate* to be for people with this condition who have cardiac or diabetic complications?** ***Standardised mortality rate = the number of deaths observed in a population over a given period divided**	I do not have an exact value for UK patients

	by the number that would be expected over the same period if the study population had the same age-specific rates as the standard population	
EAG issue 9	**Health related quality of life in people who are transfusion dependent** • **Since the condition is inherited/ starts from early childhood. How likely is it that people with this condition get used to the symptoms over time?** • **Do you have any other comments about the quality of life of people living with this condition?**	People may consider very poor quality of life as 'normal' as they do not know any alternative. People may only realise how much better their QoL can be once they achieve transfusion independence
EAG issue 12-14	**Would the introduction of exa-cel have any impact on health inequalities? If so, how?**	Exa-cel will allow a new therapy to be made available to a group of people who have faced decades of research underfunding, leading to poor drug development. Besides, patients experience discrimination and racism in their own hospitals and are ofen overlooked during quality improvement investments projects
	Economic modelling specific issues **(Focus of issues are less clinical and more methodological/conceptual please refer to section 1 of EAR to more details)**	
EAG issue 11	**Using eMIT costs instead of national tariff**	I do not have expertise to comment
	Other issues that need clinical expert opinion:	
	Baseline osteoporosis and diabetes complication rates: **Do you agree with the following statement:**	Osteoporosis complications may improve due to improvement in iron deposition and avoidance of bone and

	• **The pathogenesis of beta-thalassaemia-related osteoporosis is not well understood but it is theorised to be a result of many factors such as inherent genetic factors, ineffective erythropoiesis, high iron levels, and low levels of vitamin D. Exa-cel treatment may impact some of these factors.** **Do you expect exa-cel treatment would reverse osteoporosis symptoms or complications?**	joint damage from iron chelators. However, I cannot comment if exa-cel will completely reverse osteoporosis
	Risk of initial graft failure: **The CLIMB THAL-111 trial showed there were no engraftment rejections (failures). But 6.9% initial engraftment failure have been reported in haematopoietic stem cell transplant.** • **Is it reasonable to assume 100% initial engraftment success in clinical practice?** • **If not, what is the range of initial engraftment failures seen in clinical practice?**	Yes, the absence of an allogeneic stem cell source makes it unlikely that an immune mediated graft rejection will happen
	Iron normalisation period: **How long does it take for people with transfusion-independent beta-thalassaemia to achieve normalised iron levels in all organ systems:** • **Four years (company assumption)** • **Five years (EAG assumption)** • **Other?**	Four years
	Severity modifier: **Please refer to Table 2a below to help answer this question. Table 2a presents the utility values and undiscounted life years (LYs) split by health state from the EAG and company models. Life years are the**	

	amount of time someone spends in that state in the model in years. **Considering both the EAG and company values, can you comment on the utility values per health state? (for example, are the differences in utility values between the health states too high, too low or reasonable)?** **Considering both the EAG and company values, can you comment on the undiscounted life years for a person living with transfusion-dependent beta thalassemia who is accessing standard of care? (for example, are the figures too high, too low or reasonable)?**	
	Do you have any further comments on the other issues not included within this list?	
	Are there any important issues that have been missed in EAR?	

Table 2a. Company and EAG estimates for utility values and undiscounted life years (LYs)

Health state	Utility value	Undiscounted LYs for standard of care
Company estimates		
Transfusion independent	**0.93**	[redacted]
Transfusion reduction	**0.75**	[redacted]
Transfusion dependent	**0.73**	[redacted]
EAG estimates		
Transfusion independent	**0.93**	[redacted]
Transfusion reduction	[redacted]	[redacted]
Transfusion dependent	[redacted]	[redacted]

Estimates based on the IA2 clinical trial data cut.

[redacted]

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Exa-cel will be a technologically revolutionary treatment that will provide transfusion independence to beta thalassaemia patients

Exa- cel treatment will improve patient quality of life

Exa- cel will improve patient life expectancy

Exa-cel will reduce complications related to iron overload in patients with transfusion dependent thalassaemia

Exa-cel will help reduce inequalities in a historically underserved and minoritised patient group

Clinical expert statement

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Single Technology Appraisal

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The deadline for your response is **5pm** on **Monday 6 November 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Part 1: Treating transfusion-dependent beta-thalassaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Clare Samuelson MBChB MRCPCH FRCPath MA PhD
2. Name of organisation	UK Thalassaemia Society
3. Job title or position	Scientific Advisor
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 transfusion-dependent beta-thalassaemia? ☒ A specialist in the clinical evidence base for transfusion-dependent beta-thalassaemia 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 did not submit one, I do not 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. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for transfusion-dependent beta-thalassaemia?	Reduce or remove the need for blood transfusion Reduce or remove the need for iron chelation treatment Reduce the development of secondary complications

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Reduce the amount of time spent engaging in necessary healthcare activities Improve quality of life
9. 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)	Maintenance of an adequate haemoglobin level without regular transfusion, or with significantly reduced frequency of transfusion required Significant reduction in the requirement for iron chelation therapy, once de-ironed after curative treatment Improvement in health-related quality of life
10. In your view, is there an unmet need for patients and healthcare professionals in transfusion-dependent beta-thalassaemia?	Yes. Without doubt there is a very significant level of unmet need for patients with transfusion-dependent thalassaemia (TDT). Only a small proportion of patients have the option of curative treatment currently, as this relies on the availability of a matched donor which precludes its availability for most people affected by TDT. The current standard treatment for those for whom a cure is not a possibility is very burdensome both for patients and their families. Regular transfusions require a significant amount of time spent in hospital, can cause acute transfusion reactions, and inevitably result in iron overload for which patients receive life-long iron chelation therapies. Venous access for transfusion can be painful and traumatic. For some patients, accessing the peripheral veins is not feasible and they require indwelling central lines, which confer increased risk of thrombosis and infection. Most patients live with chronic pain and fatigue, only partially and temporarily relieved by each transfusion. The iron chelation therapies themselves cause multiple side effects and complications. Those using the subcutaneous infusions often experience painful swellings in the areas where treatment is administered, which can make it difficult for them to mobilise and for many make comfortable sleep impossible. These infusions also increase the risk of local infection and life-threatening sepsis, and carry a risk of damage to vision and hearing.

	Oral iron chelators are not an easy option for many patients either. A significant proportion will experience gastrointestinal side effects including nausea and vomiting, abdominal pain, loose stool and faecal incontinence. For some, this is so severe that even young people have to wear incontinence pants when attending work or educational establishments. Other side effects include joint pains, kidney and liver damage which can in some cases be severe and long-lasting. For some, these prohibit safe use of the oral iron chelators at all. Due to the side effect profile, even with modern treatment options, many patients struggle to take adequate iron chelation doses or doses are limited by toxicities, and as a result patients suffer serious complications of iron overload. Progressive iron loading leads to multiple secondary complications and shortened life expectancy. Even with the best currently available treatment and monitoring, this is the reality for many of trying to live with TDT. Recent data from the National Haemoglobinopathy Registry reports on deaths in patients with TDT since 2004. Average age of death over this period of time was 34 years. Even when looking at the most recent time period of 2021-23, average age of death was only 41 years. This is dramatically lower than a normal life expectancy in the UK, and it must be noted that these data are the most up-to-date and reflect recent practice since the availability of oral iron chelation and reliable monitoring techniques. I do not expect life expectancy to improve significantly unless alternative treatment options are made available. Under current treatment schedules, patients (and families) are required to spend a high proportion of their time engaging with treatment and monitoring schedules which unavoidably results in an unacceptably high number of days out of education and employment.

	Quality of life is severely affected. The prospect of living with TDT for the rest of their lives is unbearable for many, and despite maximal levels of support provided by clinical teams, young patients lose hope for themselves and their future.
11. How is transfusion-dependent beta-thalassaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	There are comprehensive national guidelines for the treatment of TDT, published by the UK Thalassaemia Society. The 4th edition is now available and can be accessed via the link below: https://ukts.org/3d-flip-book/standards-for-the-clinical-care-of-children-and-adults-living-with-thalassaemia-in-the-uk-4th-edition-2023/ There are also a number of relevant guidelines published by the British Society for Haematology, which cover screening methods and pathways, transfusion, and the management and monitoring of iron chelation. BSH guidelines are available at the following website: https://b-s-h.org.uk/guidelines As a result of national guidelines and also the NHSE-commissioned network of Specialist Haemoglobinopathy Centres, and regional Haemoglobinopathy Coordinating Centres, care is increasingly standardised across England. Despite standardisation of care and wide availability of specialist treatment and monitoring, outcomes for patients remain inadequate. This technology would represent a significant improvement in care, by allowing suitable patients who lack a matched donor to access curative treatment. For most, based on the clinical trial data presented, this would obviate the need for regular transfusions and iron chelation therapy (after de-ironing where applicable), prevent the accumulation of secondary complications of thalassaemia and iron overload, and enable patients to live a normal and healthy life after exa-cel therapy.

12. 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? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Current care requires life-long and regular healthcare input, including regular transfusions every 2-4 weeks and iron chelation treatment up to multiple times each day, alongside monitoring for complications of the disease and its treatment. For the majority of patients treated with exa-cel, there will be a single, intensive episode of care when this is delivered, but following this patients will be able to live normal lives without the ongoing intensity of treatment and monitoring which would otherwise be required. It would be appropriate for exa-cel to be delivered by specialist centres which already have expertise in delivering haematopoietic stem cell transplantation and other cellular therapies. These centres are experienced in stem cell collection, the delivery of myeloablative chemotherapy conditioning and care of patients during and after stem cell delivery. In this case, there would be very little need for additional facilities or equipment, and only a moderate amount of additional training of these teams would be required.
13. 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? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. Exa-cel allows more patients to access a long-term cure for TDT which is currently not a possibility for most. It is expected that those treated with exa-cel who become transfusion-independent will have an extension to their life expectancy and an improved health-related quality of life. With current care, both are severely impaired with no realistic prospect of significant improvement.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes, it should be noted that there are patients for whom exa-cel will not be an appropriate treatment option. Those with severe iron loading, significant organ dysfunction or poor performance status would not be suitable for this treatment and would continue on standard care.

	Some clinically eligible patients may also choose not to receive exa-cel treatment, due to concerns around being one of the first to receive a novel therapy; concerns around loss of fertility; or other personal factors. Therefore the number of patients who will receive exa-cel treatment in reality is expected to be significantly lower than the total population of potentially eligible patients. This should not be taken to infer that those choosing not to receive exa-cel are not significantly affected by their condition; it speaks more to their personal priorities (such as fertility), views and experiences – for example, some patients have had poor experiences of healthcare and would be more anxious about trusting a new treatment proposal.
15. 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)	Overall, exa-cel treatment will be a better and easier option for many patients than standard care and will also reduce healthcare requirements long-term. Current care requires lifelong, burdensome treatment which is not only difficult for patients to manage but also confers multiple risks and complications. Exa-cel is a single treatment which delivers long-term cure for most patients. The single treatment episode does involve an intensive level of care including myeloablative chemotherapy and a period of inpatient stay, but following engraftment and recovery from treatment (including de-ironing), healthcare needs are expected to be minimal. Patients are expected to live a normal life after exa-cel treatment, in comparison to standard care with which quality of life would continue to decline with the accumulation of secondary complications, and life expectancy would remain limited.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Exa-cel involves a single episode of treatment. There would be strict eligibility criteria against which patients would be comprehensive assessed before being considered for treatment, and there would also be an in-depth consent process.

17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes. Following exa-cel treatment most patients will require minimal healthcare involvement and can go on to lead a normal life. There are two main benefits of this which are not adequately represented in QALY calculations. The first is that the psychological burden of living with a life-long, life-limiting condition which requires such intensive and unpleasant treatment would be removed, allowing patients to plan and hope for their future in a way which is not currently possible. The second is that the number of days patients are required to spend in hospitals will be much reduced, allowing them to attend school, further education and employment regularly, fulfil professional and personal responsibilities and ambitions in a way that is currently impossible for the majority.
18. 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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, exa-cel offers the option of a cure to patients which TDT, which is unavailable to most currently. It is without doubt a step-change in management as it results in long-term cure for most, with patients becoming transfusion-independent or at least having very significantly reduced transfusion requirements after treatment. The removal of regular transfusions means that any residual iron can be removed quickly and effectively with either venesection or lower-dose iron chelation, and following this the patient is not expected to develop any further complications of TDT or of iron loading. Exa-cel addresses the unmet need of the vast majority of the TDT population to have access to a curative treatment. This chance is only currently available to a small minority with a matched donor.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The delivery of exa-cel requires chemotherapy conditioning and a period of isolation in hospital due to the risks associated with low blood counts until exa-cel engrafts and blood counts recover. There are particular side effects and risks associated with this early phase of treatment but after engraftment, patients are expected to recover quickly and all of these side-effects are anticipated to be short-term only and to fully resolve.

	Given the toxicities associated with the chemotherapy conditioning, exa-cel treatment would not be suitable for patients with poor performance status or additional risk factors such as severe iron loading. There is also a small increase in the long-term risk of malignancy associated with busulphan, and fertility would be impacted therefore fertility-preservation options would be offered prior to treatment.
20. Do the clinical trials on the technology reflect current UK 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? • 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?	Yes, patient demographics and treatment prior to exa-cel are representative of the TDT patient population and current treatment in the UK The most important outcomes are maintenance of an adequate haemoglobin level independent of transfusion, and this was the primary efficacy outcome measured in the trial. Safety outcomes are also very important and were examined in-depth during the clinical trial. Meaningful clinical outcomes rather than surrogate markers were used in the trial, therefore the use of surrogate outcomes is not a concern in this case. There have not been any adverse effects of exa-cel treatment which have come to light since initiation of the clinical trial but which were not reported in the ongoing trial, to the best of my knowledge.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Trial data are representative of real-world experience
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this	Yes, there are significant inequalities related to race and ethnicity which affect the population of patients with TDT. Most individuals with TDT are from a South Asian, South East Asian, Middle Eastern or Mediterranean background. In the UK, most are from a South Asian ethnicity. Individuals from a Pakistani or

treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	Bangladeshi background are particularly at risk for TDT inheritance, and are also more likely to be living in the most socioeconomically deprived areas of the country. It is my opinion that one of the reasons that curative treatment is only now being developed for the vast majority of people with TDT is that it is a condition which predominantly affects people of minority ethnic backgrounds. Treatment options and research into curative therapeutic strategies have lagged behind those for equivalent conditions which affect Caucasian populations. Making exa-cel available to eligible patients with TDT would be a very welcome step towards equal treatment and equitable prioritisation of individuals affected by this condition.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue impacting decision making:	Description:	
EAG issue 1	**Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile:** **Permanence of transfusion independence: after successful exa-cel treatment (defined as achievement of transfusion independence) how likely is:** • **the risk of thalassaemia recurrence** • **a 0% rate of thalassaemia recurrence** **Safety: the company notes that exa-cel's mechanism of action eliminates any risk of treatment-related**	The data presented by the company demonstrate highly stable *BCL11A* editing levels in the peripheral blood and, even more importantly, in the bone marrow after treatment – with follow-up of 2 years for many patients. Patients who have achieved TI12 have also maintained it without exception. These facts, taken together, provide substantial reassurance that this treatment is long-lasting and that maintenance of an adequate haemoglobin without the requirement for regular transfusion will be permanent.

	cancer (risk of mutagenesis and transcriptional deregulation) • **Do you agree?** • **Do you have any further comments on exa-cel's safety?**	The stable editing levels, in particular, demonstrate that the long-term repopulating haematopoietic stem cells were successfully edited in this treatment. Since these cells are the ones which will replicate and differentiate to populate mature blood cell lineages in the future, all their progeny will benefit from the introduced edit. There is no mechanism by which a stem cell might be expected to 'lose' its editing. Because exa-cel relies on non-homologous end joining mechanism of genome editing (rather than introduction of a new gene such as was used in the Bluebird Bio Lentiglobin™ product), there is no risk of loss of activity. There were no engraftment failures reported to date in the clinical trial, and secondary or late graft rejection is not considered to be a realistic risk. The reports of late graft failure after donor haematopoietic stem cell transplantation relate to immunological processes, whereby the donor cells are recognised are 'foreign' and the immune system subsequently rejects them. Since exa-cel works by modifying a patient's own stem cells, there is no risk that they will be recognised as 'foreign' and rejected, and the chance of late graft failure and late loss of efficacy are therefore not considered mechanistically plausible.
EAG issue 2	**Definition of transfusion independence** **Do you have any comments on the most appropriate definition, and/or advantages and disadvantages of the definitions below:** • **maintaining a weighted average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at**	The TI12 definition provides the most robust marker of long-term transfusion independence. However, the number of patients who are transfusion-free after a 60-day washout period since last transfusion is also an important, albeit earlier, marker of efficacy and likely to predict for TI12 since

	least 12 consecutive months any time after exa-cel infusion (CLIMB THAL-111 primary outcome – 'TI12') • **as people who are transfusion-free starting 60 days after the last blood transfusion for post-transplant support or disease management**	60 days would be a very long time for someone to go between transfusions if they were still reliant on regular transfusion therapy. Both therefore hold value and should be reported, and taken into consideration in cost effectiveness analyses.
EAG issue 3	**Uncertain relationship between transfusion status and final outcomes** • **Can you comment on how transfusion status (transfusion independent, reduced, dependent) is related to iron levels, risk of chronic complication, mortality rates and quality of life?** • **What are some of the advantages and disadvantages of assuming a link between transfusion status and these outcomes without direct evidence?** • **Are there any evidence sources that can be used to help inform the link between transfusions status and the outcomes listed above?**	Transfusion dependent patients have a much higher risk of iron loading, development of chronic complications and early mortality. Quality of life is also lowest in this group. Patients who have a significant reduction in their transfusion requirements would have meaningful improvements across all domains. Patients who become transfusion independent would cease accumulating iron and could safely and quickly be de-ironed with venesection and/or iron chelation treatment (the latter being required at much lower doses than in patients who are transfusion-dependent in order to achieve a negative iron balance). They would not be expected to develop any new endocrine complications, and for those with osteoporosis or osteopenia, this would be anticipated to improve and resolve. Quality of life would increase to that of the normal population, and life expectancy also increase in line with healthy populations, provided no irreversible secondary complications had already occurred. For those achieving transfusion independence, there is a wealth of data from patients who have undergone an

		autologous (own cells) haemopoietic stem cell transplant – which is the equivalent to exa-cel treatment – to reassure us that the treatment itself will not decrease life expectancy significantly. Therefore the data from non-TDT populations in terms of quality of life and life expectancy should be applied. There is a paucity of data to predict with certainty the effects of becoming transfusion-reduced, and therefore all calculations pertaining to that group will necessarily be heavily based on assumptions.
EAG issue 5	**Omission of withdrawals from exa-cel treatment in the economic analysis** • **What proportion of people would you expect will withdraw/be unwilling to proceed after cell collection, but before the exa-cel infusion?**	This should be an exceedingly rare event as patients should be counselled and consented comprehensively prior to starting exa-cel treatment. Only those who are certain they wish to proceed with treatment should commence on the treatment pathway.
EAG issue 6	**Frequency of red blood cell transfusions** • **A UK chart review reported that people with transfusion dependent beta-thalassaemia on average will have 13.7 transfusions per year** • **Do you agree with this estimate?** • **What is the range you would expect to see in clinical practice?**	The majority of patients in my experience require blood transfusions on a 3-weekly basis, which equates to an average of 17.3 transfusion episodes per year. There are a smaller number of patients who attend 4-weekly, but for most that would result in unacceptably severe symptoms of bone pain and fatigue in the 1-2 weeks prior to transfusion, and an inability to maintain an adequate haemoglobin level. It is also not uncommon for patients to require 2-weekly blood transfusion. Therefore in my opinion the quoted 13.7

		transfusions per year is an underestimate of current UK practice.
EAG issue 7	**Non-reference discount rate** **According to the NICE manual for a non-reference discount rate to be applicable a set of criteria need to be met. The questions below have been tailored to the criteria.** **Are people with transfusion dependent beta-thalassaemia on current standard care more likely to die or have a very severely impaired life compared with the general population?** • **What is the life-expectancy of people being offered current standard care with this condition?** • **How different is the mortality rate compared with the general population? (for example is 5 times higher a reasonable approximation?)** • **How different is the quality of life of people with this condition?** **Is treatment with exa-cel likely to restore people with the condition to full or near-full health:** • **Does this condition already cause permanent damage from pre-existing complications (for example cardiac or liver complications) that cannot be reversed by exa-cel treatment?**	It is my view that the conditions required for application of the 1.5% discount rate are met in the case of exa-cel. Patients with TDT receiving standard care undoubtedly have a reduced life expectancy, with standardised mortality rate at least 5x that of the general population and life expectancy estimates ranging from 34 – 55 years, all of which are significantly below that of the general population. Quality of life is also severely impaired, due to the development of secondary complications, side effects of treatment and the heavy burden of lifelong transfusions and iron chelation. Treatment with exa-cel is expected to remove the requirement for transfusion for the majority of patients receiving it, and at least significantly reduce transfusion burden in all. This in turn alleviates iron loading and its complications, along with the need for toxic iron chelation therapies. For those patients who achieve transfusion independence, it is anticipated that quality of life and life expectancy will return to normal for most.

	• **If yes, what proportion of people are likely to experience this?** **The benefits of exa-cel are likely to be sustained over a very long period.** • **Do you expect the benefits of exa-cel observed during a maximum of 42 months of follow-up to be sustained over time?** • **If no, why not?**	Some secondary complications such as osteoporosis and possibly hepatic fibrosis would be expected to improve in such a scenario, without ongoing iron loading. Others, such as diabetes or hypothyroidism, would not be expected to improve but further progression would be prevented. For example, for a patient who has impaired glucose tolerance or early diet-controlled diabetes, progression to medication- or insulin-dependent diabetes would be prevented. For reasons given in detail above, I expect that the benefits of exa-cel will be sustained over the very long term. There are no signals to suggest even an early or partial loss of efficacy in any treated patient, and its mechanism of action means that late graft loss, or late loss of efficacy by any other means, is not biologically plausible.
EAG issue 8	**Mortality for people with transfusion dependent beta-thalassaemia, and mortality associated with complications** • **What would you expect the mortality rate or standardised mortality rate* to be for people with this condition who have cardiac or diabetic complications?** ***Standardised mortality rate = the number of deaths observed in a population over a given period divided by the number that would be expected over the same period if the study population had the same age-specific rates as the standard population**	The figures will depend on the precise definition of 'cardiac complications' but the company's proposed figures for both are evidence-based and reasonable.

EAG issue 9	**Health related quality of life in people who are transfusion dependent** • **Since the condition is inherited/ starts from early childhood. How likely is it that people with this condition get used to the symptoms over time?** • **Do you have any other comments about the quality of life of people living with this condition?**	The quality of life of many patients living with TDT is dismal. The transfusions are burdensome, the iron chelation therapy causes daily side effects and serious complications, and for many it is impossible for them to progress in education and to manage regular employment. In short, for many it is impossible to live anything close to a normal life. It is true that people adapt and become accustomed to all sorts of conditions which to an observer appear impossible to live with. This is true of many with TDT, but it does not mean that patients are necessarily coping well with their condition and its treatment, as reflected in the high rates of anxiety and low mood in this population. However, it is true that patients have never experienced what it would be like to live without TDT and therefore their frame of reference when self-assessing their quality of life is itself impaired.
EAG issue 12-14	**Would the introduction of exa-cel have any impact on health inequalities? If so, how?**	Yes. As described in detail above, introduction of exa-cel would improve health inequalities markedly. TDT affects people mainly of South Asian descent in the UK, who are already disproportionately represented in the most socioeconomically deprived areas of the country. The financial burden, impact on educational attainment and on the ability to manage regular employment, are all notable for patients with TDT, further exacerbating such inequalities. Exa-cel would offer a curative treatment option and thus

		would be expected to reduce inequalities affecting the TDT population.
	Economic modelling specific issues **(Focus of issues are less clinical and more methodological/conceptual please refer to section 1 of EAR to more details)**	
EAG issue 11	**Using eMIT costs instead of national tariff**	
	Other issues that need clinical expert opinion:	
	Baseline osteoporosis and diabetes complication rates: **Do you agree with the following statement:** • **The pathogenesis of beta-thalassaemia-related osteoporosis is not well understood but it is theorised to be a result of many factors such as inherent genetic factors, ineffective erythropoiesis, high iron levels, and low levels of vitamin D. Exa-cel treatment may impact some of these factors.** **Do you expect exa-cel treatment would reverse osteoporosis symptoms or complications?**	Yes. I anticipate that after successful exa-cel treatment, osteoporosis would improve as bone remodelling would normalise. Other modifiable factors should have been treated, or would be amenable to treatment as well, such as vitamin D deficiency. The risk of developing future osteoporosis would also at least significantly reduce.
	Risk of initial graft failure: **The CLIMB THAL-111 trial showed there were no engraftment rejections (failures). But 6.9% initial engraftment failure have been reported in haematopoietic stem cell transplant.** • **Is it reasonable to assume 100% initial engraftment success in clinical practice?**	Yes. Graft failure in donor haematopoietic stem cell transplantation is immune-mediated and based on recognition of the donor stem cells as ‘foreign’ by the host immune system. This is not a relevant factor where the patient’s own stem cells are used, as is the case in exa-cel therapy. Therefore, assuming secure processing, manufacturing and delivery systems to maintain the health

	• **If not, what is the range of initial engraftment failures seen in clinical practice?**	of the stem cells used, graft failure is not a risk for patients treated with exa-cel.
	Iron normalisation period: **How long does it take for people with transfusion-independent beta-thalassaemia to achieve normalised iron levels in all organ systems:** • **Four years (company assumption)** • **Five years (EAG assumption)** • **Other?**	The time taken to iron normalisation will depend on iron loading levels at the time of commencement of de-ironing, and on patient tolerance of de-ironing treatment. For those with only mild or moderate iron loading, who tolerate regular venesection and/or more intensive iron chelation treatment, this would be completed in most within a significantly shorter time period than 4 years. For those in whom these are not the case, or if adherence to treatment were problematic, the time period would be longer. There may be an occasional outlier who, for example, is less adherent to de-ironing treatment, but the median or at least interquartile range of time to iron normalisation should be considered rather than the greatest time of a full range. In my experience, it is quick and simple to de-iron a patient once they no longer require regular transfusions (such as after donor HSCT). With a good haemoglobin level, this can often be achieved with venesection alone which carries less risk, side effect and cost than iron chelation therapies.
	Severity modifier:	The EAG report underestimates reduction in life expectancy for patients who are transfusion dependent receiving

	Please refer to Table 2a below to help answer this question. Table 2a presents the utility values and undiscounted life years (LYs) split by health state from the EAG and company models. Life years are the amount of time someone spends in that state in the model in years. **Considering both the EAG and company values, can you comment on the utility values per health state? (for example, are the differences in utility values between the health states too high, too low or reasonable)?** **Considering both the EAG and company values, can you comment on the undiscounted life years for a person living with transfusion-dependent beta thalassemia who is accessing standard of care? (for example, are the figures too high, too low or reasonable)?**	standard care. For those who are in the 'transfusion reduced' category, of course this would depend on by how great a proportion the transfusion requirement was reduced. For those in the clinical trial who had not achieved TI12 in the PES, transfusion requirements were reduced to such a large extent however that in my view the company underestimated the utility value in this group, and the EAG approach of estimating the utility value to be at least closer to the midpoint between transfusion dependent and transfusion independent appears reasonable, although this figure is necessarily based more on assumptions than evidence.
	Do you have any further comments on the other issues not included within this list?	No
	Are there any important issues that have been missed in EAR?	

Table 2a. Company and EAG estimates for utility values and undiscounted life years (LYs)

Health state	Utility value	Undiscounted LYs for standard of care
Company estimates		
Transfusion independent	**0.93**	[redacted]
Transfusion reduction	**0.75**	[redacted]
Transfusion dependent	**0.73**	[redacted]
EAG estimates		
Transfusion independent	**0.93**	[redacted]
Transfusion reduction	[redacted]	[redacted]
Transfusion dependent	[redacted]	[redacted]

Estimates based on the IA2 clinical trial data cut.

[redacted]

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is significant unmet need for patients with transfusion-dependent thalassaemia

Life expectancy and quality of life are both severely reduced with current treatment options for transfusion-dependent thalassaemia

Exa-cel offers a curative option for suitable patients with transfusion-dependent thalassaemia, which is not currently available to most patients

Patients who achieve transfusion independence after exa-cel treatment are expected to maintain this status in the very long-term

Provision of exa-cel treatment for eligible patients will reduce health inequalities

Thank you for your time.

Your privacy

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

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **Monday 6 November 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Table 1 About you

Your name	Drs [redacted] and [redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	British Society of Haematology General Haematology Task Force
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**None to declare**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None to declare**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Issue impacting decision making:	Description:	Does this response contain new evidence, data or analyses?	Response
EAG issue 1	**Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile:** **Permanence of transfusion independence: after successful exa-cel treatment (defined as achievement of transfusion independence) how likely is:** • **the risk of thalassaemia recurrence** • **a 0% rate of thalassaemia recurrence** **Safety: the company notes that exa-cel's mechanism of action eliminates any risk of treatment-related cancer (risk of mutagenesis and transcriptional deregulation)** • **Do you agree?** • **Do you have any further comments on exa-cel's safety?**	**Yes**	**The data presented thus far in CLIMB-111 is very promising to date. The follow up time of minimum 12 months of transfusion independence provides strong confidence that this represents sustained engraftment and therefore a sustained 0% risk of thalassaemia recurrence.** **Drawing comparison to the sibling bone marrow transplant group, there is very little evidence of delayed graft failure beyond this point suggesting a 0% rate of thalassaemia recurrence is not unreasonable.** **It could be argued that there is more chance of graft failure in the sibling BMT context due to the ongoing risk of graft versus host disease, which will not be present in this context as it is essentially an autograft.**

			Regarding safety, this gene therapy technology appears to be safe and efficacious. Rigorous investigation of off target effects has been reassuring. **The therapy requires myeloablative chemotherapy as part of its pre-conditioning protocol. This undoubtedly caries some mutagenesis risk, but this will be comparable to those already offered sibling allograft bone marrow transplants. In a French report of 107 patients with median 12 year follow up post sibling BMT no secondary cancers were identified (Haematologica. 2018 Jul; 103(7): 1143–1149).**
EAG issue 2	**Definition of transfusion independence** **Do you have any comments on the most appropriate definition, and/or advantages and disadvantages of the definitions below:** • **maintaining a weighted average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months any time after exa-cel infusion (CLIMB THAL-111 primary outcome – 'TI12')** • **as people who are transfusion-free starting 60 days after the last blood transfusion for post-transplant support or disease management**	**No**	**These seem reasonable and appropriate definitions.**

EAG issue 3	**Uncertain relationship between transfusion status and final outcomes** • **Can you comment on how transfusion status (transfusion independent, reduced, dependent) is related to iron levels, risk of chronic complication, mortality rates and quality of life?** • **What are some of the advantages and disadvantages of assuming a link between transfusion status and these outcomes without direct evidence?** • **Are there any evidence sources that can be used to help inform the link between transfusions status and the outcomes listed above?**	**Yes**	**Once patients achieve transfusion independence, they will be relieved of almost all of the burdens of their pre-existing disease including symptomatic anaemia and the need for regular hospital attendances for transfusion. A transfusion programme requires the patient to attend every 3-4 weeks for a blood test and transfusion, which takes up a whole day each time and is burdensome and restrictive to their lifestyle.** **Once transfusion independent, they will no longer accumulate iron.** **Iron chelation therapy will rapidly de-iron their organs leading in most cases to full reversal of their organ-related disease and symptom burden.** **This will significantly improve their quality of life. Mortality rates can also be expected to significantly fall as a result of these benefits.** **A significant proportion of TDT patients are unable to comply with iron chelation therapy due to poor tolerance and inconvenience of the administration of these regimens. This results in endocrine, cardiac and liver dysfunction, often leading to complications such as hypogonadism, infertility, diabetes, liver cancer and sudden cardiac death.**

EAG issue 5	**Omission of withdrawals from exa-cel treatment in the economic analysis** • **What proportion of people would you expect will withdraw/be unwilling to proceed after cell collection, but before the exa-cel infusion?**	**Yes**	**Patients with transfusion dependent thalassaemia are very motivated to receive this treatment should it become available. I do not anticipate there being many, if any, patients who would withdraw or unwilling to proceed in the time between cell collection and cell infusion.** **All patients being currently prepared for a sibling BMT go through extensive counselling and preparation prior to committing to the procedure. This ensures they are fully aware of the necessary time commitment, as well as short and longterm health risks.** **By doing so, patients are fully engaged in their process and therefore very unlikely to withdraw at such a late point. I anticipate the same standard of care will be applied to those being considered for exa-cel infusion, with the same extremely low rates of drop out.**
EAG issue 6	**Frequency of red blood cell transfusions** • **A UK chart review reported that people with transfusion dependent beta-thalassaemia on average will have 13.7 transfusions per year** • **Do you agree with this estimate?** • **What is the range you would expect to see in clinical practice?**	**Yes**	**We agree with this estimate. In our experience, patients typically require transfusion every 3-4 weeks. This is in keeping with the calculated 13.7 transfusion episodes per year. Some patients will require more frequently such as fortnightly, but it is unusual to have people who are able to extend to 5 or 6 weekly.**

EAG issue 7	**Non-reference discount rate** **According to the NICE manual for a non-reference discount rate to be applicable a set of criteria need to be met. The questions below have been tailored to the criteria.** **Are people with transfusion dependent beta-thalassaemia on current standard care more likely to die or have a very severely impaired life compared with the general population?** • **What is the life-expectancy of people being offered current standard care with this condition?** • **How different is the mortality rate compared with the general population? (for example is 5 times higher a reasonable approximation?)** • **How different is the quality of life of people with this condition?** **Is treatment with exa-cel likely to restore people with the condition to full or near-full health:** • **Does this condition already cause permanent damage from pre-existing complications (for example cardiac or liver complications) that cannot be reversed by exa-cel treatment?** • **If yes, what proportion of people are likely to experience this?**	**Yes**	**Patients with TDT on standard care of transfusions and iron chelation are at greatly increased risk of death compared to the general population.** **It is difficult to estimate the morality rate compared to the general population , but >5 times higher has been reported recently, alongside a mean age of death of 55yrs and this fits with our clinical impression.** **As these patients age, they develop multiple organ dysfunction (including diabetes, osteoporosis, cardiovascular, and endocrine and fertility complications) at far higher rates than the general population.** **Patients can also develop chronic leg ulcers and poorly defined pain episodes that are not well described, as well as severe fatigue that is often poorly measured by standard tools. These have significant effects on the quality of life for these patients.** **We would expect exa-cel to prevent and reverse most of the organ damage and restore these patients to near full health. All common complications are potentially reversible post exa-cel, with the exception e.g. of liver cirrhosis.** **The literature shows sustained health and haematopoiesis in the sibling BMT context. There is no reason why sustained effects would not be maintained in the context of**

	The benefits of exa-cel are likely to be sustained over a very long period. • **Do you expect the benefits of exa-cel observed during a maximum of 42 months of follow-up to be sustained over time?** • **If no, why not?**		**exa-cel therapy as well. Once engraftment is established and sustained beyond 1-5 years, the likelihood of the graft starting to fail is small.**
EAG issue 8	**Mortality for people with transfusion dependent beta-thalassaemia, and mortality associated with complications** • **What would you expect the mortality rate or standardised mortality rate* to be for people with this condition who have cardiac or diabetic complications?** ***Standardised mortality rate = the number of deaths observed in a population over a given period divided by the number that would be expected over the same period if the study population had the same age-specific rates as the standard population**	**Yes**	**A recently published Italian study looked at mortality rates in TDT patients with pulmonary hypertension and reported 53% crude mortality rate over a 10 year follow up, demonstrating that mortality rates are much higher than the general age matched population.** **I would estimate the standardised mortality rate for these patients with cardiac or diabetic complications to be around 5 x the general population.**
EAG issue 9	**Health related quality of life in people who are transfusion dependent** • **Since the condition is inherited/ starts from early childhood. How likely is it that people with this condition get used to the symptoms over time?**	**Yes**	**Patients with this condition do learn to get on with their life. It is human nature to make the most of one's life circumstances, especially if these circumstances are deemed unchangeable and they have never experienced any other state of being.** **For this reason, patients with TDT will tend to under-report their symptoms and the burden of disease in standard quality of**

	• **Do you have any other comments about the quality of life of people living with this condition?**		**health questionnaires. However, most of our patient cohort find themselves unable to work fulltime and are relatively economically inactive. Many have been unable to establish longterm relationships and enjoy normal family life.** **Once a new and improved normality is established (e.g., in the context of those post sibling BMT) patients are able to look back and recognise the limitations their disease placed on them and how much better the quality of their life is now that they have successfully had a curative therapy. This has been demonstrated in quality of life studies pre- and post-HSCT and from gene therapy trial data.**
EAG issue 12-14	**Would the introduction of exa-cel have any impact on health inequalities? If so, how?**	**Yes**	**As has already been well documented in the scoping exercise, patients with thalassaemia typically come from non-white backgrounds.** **Research and development in thalassaemia has been significantly neglected historically almost certainly due to this inherent racial bias, and has no doubt contributed to the complete lack of other disease modifying therapies emerging until now.** **The introduction of exa-cel offers a very real opportunity to correct this imbalance and demonstrate that the health needs of those from non-white backgrounds are no longer being over-looked.**
	Economic modelling specific issues		

	(Focus of issues are less clinical and more methodological/conceptual please refer to section 1 of EAR to more details)		
EAG issue 11	**Using eMIT costs instead of national tariff**	**Yes/No**	**Unable to comment**
	Other issues that need clinical expert opinion:		
	Baseline osteoporosis and diabetes complication rates: **Do you agree with the following statement:** • **The pathogenesis of beta-thalassaemia-related osteoporosis is not well understood but it is theorised to be a result of many factors such as inherent genetic factors, ineffective erythropoiesis, high iron levels, and low levels of vitamin D. Exa-cel treatment may impact some of these factors.** **Do you expect exa-cel treatment would reverse osteoporosis symptoms or complications?**	**Yes**	**Yes, this is a reasonable summary of the pathogenesis of osteoporosis.** **Exa-cel treatment would be expected to lead to significant improvement in bone health and reversal of osteoporosis symptoms.** **A relatively small Chinese study looked at a thalassaemia population before and after sibling bone marrow transplant, and compared it to those continued on transfusion and iron chelation therapy. They found a significant improvement in bone mineral density in the transplanted cohort. I anticipate, due to the same resolution of ineffective erythropoiesis seen with exa-cel, that the same improvement would be seen.** **https://doi.org/10.1038/sj.bmt.1705053**
	Risk of initial graft failure: **The CLIMB THAL-111 trial showed there were no engraftment rejections (failures). But 6.9% initial engraftment failure have been reported in haematopoietic stem cell transplant.** • **Is it reasonable to assume 100% initial engraftment success in clinical practice?**	**Yes**	**Most graft failure in the allograft setting is due to rejection due to the allo-immune barrier, and exacerbated by those with reduced intensity conditioning regimens. This is not expected to be such an issue in the autograft setting of exa-cel therapy, especially with the myeloablative conditioning. Therefore, we expect the**

	• **If not, what is the range of initial engraftment failures seen in clinical practice?**		**engraftment failure rate to be much lower than the 6.9% reported in HSCT. In the absence of larger datasets, it is difficult to estimate, but likely anticipate less than 1% graft failure rate.**
	Iron normalisation period: **How long does it take for people with transfusion-independent beta-thalassaemia to achieve normalised iron levels in all organ systems:** • **Four years (company assumption)** • **Five years (EAG assumption)** • **Other?**	**Yes**	**This obviously depends on the degree of iron overload in the patient prior to exa-cel treatment, however, we know from sibling BMT experience the lower the organ iron load prior to transplant, the better the outcomes and therefore there is always a focus on removing as much iron prior to proceeding with BMT as possible. Regardless, in most cases, patients would have sufficiently cleared the iron from their organs within 4 years of good chelation therapy. In the majority of cases we would see this within 2-3 years.**

Additional issues

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Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Technical engagement response form

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NICE National Institute for Health and Care Excellence

About you

Table 1 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 funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Cell and Gene Therapy Catapult received funding of approx. £50K from Vertex to support an advisory board for NHS readiness for the delivery of exa-cel. This collaboration has now ceased.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Issue impacting decision making:	Description:	Does this response contain new evidence, data or analyses?	Response
EAG issue 1	**Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile:** **Permanence of transfusion independence: after successful exa-cel treatment (defined as achievement of transfusion independence) how likely is:** • **the risk of thalassaemia recurrence** • **a 0% rate of thalassaemia recurrence** **Safety: the company notes that exa-cel's mechanism of action eliminates any risk of treatment-related cancer (risk of mutagenesis and transcriptional deregulation)** • **Do you agree?**	**No**	**Please provide your response to this key issue, including any new evidence, data or analyses** Based on the current data for exa-cel, there is uncertainty about its sustained efficacy and safety as seen with most gene therapies. Data from long-term follow-up studies and real-world evidence studies would help to resolve this uncertainty while the company pursues a patient access scheme with the NHSE and is clear on the responsible party for the cost should the transfusion independence fail (i.e. thalassaemia recurrence) after the end of the agreement. The data on late recurrences (2%; 3 out of 137 cases) following allogeneic SCT reported in Santarone et al. 2022 (referred by EAG) come from the Italian cohort of patients with thalassaemia major only and had more

	• **Do you have any further comments on exa-cel's safety?**		than half of the patients above the age of 10. Thus, the rate of late thalassaemia recurrence is likely to be very low following exa-cel. Reference Santarone, S., Angelini, S., Natale, A., Vaddinelli, D., Spadano, R., Casciani, P., ... & Di Bartolomeo, P. (2022). Survival and late effects of hematopoietic cell transplantation in patients with thalassemia major. Bone Marrow Transplantation, 57(11), 1689-1697.
EAG issue 2	**Definition of transfusion independence** **Do you have any comments on the most appropriate definition, and/or advantages and disadvantages of the definitions below:** • **maintaining a weighted average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months any time after exa-cel infusion (CLIMB THAL-111 primary outcome – 'TI12')** • **as people who are transfusion-free starting 60 days after the last blood transfusion for post-transplant support or disease management**	**Yes/No**	**Please provide your response to this key issue, including any new evidence, data or analyses** No comments
EAG issue 3	**Uncertain relationship between transfusion status and final outcomes** • **Can you comment on how transfusion status (transfusion independent, reduced, dependent) is related to iron levels, risk of chronic**	**Yes/No**	**Please provide your response to this key issue, including any new evidence, data or analyses** No comments

	complication, mortality rates and quality of life? • **What are some of the advantages and disadvantages of assuming a link between transfusion status and these outcomes without direct evidence?** • **Are there any evidence sources that can be used to help inform the link between transfusions status and the outcomes listed above?**		
EAG issue 5	**Omission of withdrawals from exa-cel treatment in the economic analysis** • **What proportion of people would you expect will withdraw/be unwilling to proceed after cell collection, but before the exa-cel infusion?**	**Yes/No**	**Please provide your response to this key issue, including any new evidence, data or analyses** No comments
EAG issue 6	**Frequency of red blood cell transfusions** • **A UK chart review reported that people with transfusion dependent beta-thalassaemia on average will have 13.7 transfusions per year** • **Do you agree with this estimate?** • **What is the range you would expect to see in clinical practice?**	**Yes/No**	**Please provide your response to this key issue, including any new evidence, data or analyses** No comments
EAG issue 7	**Non-reference discount rate** **According to the NICE manual for a non-reference discount rate to be applicable a**	**No**	**Please provide your response to this key issue, including any new evidence, data or analyses**

	set of criteria need to be met. The questions below have been tailored to the criteria. **Are people with transfusion dependent beta-thalassaemia on current standard care more likely to die or have a very severely impaired life compared with the general population?** • **What is the life-expectancy of people being offered current standard care with this condition?** • **How different is the mortality rate compared with the general population? (for example is 5 times higher a reasonable approximation?)** • **How different is the quality of life of people with this condition?** **Is treatment with exa-cel likely to restore people with the condition to full or near-full health:** • **Does this condition already cause permanent damage from pre-existing complications (for example cardiac or liver complications) that cannot be reversed by exa-cel treatment?** • **If yes, what proportion of people are likely to experience this?**		We understand that the choice of discount rate generally has profound effect on the cost-effectiveness of gene therapies when there is a high upfront cost and potential long-term health benefits. Given the biological plausibility of exa-cel and precedent for cure in TDT with allogeneic HSCT, we expect the benefits of exa-cel observed in the trial follow to sustain over a long period. The mortality rates seem higher in the TDT population compared with the general population. Jobanputra et al. (2020) show that the crude 10-year mortality rates in the TDT in the patient population eligible for exa-cel with age range between 10 and 34 are significantly greater than age/sex-adjusted mortality rate of the general population (P < 0·05) except for the age range between 20 and 24. These data support the notion of high rates of mortality in TDT population. Reference Jobanputra, M., Paramore, C., Laird, S. G., McGahan, M., & Telfer, P. (2020). Co-morbidities and mortality associated with transfusion-dependent beta-thalassaemia in patients in England: a 10-year retrospective cohort analysis. British Journal of Haematology, 191(5), 897-905.

	The benefits of exa-cel are likely to be sustained over a very long period. • **Do you expect the benefits of exa-cel observed during a maximum of 42 months of follow-up to be sustained over time?** • **If no, why not?**		
EAG issue 8	**Mortality for people with transfusion dependent beta-thalassaemia, and mortality associated with complications** • **What would you expect the mortality rate or standardised mortality rate* to be for people with this condition who have cardiac or diabetic complications?** ***Standardised mortality rate = the number of deaths observed in a population over a given period divided by the number that would be expected over the same period if the study population had the same age-specific rates as the standard population**	**Yes/No**	**Please provide your response to this key issue, including any new evidence, data or analyses** No comments
EAG issue 9	**Health related quality of life in people who are transfusion dependent** • **Since the condition is inherited/ starts from early childhood. How likely is it that people with this condition get used to the symptoms over time?**	**No**	**Please provide your response to this key issue, including any new evidence, data or analyses** It is likely that the impact of the condition on patients is not captured effectively by the generic EQ-5D measure. Some drawbacks of EQ-5D in this population have been discussed in a few recent studies. For example, a ceiling effect was observed for EQ-5D-3L in

	• **Do you have any other comments about the quality of life of people living with this condition?**		Shafie et al. 2021 (67.35% reported perfect health). In this study, Malaysian patients with transfusion-dependent thalassemia (mean age of 17 years) had a mean utility score of 0.893. Fatigue is considered to be an important symptom of TDT. An international survey of patients with chronic conditions suggested that the 'fatigue' domain was one of the most important QoL aspects that changed throughout the illness, and significant clinical changes in this domain might not be captured by the EQ-5D-5L tool (Efthymiadou et al. 2018). We understand that NICE is open to using alternative HRQoL methods in circumstances when the EQ-5D is not appropriate as indicated in the manual for NICE health technology evaluations (NICE, 2022). In the light of potential drawbacks of EQ-5D in this population and the lack of clarity on the impact of using utility values derived using vignettes, improvements measured by disease-specific measures such as FACT-BMT should be taken into consideration. References Shafie, A. A., Chhabra, I. K., Wong, J. H. Y., & Mohammed, N. S. (2021). EQ-5D-3L health state utility values in transfusion-dependent thalassemia patients in Malaysia: a cross-sectional assessment. Health and quality of life outcomes, 19, 1-12. Efthymiadou, O., Mossman, J., & Kanavos, P. (2019). Health related quality of life aspects not captured by

			EQ-5D-5L: Results from an international survey of patients. Health Policy, 123(2), 159-165. National Institute for Health and Care Excellence (NICE). (2022). NICE health technology evaluations: the manual. Available at: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741
EAG issue 12-14	**Would the introduction of exa-cel have any impact on health inequalities? If so, how?**	**Yes/No**	**Please provide your response to this key issue, including any new evidence, data or analyses** No comments
	Economic modelling specific issues **(Focus of issues are less clinical and more methodological/conceptual please refer to section 1 of EAR to more details)**		
EAG issue 11	**Using eMIT costs instead of national tariff**	**No**	**Please provide your response to this key issue, including any new evidence, data or analyses** We agree that eMIT costs are more appropriate to be used for the drugs involved in the treatment pathway than the NHS tariff costs as the former represents the average costs to the treatment centre.
	Other issues that need clinical expert opinion:		
	Baseline osteoporosis and diabetes complication rates: **Do you agree with the following statement:**	**Yes/No**	**Please provide your response to this key issue, including any new evidence, data or analyses** No comments

	• **The pathogenesis of beta-thalassaemia-related osteoporosis is not well understood but it is theorised to be a result of many factors such as inherent genetic factors, ineffective erythropoiesis, high iron levels, and low levels of vitamin D. Exa-cel treatment may impact some of these factors.** **Do you expect exa-cel treatment would reverse osteoporosis symptoms or complications?**		
	Risk of initial graft failure: **The CLIMB THAL-111 trial showed there were no engraftment rejections (failures). But 6.9% initial engraftment failure have been reported in haematopoietic stem cell transplant.** • **Is it reasonable to assume 100% initial engraftment success in clinical practice?** • **If not, what is the range of initial engraftment failures seen in clinical practice?**	**Yes/No**	**Please provide your response to this key issue, including any new evidence, data or analyses** No comments
	Iron normalisation period: **How long does it take for people with transfusion-independent beta-thalassaemia to achieve normalised iron levels in all organ systems:** • **Four years (company assumption)**	**Yes/No**	**Please provide your response to this key issue, including any new evidence, data or analyses** No comments

	• **Five years (EAG assumption)** • **Other?**		

Additional issues

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Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **Monday 6 November 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Table 1 About you

Your name	[redacted] / [redacted] / [redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Haemoglobinopathies Clinical Reference Group (CRG), NHS England Pharmacy and Clinical Support Team, NHS England Innovative Treatments Team, Highly Specialised Commissioning, NHS England
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Issue impacting decision making:	Description:	Does this response contain new evidence, data or analyses?	Response
EAG issue 1	**Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-**	**Yes**	Allogenic transplantation relies simplistically on engraftment of donor stem cells into a recipient. Hence this is the need for long term immunosuppression and therefore potential for rejection and thus late relapse. In an autologous stem cell transplant the risk of rejection and therefore late relapse is not expected to be a problem in a patient who has appropriately engrafted and developed transfusion independence post Exa-Cel treatment. Late effects post-transplant may develop due to the conditioning regime with busulfan which we expect to be the same for other disorders using busulfan as pretransplant conditioning. We agree the risk of mutagenesis is much lower with Exa-Cel mechanistically compared to other therapies. Iron overload over time is itself associated with an increased risk of malignancy particularly hepatocellular carcinoma. We do not think the concern over potential mutagenesis is currently warranted based on Mechanism of Action.

	term safety profile: **Permanence of transfusion independence: after successful exa-cel treatment (defined as achievement of transfusion independence) how likely is:** • **the risk of thalassa**		

	emia recurrence • **a 0% rate of thalassaemia recurrence** **Safety: the company notes**		

	that exa-cel's mechanism of action eliminates any risk of treatment-related cancer (risk of mutagenesis and transcriptional deregulation) • **Do you agree?** • **Do you have an**		

	y further comments on exa-cel's safety?		
EAG issue 2	**Definition of transfusion independence** **Do you have any comments on the most appropriate definition**	**Yes**	Maintaining a Hb above 9g/dl (90g/l) is the most appropriate definition for long term transfusion independence. It is however important to caveat this with the fact that thalassaemia major patients who have not been transfused for 60 days are also effectively transfusion independent during that period. This reflects short term independence and if Hb is maintained then this does translate into long term independence in an autologous transplant setting as this is only attained with engraftment of the stem cells. The Hb Above 9g/dl reflects persistence of transfusion independence over a prolonged period of time and should effectively be considered 'curative in the medium/long term'. Neither definition is incorrect or inappropriate however they reflect the early or long-term nature of the response.

	, and/or advantages and disadvantages of the definitions below: • **maintaining a weighted average Hb ≥9 g/dL without ou**		

	tred bloodcell (RBC) transfusions for at least 12 consecutive month		

	sanytimeafterexa-celinfusion(CLIMBTHAL-1111primaryoutc		

	ome – ‘TI12’) • **aspeoplewhoaretransfusion-freestarting60daysafter**		

	the last blood transfusion for post-transplant support or disease man		

	agement		
EAG issue 3	**Uncertain relationship between transfusion status and final outcomes** • **Can you comment on how transfusion**	**Yes**	Transfusion independence means that iron accumulation stops. Patients will then receive venesections or iron chelation to remove any excess iron that was there prior to transplantation with Exa-Cel. Once the excess iron is removed (as measured by MRI assessments and serum ferritin) then transfusion independence means the patient no longer needs to take any more iron chelation therapy. If they have not developed any iron overload complications, then they will not need to take any other treatments. Complications (endocrine, cardiac, exocrine and bone) are the most common problems patients develop but these are related to both the severity of the iron overload and the duration the high iron levels persisted. If patients are managing to keep their iron levels in good control prior to transplant, then the expectation of them developing any significant complication related to the previous thalassaemia and iron overload is very low. Data from bone marrow transplant post procedure follow up report the following: Quality of life studies demonstrate great improvements for patients following stem cell transplantation and long-term superiority of outcomes, particularly in relation to role limitation, bodily pain and social functioning.(La Nasa et al., 2013, Javanbakht et al., 2015). In response to: What are some of the advantages and disadvantages of assuming a link between transfusion status and these outcomes without direct evidence? We know from the non-transfusion dependant thalassaemia population that patients with Hb values above 90g/dl generally are clinically well and rarely develop significant complications. They may develop iron overload due to ineffective erythropoiesis but this is not what is expected in the post Exa-Cel setting as ineffective erythropoiesis should have resolved. There is a direct relationship between iron overload and transfusion dependence. If patients stop needing transfusions and the excess iron is removed, their risk of developing iron overload complications or complications due to iron chelators will be minimal. The NHR annual report (to be published soon) looks at annual data and reports: [redacted]

	status (transfusion independent, reduced, dependent) is related to iron le		[redacted]. Patients still develop iron overload complications and die prematurely due to complications from their disease /iron overload. We know from long term registry data that patients born in the era of good chelation availability have fewer complications than those who were poorly chelated, the inference from this is that once iron is removed then complication risk is low. Reference Borgna Pignatti 1998, 2005, and Forni GL 2023, for survival and complication data based on iron burden (inferred from availability of chelation and birth year cohort analysis). We would recommend some degree of caution when looking at HRQOL data in post Allogenic BMT patients as post-transplant complications such as graft versus host disease may impact on QOL. This is not seen in autologous stem cell transplant.

	vels, risk of chronic complication, mortality rates and quality of life? • **What**		

	are some of the advantages and disadvantages of assuming a link betw		

	een transfusion status and these outcomes without direct evidence?		

	• **Are there any evidence sources that can be used to help inform the link**		

	between transfusions status and the outcomes listed above?		
EAG issue	**Omission of withdrawals from**	**Yes/No**	We would expect very few if any patients to withdraw after stem cell collection. Members of the CRG looking after large cohorts of thalassaemia patients expect patients to have all been appropriately counselled and consented prior to the stem cell collection and appropriately selected patients will be fully committed to a curative therapeutic intervention.

ue 5	**exa-cel treatment in the economic analysis** • **What proportion of people would you expect will withdra**		

	w/ be un wi lli ng to pr oc ee d aft er ce ll co lle cti on , bu t be fo re th e ex a- ce l inf		

	usion?		
EAG issue 6	**Frequency of red blood cell transfusions** • **AUK chart review reported that people with transfu**	**Yes**	The average adult patient will receive a 3 or 4 weekly transfusion regime generally of between 2 to 4 units of red cells. Therefore, the range is between 13 and 17.3 transfusion episodes a year. This will equate to between 26-69 units of red cells being given per annum. The average patient will most likely be on a 3 units every 3 to 4 weeks schedule. Recent data linking HES data with CPRD data set has identified that there are on average 17.4 inpatient visits and 16.7 outpatient visits. Whilst accepting the vagaries of coding, it is highly likely that the inpatient visits are for transfusions in the vast majority (manuscript in preparation) ref: Udeze C et al ASCAT 2023 (attached poster).

	sion dependent beta-thalassaemia on average will have 13.7 transfusion		

	s per ye ar • **D o yo u ag re e wi th thi s es ti m at e?** • **W ha t is th e ra ng e yo u**		

	would expect to see in clinical practice?		
EAG issue 7	**Non-reference discount rate** **According to the NICE manual for a non-reference discount rate to be applicabl**	**Yes**	Patients with thalassaemia are more likely to die compared to their age matched cohorts. A recent study looking at CPRD data and cross linking with HES data for patients with TDT over 10 years identified a mortality rate of 7.17% compared to age matched and deprivation index matched controls and an average of death at 55 years (BSH23-OR05 | Mortality and clinical complications among patients with transfusion-dependent β- thalassemia in England) This is despite standard of care with optimal iron chelation regimes and safe blood transfusion. Looking at the Italian registry data by Forni et al, there were 11 deaths (excluding those due to bone marrow transplantation) in 251 patients born after 1979 (this cohort has had lifelong access to optimal chelation regimes). The average age of death was 23 years in the full cohort of 93 deaths in 797 patients. There is a significant impact on HRQOL for patients. A survey led by the UK thalassaemia society in 2021 showed *86.4% of respondents reported having a moderate to severe impact on their overall quality of life. Responders also reported thalassaemia having a significant emotional and social impact on patients and their families. 78.2% of patients reported feelings of anxiety, depression, and fear due to their condition and reported experiencing stigma and discrimination during several aspects of their lifetime.*

	e a set of criteria need to be met. The questions below have been tailored to the criteria. **Are people with transfusion dependent beta-thalassaemia on current standard care more likely to die or have a very severely impaired**		More recent data from a longitudinal survey in 155 patients described presented in 2022 identified *Fatigue is a common symptom identified by patients on patient reported outcome questionnaires, with about 45% of patients complaining of significant fatigue within the last 7 days. More significantly using a standard validated EQ 5D questionnaire 61% reported anxiety and depression and 59% reported impairment in activity on the day of completing the questionnaire (Li N. et al., 2022).* *More detailed analysis of participants responses identified problems with pain (73%) with 41% reported moderate-to severe pain or discomfort. Of the 61% reporting anxiety and depression, 29% reported moderate-to extreme anxiety or depression (N Li et al., 2023).* Is exa-cel likely to restore people with the condition to full or near-full health? Clinical representatives on the CRG have enrolled patients into the trials and those patients have been cured with Exa-Cel who are now clinically free of transfusion and iron chelation. This therapy has been transformative for these patients, and they now lead normal lives. Clinical endocrine complications that pre-exist such as diabetes or hypothyroidism will remain, and patients may still require therapy such as hormone therapy etc. Cardiac iron overload however will be reversed with chelation to remove the excess iron. Other complications are likely to remain stable. It is fully expected for this therapy to provide a sustainable benefit in the long term? Exa-Cel is essentially a curative therapy. Once a patient has engrafted the changes of immune rejection is not there as this is an *autologous* transplant.

	life compared with the general population? • **What is the life-expectancy of people being offered curr**		

	ent standard care with this condition? • **How different is the mortality rat**		

	e co m pa re d wi th th e ge ne ral po pu lat io n? (fo r ex a m pl e is 5 ti m es hi gh		

	era reasonable approximation?) • **How different is the quality of life of pe**		

	ople with this condition? **Is treatment with exa-cel likely to restore people with the condition to full or near-full health:** • **Does this cond**		

	itionalreadycausepermanentdamagefrompre-existingcomplications		

	(for example cardiac or liver complications) that cannot be reversed by ex		

	a-cel treatment? • **If yes, what proportion of people are likely to experie**		

	nce this? **The benefits of exa-cel are likely to be sustained over a very long period.** • **Do you expect the benefits of exa-**		

	cell observed during a maximum of 42 months of follow-up to be sustaine		

	d over time? • **If no, why not?**		
EAG issue 8	**Mortality for people with transfusion dependent beta-thalassaemia, and mortality associated with complications** • **What**	**Yes**	Some of this has already been addressed above. It is important to note there is despite good iron chelation and transfusion an increase in mortality in the UK population from the NHR and the CPRD/HES linkage data set but also globally in other countries. In particular the data from Forni et al from the Italian registry data shows that mortality remains an issue with an average age of death of around 23 years. We know from the CPRD data set that UK average age at death is around 55 years of age. For patients with cardiac complications, we would expect the standardised mortality rate to be at a much younger age compared to the general population. Likewise, 40% of patients are diabetic in the Whittington cohort of patients and the expectation is that they will develop complications and die earlier than age matched peers. The Forni et al data set shows patients dying at younger ages with *Risk factors that were independently and significantly associated with death at the p < 0.1 level included: heart disease (hazard ratio [HR]: 4.63, 95%CI: 1.78–12.1, p = 0.002), serum ferritin >1000 ng/mL (HR: 15.5, 95%CI: 3.52–68.2, p < 0.001), male sex (HR: 2.75, 95%CI: 0.89–8.45, p = 0.078), and splenectomy (HR: 6.97, 95%CI: 0.90–54.0, p = 0.063).*

	would you expect the mortality rate or standardised mortality rate* to be fo		

	r pe op le wi th thi s co nd iti on w ho ha ve ca rdi ac or di ab eti c co m pli ca tio ns ?		

	***Standardised mortality rate = the number of deaths observed in a population over a given period divided by the number that would be expected over the same period if the study population had the same age-specific rates as the standard**		

	population		
EAG issue 9	**Health related quality of life in people who are transfusion dependent** • **Since the condition is inherited / starts fro**	**Yes/No**	The impact of disease burden on quality of life should not be underestimated. Over many years patients have worked hard to ensure that their disease does not impact their life chances for a career and family. Thalassaemia is a multisystem disorder with a very large burden of care for patients. The transfusion cycle is equivalent to a patient losing a pint of blood a week. This means that post transfusion they might feel well but the week before transfusion they will be progressively more tired, have more bone pain and other symptoms. Questionnaires such as the EQ5D identify symptoms at a fixed time point when the questionnaire is done. Even though they are completed at a number of time points in a study (e.g. baseline, month 3 etc) they will not provide information on the variation in symptoms over a transfusion cycle.. A recent study presented at ISPOR 2023 showed 29.6% of participants (n = 8/27) commented that the EQ-5D-5L DS did not capture how their experience of living with TDT changes depending on where they were in their RBCT cycle (Boateng-Kuffour, et al ISPOR oral presentation 2023) In addition, the psychological factors of a patient who is determined to lead a normal life means that they will tend to respond positively to a questionnaire about their health status. Clinicians on the CRG looking after a large cohort of patients based at Whittington, Barts Health, Birmingham all describe patients being impacted by the transfusion cycle (almost universally), bone pain and fatigue and anxiety and depression in their patients. The multiple hospital visits for transfusion, investigations and clinic consultations with various specialists means they need to take time off work and may need to use annual leave or work part-time to meet the demands of their treatment. The HRQOL survey by Li N et al shows the impact of fatigue, pain and anxiety is considerable.

	m ea rly ch ild ho od . H o w lik el y is it th at pe op le wi th thi s co nd iti on ge t us		

	ed to the sy mpt o ms ov er ti m e? • **D o yo u ha ve an y ot he r co m m en ts ab**		

	out the quality of life of people living with this condition?		
EAG issue 12-14	**Would the introduction of exa-cel have any**	**Yes/No**	It is fully expected to significantly improve patients' quality of life. We know that post bone marrow transplantation patients have a significant improvement in their HRQOL (La Nasa et al., 2013, Javanbakht et al., 2015). This is in a cohort of patients who had a more challenging stem cell transplant using a matched sibling donor (therefore allogeneic, i.e. not your own stem-cells). Exa-Cel is an autologous (i.e. your own stem-cells) bone marrow transplant and associated with less treatment burden in the post-transplant setting (i.e. Absence of need for

	impact on health inequalities? If so, how?		immunosuppression). Hence the HRQOL should improve considerably. CRG members report significant improvement in their patients who have been treated with gene therapy in clinical trials.
	Economic modelling specific issues **(Focus of issues are less clinical and more methodological/conceptual please refer to section 1 of EAR to more details)**		
EAG issue 11	**Using eMIT costs instead of**	**Yes**	Yes, eMIT costs should be used, it is highly unlikely these drugs are prescribed in primary care. Commissioning criteria and local formularies specify these drugs fall under specialist service provision (secondary care). Advice has been sought from two specialist haemoglobinopathy pharmacists and the below data also sourced to verify this; Open prescribing data for all GP practices across England in the last year shows:

	national tariff		Deferiprone – <10 items/month prescribed Deferasirox – ≤20 items/month prescribed Desferrioxamine – 1 item/month prescribed Data from the Define system for all hospital trusts in England for the last year shows: Deferiprone – 804,858 units of VMP (virtual medicinal product) prescribed Deferasirox – 1,444,041 tablets prescribed Desferrioxamine – 155,644 units of VMP prescribed
	Other issues that need clinical expert opinion:		
	Baseline osteoporosis and diabetes complication rates: **Do you agree with the following statement:** • **The pathog**	**Yes/No**	It is too early to say at this time, however as osteoporosis is a disorder affected by multiple factors including bone marrow expansion and high iron levels it is fully expected that as erythropoiesis normalises in the post stem cell transplant setting that osteoporosis and osteopenia is likely to improve or reserve over a number of years (theoretically). Old papers looking at BMT report *Severe BMD deficit was less common among BMT than BT patients (6 vs 35%; P=0.036) . Leung TF et al; Bone Marrow Transplant 2005 Aug;36(4).*

	enesis of beta-thalassaemia-related osteoporosis is not well understood		

	but it is theorised to be a result of many factors such as inherent genetic fa		

	ctors, ineffective erythropoiesis, high iron levels, and low levels of vita		

	min D. Exa-cel treatment may impact some of these factors. **Do you expect exa-cel treatment**		

	would reverse osteoporosis symptoms or complications?		
	Risk of initial graft failure: **The CLIMB THAL-111 trial showed there were no engraftment rejections (failures). But 6.9% initial engraftment failure have been reported**	**Yes/No**	Yes, it is reasonable to assume grafts should not be rejected as these are autologous transplants and should not be associated with immune rejection.

	in haematopoietic stem cell transplant. • **Is it reasonable to assume 100% initial engraftment succ**		

	ess in clinical practice? • **If not, what is the range of initial engraftmen**		

	t failures seen in clinical practice?		
	Iron normalisation period: **How long does it take for people with transfusion-independent beta-thalassaemia to achieve normalis**	**Yes/No**	For most patients normalisation of iron is dependent on the severity of the iron overload on entering into the Exa-cel treatment. In the clinical setting we would expect that most people will have completely cleared iron from the liver and other organs within 3 to 4 years including cardiac iron overload (if any is present at time of transplant as this generally takes 4 years) this rate of removal is what we would see with simple venesection to remove iron. In a patient who received iron chelation then generally 2 to 3 years should have bought the iron burden into the desired range. Five years is much longer than we would expect.

	ed iron levels in all organ systems: • **Four years (company assumption)** • **Five years (EAG assumpti**		

	on) • **Other?**		

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EARIssue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: The EAG invite input from NHS England to inform the appropriate tariff costs for administration of exa-cel	4.2.8.1 Points for Critique, page 89	No	It is our view that using the autologous stem cell transplant (auto-SCT) tariff would understate the costs to the NHS of delivering exa-cel. There is no existing tariff for transplantation with CRISPR-edited cells as this is a completely new technology for the NHS. Our experiences of rolling out other novel therapies such as CAR-T have identified that it takes time and therefore resource for NHS professionals to develop and embed the processes associated with using such technologies which would not be captured in the published reference costs for an established service such as auto-SCT. Furthermore, the novel nature of the therapy introduces additional costs over and above an auto-SCT for example regarding consenting to the use of gene therapy, post procedure cytopenia and fertility considerations. Length of stay is also potentially longer than auto-SCT. Our recommendation for use of the CAR-T tariff gives an indicative package price which captures the delivery episode and the additional pre-transplant mobilisation and apheresis service costs listed by the company (drugs are considered separately). Prior to submission of our budget impact analysis, we consulted with the National Specialty Advisor for Hemoglobinopathies and in their view “the CAR-T tariff should be used rather than a BMT tariff as the procedure mimics the former more than the latter”

Additional issue 2: The EAG is unclear whether it is the company or the NHS who bears the cost of manufacturing exa-cel 1when patients withdraw or become ineligible for treatment after gene editing has been performed prior to infusion.	6.1.2 Exploratory and sensitivity analyses undertaken by the EAG: Accounting for cost and health outcomes where patients are unable to receive exa-cel transfusion, page 101	No	In usual circumstances the company would bear the cost of any product manufactured and not delivered. The company should factor any costs associated with such doses into cost of manufacturing used to support the pricing structure for products which are successfully administered to patients. The only alternative presentation would be for the costs of manufacture for non-administered doses to be separately included in the economic model with a corresponding clinical benefit of zero for those patients.
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

NICE National Institute for Health and Care Excellence

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.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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The deadline for comments is **5pm** on **Monday 6 November 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted] – [redacted] the UK Forum on Haemoglobin disorders
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	UK Forum on Haemoglobin disorders
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Vertex Pharmaceuticals has provided an unrestricted educational grant to support the UK forum's educational meetings in 2023 this was for 1000 GBP. This funding is applied for and provided by pharmaceutical companies to the UK forum without restriction to support educational events aimed at its membership and affiliates. The funding provided is in no way related to the any products mentioned in the stakeholder list.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**Nil**

NICE National Institute for Health and Care Excellence

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Issue impacting decision making:	Description:	Does this response contain new evidence, data or analyses?	Response
EAG issue 1	**Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile:** **Permanence of transfusion independence: after successful exa-cel treatment (defined as achievement of transfusion independence) how likely is:** • **the risk of thalassaemia recurrence** • **a 0% rate of thalassaemia recurrence** **Safety: the company notes that exa-cel's mechanism of action eliminates any risk of treatment-related cancer (risk of mutagenesis and transcriptional deregulation)** • **Do you agree?** • **Do you have any further comments on exa-cel's safety?**	**Yes**	***Long term efficacy:*** **Gene therapy utilises autologous haematopoietic stem cells (HSC) derived from the patient themselves. These are then returned to the patient after they have undergo chemotherapy to "create a room" in their marrow niche to facilitate the gene therapy modified HSC engraftment in their marrow .** **These cells in no way differ immunologically from the patient, which results in the avoidance of the major immunological complications associated with allogeneic stem cell transplant (Allo HSCT), where there will be some guaranteed differences with the host immune system (unless the donor is an identical twin).** **So unlike allo HSCT where immune tolerance has to develop, with an autologous**

			procedure there is no risk of the immune system rejecting the transplanted cells at a later date. Hence the risk of thalassaemia recurrence after a successful gene therapy procedure is likely negligible. **It is worth noting that gene therapy using gene corrected haematopoietic stem cell has been used in a large number of conditions including primary immunodeficiency syndromes since the 1990s, which all show the ongoing regenerative capacity of gene-modified haematopoietic stem cells.** *Reference included with submission: Richard A. Morgan, et al. Hematopoietic Stem Cell Gene Therapy: Progress and Lessons Learned, Cell Stem Cell, Volume 21, Issue 5, 2017, Pages 574-590* ***Safety*: Unlike the insertional mutagenesis risk posed by gene therapy approaches that involve addition of a gene such as the lenti viral approach, targeted gene editing allows specific genome modification and eliminates this risk. This has been shown by a number of studies in a variety of disease areas, additionally this method of gene therapy ensures the expression of the gene remains under endogenous (the cells own) control. So, we agree with the company's assessment.**

			We would only note here that while there is a low risk of secondary malignancies attributed to the conditioning regimen, Busulphan, an alkylating agent, this risk even in a cohort of patients who had received multiple lines of chemotherapy, was quoted as 0.5% in one publication (Long-Boyle et all – submitted). The risk is likely to be much lower in this chemo naïve group of patients. **We would also note here that even in the absence of exposure to chemotherapy, in transfused thalassaemia patients with iron overload, there is also a well-recognised risk of malignancy such as hepatocellular carcinoma.** *Reference (included with submission):* *Ref: Long-Boyle JR, et al. Busulfan and subsequent malignancy: An evidence-based risk assessment. Pediatr Blood Cancer. 2023 Oct 19:e30738. doi: 10.1002/pbc.30738. Epub ahead of print. PMID: 37856098.*
EAG issue 2	**Definition of transfusion independence** **Do you have any comments on the most appropriate definition, and/or advantages and disadvantages of the definitions below:** • **maintaining a weighted average Hb ≥9 g/dL without red blood cell (RBC)**	**Yes**	**The aim of transfusion in thalassaemia is to manage the symptoms of anaemia, suppress erythropoiesis preventing extramedullary haemopoiesis and allow normal growth and development. A treatment that maintained Hb greater than or equal to 90g/L without**

	transfusions for at least 12 consecutive months any time after exa-cel infusion (CLIMB THAL-111 primary outcome – 'TI12') • **as people who are transfusion-free starting 60 days after the last blood transfusion for post-transplant support or disease management**		**transfusion would be considered highly successful in thalassaemia**. **While we would agree both statements constitute transfusion independence, statement 1. Referring to average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months would indicate a cohort with longer follow up than statement 2, which refers to freedom from transfusion 60 days after the last transfusion for transplant or disease management.**
EAG issue 3	**Uncertain relationship between transfusion status and final outcomes** • **Can you comment on how transfusion status (transfusion independent, reduced, dependent) is related to iron levels, risk of chronic complication, mortality rates and quality of life?** • **What are some of the advantages and disadvantages of assuming a link between transfusion status and these outcomes without direct evidence?** • **Are there any evidence sources that can be used to help inform the link between transfusions status and the outcomes listed above?**	**Yes**	**Transfusion as a treatment for thalassaemia was established in the 1960's however while this treatment improved survival from infancy in patients with thalassaemia it was shown to be associated iron overload (high serum ferritin levels) and patients developed multiple complications from this including cardiac, liver and endocrine complications. These were ameliorated to a degree by the advent of chelation therapies.** **The link between transfusion dependence and iron overload and then requirement for chelation therapy is not uncertain, *it is well recognised and researched, with multiple risks very well described.*** **Evidence available in peer reviewed literature, and from current clinical practice confirms that in transfusion dependent thalassaemia patients there is a very**

			predictable and measurable rise in iron load based on the amount of blood received by a patient with a less linear association in the non-transfusion dependent thalassaemia patients who have the added complexity of increased iron absorption via their gastrointestinal system. **Iron overload is directly associated with** **Cardiac arrythmia liver damage and eventually heart failure, hypogonadism, hypothyroidism as well as pancreatic damage leading to development of diabetes. Liver damage caused by iron overload can lead to liver cirrhosis and then the additional risk of Hepatocellular carcinoma.** **Each year all of these complications are registered in thalassaemia patients managed in our health system and each year a number of young patients with thalassaemia die due to these complications.** **There is also good evidence of the negative effect of withholding transfusions from thalassaemia patients (done to reduce the complication of iron overload) with increased complications in adulthood including chronic pain, fractures, thrombosis, and pulmonary hypertension.**

			Blood transfusion itself is also associated with multiple risks including acquired infections such as hepatitis B, despite a high level of work to ensure blood safety, there remains a low but not negligible possibility of this risk. **Patients who undergo curative treatments that result in transfusion independence such as allogeneic stem cell transplant, go on eto have their iron overload managed inexpensively via a regular venesection program which can lead normalisation of their iron status within a few months without recrudescence. This removes any further risk associated with iron overload from these patients.** *References included with submission:* 1. *Borgna-Pignatti Cet al Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica. 2004 Oct;89(10):1187-93. PMID: 15477202* 2. *Lal A, et al. The transfusion management of beta thalassemia in the United States. Transfusion. 2021 Oct;61(10):3027-3039. doi: 10.1111/trf.16640. Epub 2021 Aug 28. PMID: 34453453; PMCID: PMC9292563.*

			3. *Betts M, et al Systematic Literature Review of the Burden of Disease and Treatment for Transfusion-dependent β-Thalassemia. Clin Ther. 2020 Feb;42(2):322-337.e2. doi: 10.1016/j.clinthera.2019.12.003. Epub 2019 Dec 24. PMID: 31882227.*
EAG issue 5	**Omission of withdrawals from exa-cel treatment in the economic analysis** • **What proportion of people would you expect will withdraw/be unwilling to proceed after cell collection, but before the exa-cel infusion?**	**Yes/No**	**While it is not unlikely that a patient may consider this treatment but choose to delay starting it for a variety of reasons including change in circumstance like pregnancy etc it is highly unlikely that a patient identified to fulfil criteria for this treatment, who had undergone informed consent would withdraw after cell collection. We expect none or an extremely low number of patients.**
EAG issue 6	**Frequency of red blood cell transfusions** • **A UK chart review reported that people with transfusion dependent beta-thalassaemia on average will have 13.7 transfusions per year** • **Do you agree with this estimate?** • **What is the range you would expect to see in clinical practice?**	**Yes/No**	**Transfusion dependent thalassaemia patients attend 3-4 weekly for their blood transfusions and on each occasion will receive between 2-4 units of blood.** **So while the transfusion *episodes* will range on average between 13 to 17.3 per year the total *units* of blood received will range from 26 to 70 units each year. This is fairly standard across transfusion dependent thalassaemia patient management. For each transfusion episode, almost all patient will attend a day or two prior for a blood test to ensure cross matched compatible units are ready for their transfusion episode. Hence**

			each transfusion episode requires an additional attendance. **Separate but additional to this burden patients with thalassaemia will also need to attend for: review appointments with their clinicians at least twice, but for most up to 4 times a year..** **Thalassaemia patients in addition to attendance for transfusions will also routinely attend hospitals for:** • **investigations to assess for iron overload, both cardiac and liver** • **hearing assessments** • **vision assessment both of which may be affected by their chelation therapies.** **NHS Hospital episode data showed 76% of transfusion dependent thalassaemia patients had at least one co-morbidity, while 54% had two or more. Depending on which comorbidities they develop (may be associated to either the underlying condition or the associated treatments) such as osteoporosis (thin bones), or diabetes, patients can have a large number of additional hospital episodes to attend, more than doubling their total attendances for transfusion alone.** *Reference: Betts M, et al Systematic Literature Review of the Burden of Disease and Treatment*

			for Transfusion-dependent β-Thalassemia. Clin Ther. 2020 Feb;42(2):322-337.e2. doi: 10.1016/j.clinthera.2019.12.003. Epub 2019 Dec 24. PMID: 31882227.
EAG issue 7	**Non-reference discount rate** **According to the NICE manual for a non-reference discount rate to be applicable a set of criteria need to be met. The questions below have been tailored to the criteria.** **Are people with transfusion dependent beta-thalassaemia on current standard care more likely to die or have a very sverely impaired life compared with the general population?** • **What is the life-expectancy of people being offered current standard care with this condition?** • **How different is the mortality rate compared with the general population? (for example is 5 times higher a reasonable approximation?)** • **How different is the quality of life of people with this condition?** **Is treatment with exa-cel likely to restore people with the condition to full or near-full health:** • **Does this condition already cause permanent damage from pre-existing**	**Yes/No**	**Life expectancy:** **The life expectancy for the general population of the United Kingdom as of 2023 is approximately 81 years, with women living to around 83 years and men to 79 years.** **Whereas a retrospective cohort analysis using Hospital episode data from the NHS in England showed the crude 10-year mortality rate in the TDT cohort was 6·2% which was significantly greater than the 1·2% age/sex-adjusted mortality rate of the general population (P < 0·001).Although mortality rates have decreased amongst thalassaemia patients it remains significantly reduced and this was confirmed by a retrospective cohort analysis using Hospital episode data from the NHS in England showed the crude 10-year mortality rate in the TDT cohort was 6·2% which was significantly greater than the 1·2% age/sex-adjusted mortality rate of the general population (P < 0·001).** **Quality of life:** **Although the EQ-5D health related instrument is frequently used for health**

Commented [KR1]: Jobanputra M, Paramore C, Laird SG, McGahan M, Telfer P. Co-morbidities and mortality associated with transfusion-dependent beta-thalassaemia in patients in England: a 10-year retrospective cohort analysis. Br J Haematol. 2020 Dec;191(5):897-905. doi: 10.1111/bjh.17091. Epub 2020 Oct 23. PMID: 33094842.

	complications (for example cardiac or liver complications) that cannot be reversed by exa-cel treatment? • **If yes, what proportion of people are likely to experience this?** **The benefits of exa-cel are likely to be sustained over a very long period.** • **Do you expect the benefits of exa-cel observed during a maximum of 42 months of follow-up to be sustained over time?** • **If no, why not?**		**economic assessment it is a tool that is inadequate at assessing the quality of life of patients with thalassaemia.** **One of the 5 domains of the EQ-5D focuses on "usual activities" which is confounded in individuals living with thalassaemia, as regular transfusion is essence, a "usual activity" for them and hence part of their baseline, however their symptom burden fluctuates around the transfusions.** **Patients additionally have a high carer burden, as noted above they manage multiple hospital appointments, as well as competing comorbidities,** **almost all manage a high burden of fatigue. Thalassaemia patients manage a significant chronic pain burden, mostly but not always related to osteoporosis and the damage associated. There is a recognised mental health burden with anxiety and depression.** **Treatment with Exa-cel:** **Most of the cardiac and liver complications associated with thalassaemia remains reversible for many years, the liver being a highly regenerative organ. This damage is only irreversible once liver cirrhosis occurs, however it is highly unlikely that a patient found to have liver cirrhosis would be deemed fit enough to undergo exa-cel**

			treatment due to the requirement for Busulphan conditioning. **This is also true for the cardiac complications associated with thalassaemia. Intensive inpatient iron chelation reverses/ and treats most of the cardiac comorbidity, however once cardiac chambers develop established dysfunction which culminates in heart failure then such an individual will also likely to be deemed unfit for Exa-cel treatment.** **As noted above Exa-cel is based on autologous stem cell transplant so once successfully transplanted we would expect sustained and stable function in patients, with transfusion independence once achieved to continue to be maintained, similar to successful haematopoietic stem cell-based gene therapy in other diseases.**
EAG issue 8	**Mortality for people with transfusion dependent beta-thalassaemia, and mortality associated with complications** • **What would you expect the mortality rate or standardised mortality rate* to be for people with this condition who have cardiac or diabetic complications?** ***Standardised mortality rate = the number of deaths observed in a population over a given period divided by the number that would be expected over the same period if the study**	**Yes**	**A retrospective cohort analysis using Hospital episode data from the NHS in England showed the crude 10-year mortality rate in the TDT cohort was 6·2% which was significantly greater than the 1·2% age/sex-adjusted mortality rate of the general population (P < 0·001).**

	population had the same age-specific rates as the standard population		
EAG issue 9	**Health related quality of life in people who are transfusion dependent** • **Since the condition is inherited/ starts from early childhood. How likely is it that people with this condition get used to the symptoms over time?** • **Do you have any other comments about the quality of life of people living with this condition?**	**Yes**	**Despite improvements in overall care over the past 30years, there remains huge unmet need on both disease burden and impact of the health condition on the quality of life of individuals with thalassaemia.** **Rather than the misconception of a simple condition where patients attend for transfusions and are otherwise well. It needs to be recognised that for a "well" patient with thalassaemia their reality will involves as a minimum:** **1. Attending multiple hospital appointments, as noted above this averages 13-17.3 plus the same again for pre transfusion tests just for the life saving transfusions. They must also attend additional hospital appointments for investigations and reviews which, depending on the list of their co-morbidities may be as high as 3 added per month.** **2. Venous access after a lifetime of 3-4 weekly transfusions is always problematic, with some patients developing anxiety disorders around their transfusion attendances. Multiple patients require indwelling venous access devices which are**

			associated with risk of complications including clots and infections. **3. Continuous and rigorous monitoring of their iron burden and adherence to iron chelation regimen which may be combination therapy for a percentage of patients. These medications are also associated with side effects including GI upset, rash, low blood white cell count (agranulocytosis) and hence an increased risk of neutropenic sepsis and kidney dysfunction.** **4. The actual medications used to treat iron overload involve either being attached to an infusion for 8-12 hours a day, or taking multiple tablets more than once a day. For those with the highest iron burden usually a combination of both types of chelators.** **5. A proportion of patients will be significantly impacted by transfusion reactions and alloantibody formation** **6. Another cohort who have undergone splenectomy will have additional risks including infection and development of pulmonary hypertension.** **7. Management of at least 1 other health comorbidity as shown by HES data from NHS England 76% of the whole**

			transfusion dependent thalassaemia patient has at least 1 other comorbidity and that applies even when focused on the younger age such as the age 10 and 14 cohort of whom 60% had at least 1 comorbidity. **The EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) is a generic, preference-based measure of HRQoL, It's five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) are not sensitive to the specific impact of ongoing transfusion and iron chelation. One of the domains (usual activities) could be confounded by the standard management of TDT as it is, in essence, a usual activity for individuals living with TDT.** **Thalassaemia patients have reported the EQ-5D-5L's questions are not relevant and does not recognise fluctuations in their symptoms. It also has no domains that recognise the significant burden placed on carers and the social support systems that patients require to manage their health burden.** *Reference: 1. Matza LS, Health state utilities associated with treatment for transfusion-dependent β-thalassemia. Eur J Health Econ. 2020 Apr;21(3):397-407. doi: 10.1007/s10198-019-01136-0. Epub 2019 Dec 11. PMID: 31828456; PMCID: PMC7188724.*

			2. Jobanputra M, et al. Co-morbidities and mortality associated with transfusion-dependent beta-thalassaemia in patients in England: a 10-year retrospective cohort analysis. Br J Haematol. 2020 Dec;191(5):897-905. doi: 10.1111/bjh.17091. Epub 2020 Oct 23. PMID: 33094842.
EAG issue 12-14	**Would the introduction of exa-cel have any impact on health inequalities? If so, how?**	**Yes**	**Freedom from transfusion and then the potential to have the iron burden returned to normal and not require chelation therapy** **Reduced stress from frequent attendance for venupuncture. Reduced burden of hospital contacts after successful a gene therapy procedure. Reduced risk of developing bony pain secondary to osteoporosis associated with the condition.**
	Economic modelling specific issues **(Focus of issues are less clinical and more methodological/conceptual please refer to section 1 of EAR to more details)**		
EAG issue 11	**Using eMIT costs instead of national tariff**	**no**	**The EAR notes the company used the NHS drug tariff costs rather than the electronic information tool (eMIT) costs to represent the acquisition cost associated. The EAG were directed to use the eMIT costs.** **We are unable to comment further on this point.**
	Other issues that need clinical expert opinion:		

	Baseline osteoporosis and diabetes complication rates: **Do you agree with the following statement:** • **The pathogenesis of beta-thalassaemia-related osteoporosis is not well understood but it is theorised to be a result of many factors such as inherent genetic factors, ineffective erythropoiesis, high iron levels, and low levels of vitamin D. Exa-cel treatment may impact some of these factors.** **Do you expect exa-cel treatment would reverse osteoporosis symptoms or complications?**	**Yes**	**Pathogenesis of osteoporosis in beta thalassaemia is thought to be multifactorial. It results in bone fragility contributed to by both low bone mass and micro-architectural deterioration of bone tissue. The factors thought to be involved include iron overload which causes endocrine abnormalities which contribute as well as ineffective erythropoiesis which expands the marrow space and thins the cortical bone.** **As treatment with Exa-cel is expected to impact both these factors with reduced ineffective erythropoiesis and then iron overload it would be our expectation that successfully treated patients would either not develop the osteoporosis or those with the diagnosis at the time of treatment would not progress. For patients with established diagnosis before receiving Exa-cel while we would expect their condition not to worsen and to likely stabilise, it is difficult to be certain that it may be reversible.**
	Risk of initial graft failure: **The CLIMB THAL-111 trial showed there were no engraftment rejections (failures). But 6.9% initial engraftment failure have been reported in haematopoietic stem cell transplant.** • **Is it reasonable to assume 100% initial engraftment success in clinical practice?**	**Yes**	**As noted in response to issue 1 - Gene therapy utilises autologous stem cells derived from the patient, meaning while the patient has to undergo chemotherapy to make space in the marrow niche to facilitate HSC engraftment basically "create room" in their marrow space for the gene therapy modified stem cells. These cells are in no way different from the patient immunologically. This means they avoid any**

	• **If not, what is the range of initial engraftment failures seen in clinical practice?**		**of the major immunological complications of allogeneic stem cell transplant (Allo HSCT) when the stem cells are derived from a donor separate from the patient, be they related or not.** **Unlike allo HSCT where the patient has to develop immune tolerance to ensure the graft (donor stem cells) remain and flourish, there is no similar risk with autologous stem cell transplant. The patient's immune system will not latterly reject stem cell of its own origin at a later date.** **Hence the risk of thalassaemia recurrence after a successful gene therapy procedure and the likely percentage rate to rightly be assessed at near enough 0%.** **Gene therapy using gene corrected haematopoietic stem cell has been used a large number of conditions which all show the ongoing regenerative capacity of gene-modified haematopoietic stem cells**
	Iron normalisation period: **How long does it take for people with transfusion-independent beta-thalassaemia to achieve normalised iron levels in all organ systems:** • **Four years (company assumption)** • **Five years (EAG assumption)** • **Other?**	**Yes**	**Once transfusion independence is achieved iron chelation can be augmented by a venesection program, this is standard of care for haemochromatosis, a genetic condition which results in increased iron absorption. Combining chelation medication with venesection will result in more rapid iron removal, however even where venesection is not undertaken, as the patients become transfusion independent**

			their chelation treatments will be more effective as they will not also be managing a regular iron load. To us even 4 years seems likely to be an overestimate of the time transfusion independent and treatment adherent patients would require therapy for. 5 years is definitely an overestimate of this.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **Monday 6 November 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Table 1 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)	United Kingdom Thalassaemia Society
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**UKTS received £0.00 in funding from Vertex and related comparator companies in the last 12 months.**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**NONE**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Issue impacting decision making:	Description:	Does this response contain new evidence, data or analyses?	Response (Please provide your response to this key issue, including any new evidence, data or analyses
EAG issue 1	**Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile:** **Permanence of transfusion independence: after successful exa-cel treatment (defined as achievement of transfusion independence) how likely is:** • **the risk of thalassaemia recurrence** • **a 0% rate of thalassaemia recurrence**	**Yes**	**Uncertainty about exacel's long term efficacy** To assess long-term effectiveness, the most suitable comparison is with hematopoietic stem cell transplantation (HSCT) for thalassaemia. HSCT has demonstrated the achievement of transfusion independence in patients over many decades. HSCT and Exa-cel follow a similar approach, involving the use of myeloablative therapy before transplantation to eliminate unedited cells and create space for successful replication of edited cells. We anticipate that the long-term effectiveness of Exa-cel should be comparable. It is important to note that HSCT carries additional risks, such as graft versus host disease (GVHD) and rejection, which are not observed with Exa-cel. **Safety** We agree with the company's statement. As opposed to previous iterations of gene therapy that introduced extra/ new genes through the lenti-viral

	Safety: the company notes that exa-cel's mechanism of action eliminates any risk of treatment-related cancer (risk of mutagenesis and transcriptional deregulation) • **Do you agree?** • **Do you have any further comments on exa-cel's safety?**		vector, Exa-cel, on the other hand, modifies the patient's own gene, thereby mitigating the risks associated with transcriptional deregulation and mutagenesis. Regarding the published clinical data on Exa-cel for thalassemia, there have been no reported cases of mutagenesis or degranulation. It is important to note that the use of myeloablative agents in HSCT carries a known risk of developing oncological conditions. However, based on the available clinical data, we believe that the risk associated with Exa-cel would not be greater than that seen in HSCT. Furthermore, individuals with thalassaemia face additional risks of developing cancer due to high concentrations of oxygen free radicals and iron overload (Moukhadder et al, 2017, Ding et al., 2022). It is not uncommon for adult patients with thalassemia, particularly in the UK, to develop cancers such as hepatocellular carcinoma (HCC) and breast cancer. As chelation therapy has improved and extended the lifespan of patients with thalassaemia, there has been a notable increase in the occurrence of hepatocellular carcinoma (HCC). The development of HCC in individuals with iron overload is attributed to various mechanisms, including heightened levels of reactive oxygen species (ROS), inflammatory cytokines, disruptions in hepcidin regulation, and altered ferroportin metabolism (Lin et al, 2023). **References**

			Mancuso, A., Butera, G., Rossi, M., & Maringhini, A. (2023). Hepatocellular carcinoma in thalassemia and other hemoglobinopathies. *Cancer*, *129*(10), 1614–1615. https://doi.org/10.1002/cncr.34735 Lin, P. C., Hsu, W. Y., Lee, P. Y., Hsu, S. H., & Chiou, S. S. (2023). Insights into Hepatocellular Carcinoma in Patients with Thalassemia: From Pathophysiology to Novel Therapies. *International journal of molecular sciences*, *24*(16), 12654. https://doi.org/10.3390/ijms241612654 Moukhadder, H. M., Halawi, R., Cappellini, M. D., & Taher, A. T. (2017). Hepatocellular carcinoma as an emerging morbidity in the thalassemia syndromes: A comprehensive review. *Cancer*, *123*(5), 751–758. https://doi.org/10.1002/cncr.30462
EAG issue 2	**Definition of transfusion independence** **Do you have any comments on the most appropriate definition, and/or advantages and disadvantages of the definitions below:** • **maintaining a weighted average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months any time after exa-cel infusion (CLIMB THAL-111 primary outcome – 'TI12')** • **as people who are transfusion-free starting 60 days after the last blood transfusion for post-**	**Yes**	The most important aspect of a curative option for patients with transfusion dependent thalassaemia is to completely correct anaemia and prevent any symptoms and complications associated with ineffective erythropoiesis. A successful outcome for patients with TDT who qualify and are interested in treatment can be defined as maintaining a consistent haemoglobin level of 9 or higher without the need for transfusions and without worsening of anaemia-related complications. Both definitions adequately describe transfusion independence as patients with TDT who did not receive treatment with exa-cel or any other curative option would on average have transfusions every 3 weeks.

	transplant support or disease management		
EAG issue 3	**Uncertain relationship between transfusion status and final outcomes** • **Can you comment on how transfusion status (transfusion independent, reduced, dependent) is related to iron levels, risk of chronic complication, mortality rates and quality of life?** • **What are some of the advantages and disadvantages of assuming a link between transfusion status and these outcomes without direct evidence?** • **Are there any evidence sources that can be used to help inform the link between transfusions status and the outcomes listed above?**	**Yes/No**	In transfusion dependent thalassaemia (TDT), iron obtained from regular blood transfusions can have severe and life threatening consequences if not treated appropriately. It is estimated that in each unit of blood transfused, approximately 200-250mg of iron is introduced into the patient's body. Additionally, the body has regulatory mechanisms in place to control iron absorption and excretion to maintain homeostasis. In patients with TDT or reduced transfusion frequency, do not have such mechanisms and as such absorb iron from the gastrointestinal tract at an increased level when compared to those who are not reliant on transfusions. As patients with TDT are unable to produce healthy haemoglobin and utilise iron stores, the iron retained with transfusions and those absorbed through the gut is stored leading to severe iron overload. In patients with a reduced transfusion need, the body will utilise some iron stores but there remains some strain on the body's regulatory mechanism to excrete unused iron. In patients or people who are transfusion independent, the body is able to utilise iron effectively to produce healthy haemoglobin as such the iron stores will be low or will be reduced as time goes on. Iron overload can result in organ failure (cardiac, hepatic, endocrine etc) and ultimately premature death without adequate iron chelation.

			The link between transfusion dependence, iron overload and mortality in thalassaemia have been well established and published for decades (Taher & Saliba, 2017, Shah et al, 2019,). However, despite the advances in celebrated over the years with regards to iron chelation medication, adherence to treatment has and will also be an issue. This is even absorbed in patients who have only ever been prescribed oral agents. Whilst iron chelation medication works well, they come with a myriad of side effects which not only can affect a person's daily life, but also contribute to the non-adherence. We have historically and till the present day with the advances in treatment continue to observe non-adherence in the patient population between ages 10- 40+. References De Sanctis, V., Soliman, A., & Yassin, M. (2013). Iron overload and glucose metabolism in subjects with β-thalassaemia major: an overview. *Current diabetes reviews*, *9*(4), 332–341. https://doi.org/10.2174/1573399811309040005 Taher, A. T., & Saliba, A. N. (2017). Iron overload in thalassemia: different organs at different rates. *Hematology. American Society of Hematology. Education Program*, *2017*(1), 265–271. https://doi.org/10.1182/asheducation-2017.1.265 Shah, F. T., Sayani, F., Trompeter, S., Drasar, E., & Piga, A. (2019). Challenges of blood transfusions in β-thalassemia. *Blood reviews*, *37*, 100588. https://doi.org/10.1016/j.blre.2019.100588

			Rasel, M., & Mahboobi, S. K. (2023). Transfusion Iron Overload. In *StatPearls*. StatPearls Publishing. Siri-Angkul, N., Chattipakorn, S. C., & Chattipakorn, N. (2018). Diagnosis and treatment of cardiac iron overload in transfusion-dependent thalassemia patients. *Expert review of hematology*, *11*(6), 471–479. https://doi.org/10.1080/17474086.2018.1476134 United Kingdom Thalassaemia Society – Standards for the Clinical care of Children and Adults with thalassaemia in the UK (4TH Edition), 2023.
EAG issue 5	**Omission of withdrawals from exa-cel treatment in the economic analysis** • **What proportion of people would you expect will withdraw/be unwilling to proceed after cell collection, but before the exa-cel infusion?**	**Yes**	Based on our experience, the decision to proceed with a transplant is a significant one for families, and it is never made without careful consideration. Families often invest a significant amount of time weighing the advantages and disadvantages before committing to the procedure. Once they have made the decision to proceed, we anticipate that they will follow through with all the necessary steps. We do not think individuals will withdraw, providing they have received appropriate information and given sufficient time to make the best decision for their unique situation before they are consented.
EAG issue 6	**Frequency of red blood cell transfusions** • **A UK chart review reported that people with transfusion dependent beta-thalassaemia on average will have 13.7 transfusions per year**	Yes	Patients with transfusion dependent thalassaemia usually require blood transfusions every two to four weeks, with most individuals attending every three weeks- the average would be at least 17.3 blood transfusions per year. As individuals age or develop antibodies, more secondary conditions etc, their blood requirements and frequency can increase. Based on our data

	• **Do you agree with this estimate?** • **What is the range you would expect to see in clinical practice?**		and experience, we think 13.7 is a low average and does not represent the majority of the thalassaemia population.
EAG issue 7	**Non-reference discount rate** **According to the NICE manual for a non-reference discount rate to be applicable a set of criteria need to be met. The questions below have been tailored to the criteria.** **Are people with transfusion dependent beta-thalassaemia on current standard care more likely to die or have a very severely impaired life compared with the general population?** • **What is the life-expectancy of people being offered current standard care with this condition?** • **How different is the mortality rate compared with the general population? (for example is 5 times higher a reasonable approximation?)** • **How different is the quality of life of people with this condition?**	Yes	According to data published on the National Haemoglobinopathy Registry (NHR) in 2020, individuals with thalassaemia had an average life expectancy of 45 years old. A retrospective cohort analysis conducted by Jobanputra et al. also found that patients receiving optimal care had an average life expectancy in their 40s. In comparison, the average life expectancy of the general population in the UK in 2020 was 80.90 years old, with women having a mean age of 83 and men 79.3 (Office of National Statistics; National Life tables-life expectancy in the UK 2018-2020). Therefore, the average life expectancy of someone with thalassaemia in the UK, even with optimal treatment, is significantly lower than that of the general population. It is important to acknowledge that there are differences in life expectancy among different ethnicities living with thalassaemia. The available data from the NHR and Jobanputra et al (2020) study primarily represent individuals from Mediterranean backgrounds rather than those from Asian and South Asian backgrounds. In the UK, individuals from Asian backgrounds have been observed to have a lower life expectancy rates than those from the Mediterranean. People with TDT may experience various challenges that can severely impact their quality of life. The need for regular blood transfusions and associated medical procedures can be physically demanding and time-consuming on a daily basis. This can lead to fatigue, pain, and limitations in daily and 'normal' activities which their peers without thalassaemia do not have/ experience. Additionally, individuals with TDT may require

	Is treatment with exa-cel likely to restore people with the condition to full or near-full health: • **Does this condition already cause permanent damage from pre-existing complications (for example cardiac or liver complications) that cannot be reversed by exa-cel treatment?** • **If yes, what proportion of people are likely to experience this?** **The benefits of exa-cel are likely to be sustained over a very long period.** • **Do you expect the benefits of exa-cel observed during a maximum of 42 months of follow-up to be sustained over time?** • **If no, why not?**		ongoing medication management and close monitoring of their health, which can add to the burden of the condition. With regards to anaemia, individuals living with a moderate to severe form of thalassaemia exist on a significantly lower haemoglobin level than that of the general population. As a result of this, individuals can often report symptoms of anaemia such as fatigue, headaches, lethargy, tachycardia, however, they can also experience a lack of concentration, reduction in cognitive abilities, mood disturbances experience moderate to severe bone pain as a result of ineffective haematopoiesis. Living with a chronic illness like TDT can also affect one's quality of life. The emotional stress of managing a lifelong condition, dealing with potential complications, living with daily pain, endocrinopathies issues e.g., delay in puberty, self-esteem and body image issues, and the uncertainty of the future can contribute to anxiety, depression, and decreased overall well-being. Looking at our data from surveys conducted in 2021, we found that individuals with thalassaemia not only had a considerably decreased life expectancy but also health related quality of life due to the impact of treatment, blood transfusions, hospital visits, treatment for iron overload and due to the development of secondary conditions. Most of the secondary conditions observed in thalassaemia is caused by iron overload. If transfusion independence is observed, then we have no doubts that cardiac and hepatic iron overload can be reversed and stop or reduce any disease progression. Individuals with TDT and severe iron overload who were treated with an intensive chelation regime were able to

			clear both organs. However, it must be said that this required 100% adherence which cannot always be sustained for long periods, especially when receiving additional transfusions. Iron overload is the main cause of secondary conditions seen in thalassaemia. However, if a patient achieves transfusion independence, we are confident that they will be able to reverse cardiac and hepatic iron overload and prevent or minimise disease progression. Individuals with TDT who have severe cardiac and hepatic iron overloading have successfully cleared both organs through intensive chelation therapy. It is important to note that this treatment requires strict adherence 100%, which may be challenging to maintain over extended periods, particularly when regular transfusions are needed. Based on successful engagement of HSCT, the majority of patients have remained transfusion independent and with regards to Exa-cel we would expect the results to be sustained over a long period. References United Kingdom Thalassaemia Society – Standards for the Clinical care of Children and Adults with thalassaemia in the UK (4TH Edition), 2023. https://www.gov.uk/government/publications/mortality-insights-bulletin-from-gad-july-2022/mortality-insights-bulletin-july-2022#:~:text=The%20life%20expectancy%20of%20a,the%20birth%20of%20the%20Queen.

			https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2018to2020
EAG issue 9	**Health related quality of life in people who are transfusion dependent** • **Since the condition is inherited/ starts from early childhood. How likely is it that people with this condition get used to the symptoms over time?** • **Do you have any other comments about the quality of life of people living with this condition?**	**Yes**	TDT is a progressive condition and whilst patients may try to make the best of it, it is incredibly challenging to live with. **Anaemia** Individuals living with a moderate to severe form of thalassaemia exist on a significantly lower haemoglobin level than that of the general population. As a result of this, individuals can often report symptoms of anaemia such as fatigue, headaches, lethargy, tachycardia, however, they can also experience a lack of concentration, reduction in cognitive abilities, mood disturbances experience moderate to severe bone pain as a result of ineffective haematopoiesis. It is also common for individuals' thalassaemia to present with gall stones from their 30s often requiring a cholecystectomy and have diseases of the bile duct and the liver resulting in an increase in bilirubin, liver enzymes etc. Patients also experience jaundice resulting in the yellowing of skin and the whites of the eyes which can significantly negatively affect their self-esteem and body image. Due to asplenia, individuals can have a compromised immune system and require daily prophylactic treatment with antibiotics. When an individual has an infection, this can result in an exacerbation of their symptoms and need for a transfusion.

			Often, this necessitates the care and support of a carer or member of their family to help them complete the basic everyday tasks. **Transfusions** Some people may also experience difficulties with aspects of personal care and moving around may be which may be worse during days /weeks before a transfusion. Additionally, there can be an issue with successful cannulation especially if their haemoglobin levels are low, due to vascular depletion). Additionally, as the individual grows older, the scarring of peripheral veins can worsen resulting in multiple attempts by the most experience health care professionals. This can be very distressing for patients as not only can it result in severe pain, it can also cause temporary nerve damage which can affect patient's use of their hands for up to three months each time it occurs. This is extremely painful and significantly impacts on a person's ability to complete everyday tasks and activities. 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 individuals with transfusion dependent thalassaemia can also experience transfusion reactions due to alloimmunisation etc. 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 organ damage. **Iron Chelation** Individuals with transfusion dependent thalassaemia can often be prescribed iron chelating agents to remove excess iron received from increased gastro-intestinal absorption of iron, which is much higher than that in the general population and most likely due to a paradoxical suppression of hepcidin(3). Additionally, excess iron can also be accumulated due to blood transfusions. Whilst treatment options have improved greatly over the year, adherence to iron chelating medication remains a significant challenge within the thalassaemia population affecting every individual at some or most part of their lives. In the UK, there are three chelating agents available which is prescribed according to patient needs. For those on desferrioxamine therapy, this can be used up to seven days a week for an infusion period of 12-24 hours depending on iron burden. Often this is done through a subcutaneous infusion self- administer by the patients or their care givers and can be painful especially after repeated needle punctures. The injection sites can often become painful, inflamed, and often results in medication deposits or scarred tissue which has been described as painful bumps under the skin by the patient and care givers. 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.

			Depending on the severity of the iron burden, desferrioxamine can also be administered intravenously with the use of central lines and indwelling peripheral catheters. This, however, can result in thrombosis and line infection leading to sepsis. Desferrioxamine also can cause side effects such as skin irritation, audiologic and ophthalmologic disturbances, toxicity etc. 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 can hinders their 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. Individuals with thalassaemia are also required 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. Individuals with thalassaemia can also develop a myriad of secondary conditions related to iron overload obtained during regular blood transfusions and from absorption from the gastrointestinal tract. As iron is not excreted or used to produce haemoglobin, it can deposit in vital organs of the body leading to people with thalassaemia developing multiple organ failure and other secondary conditions which can impact on daily life[(2)]. Some of the secondary conditions are as follows;

			Having to cope with the daily implications of the condition, in addition to acquiring secondary conditions as identified above, can seriously impact an individual's quality of life. The majority of patients with thalassaemia have acquired many secondary conditions. 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- this is particularly noted in cases with men[(4)]. As puberty is often delayed, people with thalassaemia can look very young in appearance[(4)]. 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 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. The unpredictable nature of thalassaemia means there is an inability to predict and plan for the future. Difficulties with aspects of personal care and moving around may be worse during days / weeks before transfusion. Patients can suffer from extreme fatigue, exhaustion, breathlessness, palpitations, bone pain (due to the bone marrow going into overdrive), headaches, lack of concentration, cognition disturbances, low mood, anxiety, depression and insomnia. Patient lives can be disrupted by becoming unwell due to infections or inflammatory flares which can last for days, weeks or months. Overall, this can negatively impact an individual's chance of having an independent life and can also affect educational, employment and social opportunities.

			Thalassaemia is a life-long genetic condition that can vary on a day-to-day basis and over time it will continue to cause patients' health to deteriorate more rapidly than their healthy peers. When an individual has an infection or becomes anaemic, it can result in an exacerbation of their symptoms, causing everyday tasks to be become extremely complex and challenging. Often, this necessitates the care and support of a carer or member of their family to help them complete basic tasks. Patients can often become bedbound until their symptoms resolve. Some of the daily challenges people with thalassaemia can have are: 1. Managing of daily medication 2. Attend and cope with daily treatment- iron chelation (oral subcutaneous (over 12-24 hours) or intravenous (over 12-24 hours) and others depending on patients' specific comorbidities identified. 3. Preparing Food 4. Food shopping 5. Household chores 6. Washing and bathing 7. Dressing and undressing 8. Standing for a prolonged period of time 9. Walking/Moving around/ ability to climb stairs The treatment burden of daily medications combined with symptoms of bone and neuropathic pain can cause the individual to become fatigued on a daily basis. The logistical challenges and pressure of individuals to be responsible for and maintain their own extensive and complex treatment routine directly impacts quality of life. Individuals may be required to self-administer intravenous or subcutaneous iron chelation treatments at home and monitor their own condition.

			The nature of thalassaemia care and treatment has significant logistical and financial implications that include a heavy burden of travel to specialist regional centres or clinics, as well as difficulties finding insurance cover for travel and critical illness. Stress, anxiety, low self-esteem, feelings of isolation and depression are all elements of an individual's condition that must be monitored and managed. **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. The birth of a child is a life changing event but receiving a diagnosis of a lifelong 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 loved 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 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.
EAG issue 12-14	**Would the introduction of exa-cel have any impact on health inequalities? If so, how?**	**Yes/No**	**Please provide your response to this key issue, including any new evidence, data or analyses**

	Economic modelling specific issues **(Focus of issues are less clinical and more methodological/conceptual please refer to section 1 of EAR to more details)**		Apart from HSCT for those with a matched donor, there are no other funded curative options available to people with thalassaemia who do not have a match and are older than age 17. Having access to a successful curative option like exa-cel for a population who have historically and continues to suffer from severe health inequalities due to racial discrimination and lack of funding directed to services, treatment options and facilities, when compared to those living with cystic fibrosis or cancers will positively affect our community. Additionally, gene therapies are offered in other parts of the world where people can afford to pay for it. This puts the UK patients at a disadvantage as our patients will not be able to afford this option and as such creates a bigger health inequality which increases the socioeconomic gap.
EAG issue 11	**Using eMIT costs instead of national tariff**	**Yes/No**	**Please provide your response to this key issue, including any new evidence, data or analyses**
	Other issues that need clinical expert opinion:		
	Baseline osteoporosis and diabetes complication rates: **Do you agree with the following statement:** • **The pathogenesis of beta-thalassaemia-related osteoporosis is not well understood but it is theorised to be a result of many factors such as inherent genetic factors,**	**Yes**	Yes, we agree with the statement. Osteoporosis occurs as a result of various factors, including bone marrow expansion caused by ineffective erythropoiesis. This expansion leads to a decrease in trabecular bone tissue alongside cortical thinning (Bhardwaj, Swe, Sinha, 2023). Additionally, iron overload can contribute to endocrine dysfunction, which in turn increases bone turnover and poses a higher risk of fractures due to low bone mineral density (Tsartsalis et al, 2018).

	ineffective erythropoiesis, high iron levels, and low levels of vitamin D. Exa-cel treatment may impact some of these factors. **Do you expect exa-cel treatment would reverse osteoporosis symptoms or complications?**		Diabetes and other endocrinopathies are also severely influenced by iron overload caused by blood transfusions required as a result due to ineffective erythropoiesis. The use of Exa-cel treatment is expected to halt the advancement and occurrence of these complications, as it corrects ineffective erythropoiesis and discontinues transfusions, thereby ending iron overload. **References** Bhardwaj, A., Swe, K. M. M., & Sinha, N. K. (2023). Treatment for osteoporosis in people with beta-thalassaemia. *The Cochrane database of systematic reviews*, *5*(5), CD010429. https://doi.org/10.1002/14651858.CD010429.pub3 Tsartsalis, A. N., Lambrou, G. I., Tsartsalis, D., Savvidis, C., Karantza, M., Terpos, E., Kanaka-Gantenbein, C., Chrousos, G. P., & Kattamis, A. (2018). The role of biphosphonates in the management of thalassemia-induced osteoporosis: a systematic review and meta-analysis. *Hormones (Athens, Greece)*, *17*(2), 153–166.
	Risk of initial graft failure: **The CLIMB THAL-111 trial showed there were no engraftment rejections (failures). But 6.9% initial engraftment failure have been reported in haematopoietic stem cell transplant.** • **Is it reasonable to assume 100% initial engraftment success in clinical practice?**	**Yes**	With regards to HSCT, rejection typically occurs because the recipient's immune system recognises the transplanted cells as foreign and launches an immune response against them. As such the transplanted stem cells are unable to establish and repopulate the recipient's bone marrow leading to engraftment failures.

	• **If not, what is the range of initial engraftment failures seen in clinical practice?**		Treatment with exa-cel differs as it offers the potential to modify the patient's own cells, eliminating the need for donor matching and ultimately the risk of rejection as it utilises the patient's own cells. Exa-cel also offers a targeted approach to correct the genetic material where as HSCT involves replacing the patient's entire immune system with that of a donor- which also has it's own risks and complications.
	Iron normalisation period: **How long does it take for people with transfusion-independent beta-thalassaemia to achieve normalised iron levels in all organ systems:** • **Four years (company assumption)** • **Five years (EAG assumption)** • **Other?**	**Yes**	We think that it would take approximately 2-3 years to achieve normalisation of iron levels. When patients no longer require transfusions, their bodies can effectively utilise iron to produce healthy haemoglobin, leading to a gradual reduction in iron stores over time. In such cases, chelation therapy is typically provided for a limited duration, and if the haemoglobin levels allow, venesections have been employed to rapidly remove excess iron. We think 4-5 years is an overestimation.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: **The use of EQ5D for gathering HRQol data in thalassaemia**	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	We do not think it is appropriate to use the EQ5D to measure HRQol data in TDT. The EQ5D instrument is a generic tool that does not include condition specific information. As a consequence of this, the true impact of the role thalassaemia has on the daily life of a person, life expectancy (and the differences noted between various ethnicities), and their carers are not taken into consideration. Previous to 2022, accurate databases and records of causes of death, incidence and age of developing secondary conditions etc were not well documented or recorded due to no commissioning arrangement in place.
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

Single Technology Appraisal (STA)

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

EAG addendum: Review of company's response to technical engagement

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Nyanar Jasmine Deng, Research Fellow, CRD, University of York Mark Corbett, Research Fellow, CRD, University of York Eleonora Uphoff, Research Fellow, CRD, University of York Joseph Lord, Research Fellow, CRD, University of York Helen Fulbright, Information Specialist, CRD, University of York Susan Griffin, Professor of Health Economics, CHE, University of York Claire Rothery, Professor of Health Economics, CHE, University of York Robert Hodgson, Senior Research Fellow, CRD, University of York
Correspondence to	Robert Hodgson, Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD
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None

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all depersonalised data (DPD) are highlighted in pink and underlined.

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Overview

This addendum to the External Assessment Report (EAR) report presents the External Assessment Group's (EAG) critique of the additional evidence provided by the company in their response to a number of key issues that were raised by the EAG in its report, which were discussed at technical engagement (TE).

The TE covered 15 key issues for consideration plus a further 8 additional issues. The company's response to technical engagement indicated that they accepted EAG preferences regards issues 10, 11,18 and 22. The company has also adopted EAG preferred assumptions in their base case in response to issue 20 but this issue remains contested. In response to issue 23 the company has presented additional scenario analysis which the EAG has accepted. A summary of the issues the EAG considers to be resolved, partly resolved or unresolved is provided in Table 1.

Table 1: Summary of the key issues

#	Issue	Resolved?
1	Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile	No
2	Definition of transfusion independence	No
3	Uncertain relationship between transfusion status and final outcomes	No
4	Modelling approach and how mortality risks are attributed to modelled patients	No
5	Omission of withdrawals from exa-cel treatment in the economic analysis	No
6	Frequency of red blood cell transfusions	No
7	Non-reference discount rate	No

8	Mortality in transfusion dependent patients and associated with complications	No
9	HRQoL in transfusion dependent patients	No
10	Additive vs multiplicative age adjustment of utilities	Yes
11	EMIT costs	Yes
12	Reweighting of QALY benefits and costs through the use of a non-reference case distributional cost-effectiveness analysis	No
13	Approach to distributional cost-effectiveness analysis	No
14	Input parameter used in the distributional cost-effectiveness analysis	Partly
15	Discounting, Severity modifier and DCEA	Partly
Additional issues		
16	Source used for baseline iron levels	No
17	Population weight used to inform cost of iron chelation agents	No
18	Baseline osteoporosis and diabetes complication rates	Yes
19	Risk of initial graft failure	No
20	Iron normalisation period	Partly
21	Ongoing risks of complications	No
22	Uncertainty in complication and infertility utility decrements	Yes
23	Underestimation of health state costs in exa-cel arm	Yes

Description and critique of additional evidence

Issue 1: Uncertainty about exa-cel's long-term efficacy (permanence of transfusion independence) and long-term safety profile

The company re-iterated its position that there is no uncertainty in the permanence of transfusion independence status. The company considers the reversion rate to be 0% because there is no known mechanism by which an edited haematopoietic stem cell could convert back to a wild-type sequence.

The EAG's response

Although the EAG's base case assumption is for a permanent treatment effect in all patients who achieve TI12, the EAG considers this assumption uncertain. As outlined in the EAR, while there are no recorded events of loss of transfusion independence, follow-up remains short. Consequently, there is insufficient trial evidence to support this assumption. Further,

the EAG highlights that the proportion of modified cells in the bone marrow and peripheral blood is not 100% and all patients still have some residual host cells present (see Figures 18 and 19 of the CS). The EAG accepts that in most cases the proportion of residual host cells is likely to remain persistent and stable, with patients remaining transfusion independent. However, uncertainty remains as to whether this is true for all patients. Given this uncertainty the EAG considers it reasonable and appropriate to consider alternatives to a 0% reversion rate.

Issue 2: Definition of transfusion independence

The company maintains its preference for using a post-hoc definition of transfusion independence (TI) in the economic model. Under this definition, TI is defined as those patients who are transfusion-free starting 60 days after the last RBC transfusion for post-transplant support or disease management. The use of this definition would mean all 42 patients achieve TI, rather than 39/42. For the three patients that have not achieved TI12 the company stated that, based on the latest D120 data cut-off, they have been transfusion-free for 10.3 months, 7.0 months, and 2.8 months, respectively (starting 60 days after the last RBC transfusion).

The EAG's response

The company's preferred definition of TI is significantly easier to achieve compared to the pre-defined primary TI outcome reported in CLIMB THAL-111. Not only is the company's modelled definition of TI much shorter than the trial definition, but it also excludes the requirement for maintaining a minimum haemoglobin level. The graph in the company's TE response clearly shows that the three patients who have not reached TI12 responded differently to the TI12 patients, and it is not (yet) understood why. Using an outcome where everyone is classed as TI ignores this important finding; the modelled transfusion reduced health state is more appropriate for the three non-TI12 patients described in the company's TE response.

The EAG reiterates its preference for using the pre-defined definition of transfusion independence used in the CLIMB THAL-111 trial. The EAG notes though that further follow-up will resolve the uncertainty about whether these three patients will reach TI12, given that TI12 in CLIMB THAL-111 was defined as maintaining a weighted average Hb ≥9 g/dL without red blood cell transfusions for at least 12 consecutive months ***any*** time after exa-cel infusion.

Issue 3: Uncertain relationship between transfusion status and final outcomes

The CLIMB THAL-111 trial reports only intermediate outcomes, most importantly transfusion status. Within the company's (original and revised) economic analysis, transfusion status is linked to final outcomes to model improvements in HRQL and survival. The EAR outlines two points of critique regarding this approach. Firstly, the surrogate relationship between transfusion status and final outcomes has not been fully substantiated. Secondly, the reliance on surrogate relationships within the company model represents an important area of uncertainty, which may impact the preferred modelling approach.

The company response states that there is a substantial body of published evidence on the relationship between iron levels and comorbidities, which was provided by the company as part of its submission. The company's response also highlights that it is widely accepted and irrefutable that TDT is associated with (iron overload-related) comorbidities and considers the removal of these in the EAG revised model is clinically unrealistic because it does fully capture the costs, health-related quality of life (HRQoL) and mortality associated with TDT.

The EAG's response

The company's response does not address either point raised in EAR and appears to misunderstand the EAG's critique. To clarify, the EAG does not dispute that there is a relationship between iron levels and complication onset, nor does the EAG dispute that TDT is associated with iron overload-related complications. The EAG's concerns, as outlined in the EAR, highlight that modelled intermediate and final outcomes, including survival, onset of complications and HRQL improvements are not informed by direct evidence from the trial. Instead, the model relies on a series of assumptions which imply that transfusion independence will positively impact these outcomes. The established relationship between iron levels and complications provides evidence to support the clinical plausibility of such relationships but alone does not substantiate them. At a minimum, validation of transfusion status as a surrogate outcome requires evidence of an association between transfusion status and the outcome under consideration. The company has not provided any such evidence. Nor has it provided any evidence that changes in transfusion status are associated with commensurate changes in final outcomes. The latter would provide the strongest evidence to support a surrogate relationship.

The EAG considers this omission important, not only because it is a requirement of the NICE methods guide but also because it necessarily means that inferred survival and HRQL benefits are subject to significant uncertainty. The uncertainty in these relationships is directly relevant to the second point raised in the EAR, i.e. the modelling approach. The company's model, as presented in the original CS and revised in the TE response, relies on multiple complex chains of evidence to link transfusion status to final outcomes. These chains rely on limited evidence and are subject to very significant uncertainty. For example, see Section 4.2.6.4 of the EAR, which discusses the complexities of modelling the relationship between iron levels and complication onset. Moreover, any model dependent on accurately modelling these relationships necessarily increases model complexity and reduces transparency. These issues represent disadvantages compared to more abstract model structures (such as the revised model structure put forward by the EAG). For clarity, the EAG emphasises that modelling approaches reliant on these relationships are not necessarily inferior to alternatives that don't. However, it is important to consider these limitations when considering the most appropriate modelling approach.

Issue 4: Modelling approach and how mortality risks are attributed to modelled patients

The EAR raised significant concerns about the model structure adopted by the company and outlined several alternative model structures which could be implemented to address the identified issues. These included redesigning the model as a patient simulation model or reducing the complexity of the presented Markov model by either modelling a single iron overload-related complication or no complications. The last of these options was implemented in the EAG as it was the only option that could be implemented within the resource constraints of the appraisal process.

The company's response recognises the limitations of the original model but rejects the EAG revised model. The company response argues that the Markov model is an appropriate modelling approach and highlights advice received by the NICE via the Early Scientific Advice programme, which suggested that a patient simulation model approach would be overly complex and unnecessary to address the decision problem. The company also emphasise the importance of fully capturing the quality-of-life benefits and costs associated with iron overload-related complications. Consequently, the company puts forward an

alternative model structure. This revised model removes complication-related mortality but retains previous assumptions whereby iron levels are linked to complication onset.

The EAG's response

The revised model only partially addresses the concerns outlined in the EAR. The removal of complication specific mortality improves face validity and addresses the overestimation of excess mortality associated with TDT. Other concerns, however, remain unaddressed. The revised model continues to apply a common mortality rate to all patients regardless of complications status. This means that the model over-accumulates patients with complications in both arms. Further, the model continues to assume a static and unchanging distribution of iron levels throughout the model time horizon, i.e. the same proportion of alive patients have low cardiac iron levels in cycle one as they do at the end of the model time horizon. This lacks face validity and misrepresents the impacts of iron overload-related complications.

The EAG recognises that the company has sought advice from the Early Scientific Advice programme, which recommended a Markov structure. The EAG agrees that a Markov model is a possible and reasonable approach. However, a Markov model cannot capture the full complexity of TDT and associated complications. This can only be achieved in a patient simulation model where it is possible to track patient history. The EAR outlines three possible modelling approaches, two of which were Markov models. As explained in the EAR, each alternative has relative strengths and weaknesses that reflect trade-offs between their ability to reflect the full complexity of TDT, uncertainties generated by the limitations of the underlying data, and model complexity.

The company's response outlines specific concerns regarding the EAG's model and emphasises the importance of fully capturing the impact of complications on HRQL and NHS resource use. The EAG does not consider this unreasonable, but this cannot be implemented in a Markov model without recourse to assumptions that undermine the credibility of the model. The choice of model should consider the advantages and disadvantages of alternatives. Further decisions about cost-effectiveness should reflect on the limitations associated with the adopted model, whether that be a Markov model or a patient simulation model.

Issue 5: Omission of withdrawals from exa-cel treatment in the economic analysis

[redacted]

The EAG's response

[redacted]

2.1 Issue 6: Frequency of red blood cell transfusions

The company's response maintains that CLIMB THAL-111 is the most appropriate source for transfusion frequency data, reasoning that more severely affected patients requiring more transfusions are more inclined to choose gene therapy as a treatment option. The company also argues that CLIMB THAL-111 is more generalisable to the population eligible for exa-cel, reasoning that the age profile of patients in Shah et al.[1] implies a higher proportion of milder genotypes. The company further states that the proposed managed access agreement will provide an opportunity to validate this assumption through data on patients treated in UK clinical practice.

The EAG's response

The EAG considers the arguments put forward predominantly speculative, and there remains uncertainty regarding whether the CLIMB THAL-111 trial is the most appropriate source of evidence to guide the number of transfusions in NHS practice.

Patients in the CLIMB THAL-111 trial were generally more severely affected patients with a higher transfusion burden at baseline compared to the Shah et al. (UK Chart review) cohort. However, it remains uncertain whether disease severity is the key determinant influencing a patient's decision to undergo treatment with exa-cel. The inclusion of older patients may

impact on patient genotype. However, this is similarly speculative as genotype is not reported in the Chart Review.

As outlined in the EAR the primary justification for utilising CLIMB THAL-111 is internally consistent with the modelled population. The EAG, however, maintains its preference for the Chart Review as it reflects UK population, making it more representative of UK transfusion frequency. Moreover, the model draws on the Chart Review to characterise UK standard of care more generally.

1.1 Issue 7: Non-reference discount rate

Consistent with CS, the company maintains that the criteria for the non-reference case 1.5% discount rate are satisfied and should apply to this appraisal. Reflecting the EAG concerns that the first criterion requiring exa-cel would restore people who would otherwise die or have a very severely impaired life to full or near full health, the company's TE response focuses on this criterion.

The company reiterates arguments that TDT patients, without treatment, would die decades earlier than members of the general population and satisfies the requirement that patients would otherwise die without treatment.

The company restates the findings of their BoI study[2], which reported a mean age of death of 55 years, and a mortality rate 5 times higher than the general population. The company states that the mortality rate is higher for those indexed between 2014 – 2018 and for those <18 years who have a rate [redacted] that of matched controls. The company argues that this provides evidence against the EAG's argument that this data is representative of an older cohort that has not benefited from recent therapeutic advances (i.e., younger, and more recently indexed patients still suffer significant excess mortality). The company also cite other studies that have found a higher mortality burden – suggesting that the BoI study may underestimate mortality. They also present studies that have examined the evolution of mortality over time. The company restate their view that the BoI study is generalisable to current UK clinical practice.

The company also describe the burden associated with iron overload-related complications and the burden of frequent and ongoing blood transfusions necessary to control TDT symptoms. The company cite the Anthony Nolan submission considered as part of this process that states that each transfusion can take 3-4 hours and patients may have to come into the clinic 1-2 days in advance for pre-transfusion blood testing meaning that time-off is

likely to be required from school or work for the patient to manage their condition. The company also cite evidence from the latest UKTS *standards*[3], which states that 85% of surveyed individuals with TDT have an impaired quality of life.

The company further argues that exa-cel would restore patients to *full or near-full health*. They describe how patients with severe cardiac damage or severe liver disease will not be eligible for treatment. As a result, given that these patients have an ongoing excess risk of developing these complications from iron overload, treatment with Exa-cel would remove this risk and thus return the patient to "full health". For other complications including iron-related endocrinopathies that a patient may have at the point of Exa-cel treatment (e.g., diabetes), the company describe how although these will not be reversible following treatment, the risk of worsening of these conditions is removed.

The company concludes that there is a substantial impact of TDT on both patients' life expectancy and quality of life.

The EAG's response

The company's response includes no new evidence to support applying a non-reference case discount rate. As outlined in the EAR, the EAG contests the company's interpretation of the evidence on both life-expectancy and HRQL.

While the company describes the BoI study as contemporary evidence on life expectancy, this misrepresents the population included in this study. The cited BoI study includes older patient groups and represents an unrestricted TDT population. Importantly, it does not reflect the impact of recent therapeutic advances, clinical practice regarding the use of iron chelation agents has evolved significantly in the last 20 years due to improvements in evidence, availability of oral ICT and increased confidence around the combination ICT. Further, the cited mean age of death (55 years) is based on the restricted mean and does not account for unobserved deaths. This will naturally tend to bias estimates of the mean downwards.

The EAG also refers to the 2016 UKTS *standards*[4] (although we accept does not appear in the latest edition of the standards) which states "*In the UK we now have a cohort of beta thalassaemia major patients who are approaching their sixties*", and "*children born in the UK today with thalassaemia are expected to survive to adult life in good health, to lead essentially normal or near normal lives in respect of career and family; and to live a normal or near normal lifespan*". Similarly, the NHS website[5] states that "*with current treatments, people are likely to live into their 50s, 60s and beyond*", although the EAG accepts that non-

compliance with chelation therapy may result in patients not attaining the outcomes described above.

It remains the EAG's position that the mortality outcomes of a contemporary cohort of patients with TDT is substantively longer than suggested by the BoI study. Furthermore, even if we accept the company's preferred mortality assumptions, standard of care patients are, on average, modelled to live to 65 years old (44 years from the start of the model). This is simply incongruous with the notion that patients "*would otherwise die"*, in the absence of treatment.

With respect to the quality of life of TDT patients, the EAG acknowledges the burden of disease in this patient group and recognises that many patients with TDT may have reduced quality of life. However, the criteria for the non-reference case discount rate require that patients have very severely impaired life". The EAG considers this to represent a high bar that would only be met by the most severe conditions. Evidence from CLIMB-THAL-111 suggests EQ-5D scores are close to the general population and this is further supported by evidence from the published literature which indicates that TDT is associated with only a modest decrement in health-related quality of life and does not result in a "very severely impaired life" from the perspective of the patient.

1.2 Issue 8: Mortality in transfusion dependent patients and associated with complications

As described under issue 7, the company's revised base case removes complication-specific mortality rates and updates the SMR applied to patients in the transfusion-dependent and transfusion-reduced health states. In the transfusion-dependent health state the SMR is increased from 3.45 to 5. The updated SMR of 5 was informed by evidence from the BoI study. The SMR applied to transfusion-reduced patients remains halfway between that of the transfusion-dependent and transfusion-independent patients and was updated from 2.35 to 3.13. No changes were made to the SMR applied in the transfusion-independent health state. Complications arising in patients who are transfusion-independent are therefore assumed not to be associated with increased mortality.

The EAG's response

As discussed in response to issue 7 the EAG does not consider the excess mortality observed in the BoI study to necessarily reflect current practice and such may overestimate mortality risks in the current cohort of patients. The EAG also highlights committee preferences in the

betibeglogene appraisal [ID968][6]. In ID968, the committee accepted an SMR of 2. However, this SMR excluded mortality related to cardiac complications. Consequently, the External Advisory Group (EAG) increased the SMR applied in its preferred analysis to 2.5. Acknowledging the lack of evidence supporting this value and the uncertainty in this parameter, the EAG has presented an additional scenario considering an SMR of 3.5. This value represents a midpoint between the company's preferred SMR and the committee's previously preferred assumptions.

The EAG additional highlights that neither the company's revised model nor the EAG's preferred model reflects excess complication-related mortality in transfusion-independent patients. The proportion of patients experiencing iron-overload-related complications within this group is likely to be smaller than in transfusion-dependent patients, but there likely remains a non-zero risk that will contribute to excess mortality. The revised company and EAG models may, therefore, underestimate mortality in the exa-cel arm of the model.

1.3 Issue 9: HRQoL in transfusion dependent patients

The EAG's original concern related to the company's use of vignette data to inform health state utilities in the model. This was despite the identification of utility data from the literature and the collection of EQ-5D data as part of the CLIMB-THAL trials. The EAG considered that this approach was not in line with the NICE reference case and instead explored scenarios with decrement values for the TD state of [redacted] (based on utility decrement for the trial population at baseline relative to the general population – D120 data), 0.1, and 0.15 (based on preferred assumptions from the betibeglogene appraisal [ID968])[6] where a decrement of "*about 0.1*" was preferred.

In their response at TE, the company reiterated their argument that EQ-5D does not adequately capture the burden of the disease – specifically, that the EQ-5D does not capture the fluctuating nature of symptoms and is potentially missing a fatigue dimension. The company also reiterate their argument that as a chronic condition that patients have experienced from birth, patients experience adaption and ceiling effects meaning that EQ-5D data are artificially high. The company also argue that the utility decrement applied by the EAG of [redacted] is lower than that applied in the betibeglogene appraisal ("*about 0.1*").

In support of their argument that the EQ-5D data collected as part of the trial was unsuitable, the company presents data from the CLIMBG-THAL trial. They describe how over [redacted] of patients in the FAS and over [redacted] of patients in the PES reported an EQ-5D value of 1 (indicating perfect health), at baseline. The company argue that this data lacks face validity

where despite being in "perfect health", these patients are willing to undertake an experimental treatment. In addition, they argue that the [redacted] increase in utility gained at 24 months in the PES population is driven only by those patients who are able to experience an improvement. As a result, the company conclude that the most robust source of utility data for use in the model is the vignette data reported by Matza et al.[7]

The EAG's response

As described in the EAR, the EAG considers that the approach taken by the company is inconsistent with the NICE reference case which states a preference for the use of EQ-5D for the measurement of HRQoL. The EAG notes that the NICE methods manual describes the evidential requirements if a case is to be made that the EQ-5D is inappropriate. The EAG considers that the company has not met these evidential requirements or otherwise made a compelling case to reject the use of EQ-5D. As outlined in the EAR, evidence based on a synthesis of peer-reviewed literature (as required by the NICE methods guidance) was not presented, with the company instead relying on a mixed-methods study which the EAG considered to have unclear methodology.

Concerning the company's arguments regarding fluctuating symptoms and a missing fatigue dimension, the EAG would argue that these are features of many other chronic conditions and not sufficient evidence to reject the appropriateness of EQ-5D. The EAG similarly rejects the company's argument that a population with high baseline EQ-5D values would not elect to undergo experimental treatment and associated risks. Decisions to undergo treatment are likely to reflect not only a patient's current quality of life but also their future quality of life.

It remains the EAG's position that EQ-5D data should be used to inform the modelled value set and a decrement should be applied for TD patients based on the EAG's preferred value of [redacted] (D120 data cut).

Issue 10: Multiplicative age adjustment

The company updated their case to use a multiplicative method of age adjustment, as advised in NICE DSU guidance[8] and the preferred approach in the NICE methods guide.[9]

The EAG's response

The EAG confirms that the company has implemented this appropriately in their updated economic analysis and considers this matter to be resolved.

Issue 11: Use of eMIT costs

Following post-clarification discussions with NICE, the EAG were advised to apply eMIT costs for all for iron chelation agents. The company has revised its updated base-case in alignment.

The EAG's response

The EAG confirms that the company has implemented this appropriately in their updated economic analysis and considers this matter to be resolved.

1.4 Issue 12: Reweighting of QALY benefits and costs through the use of a non-reference case distributional cost-effectiveness analysis

The company re-iterate the same arguments presented in the company submission to support the use of DCEA. The company reference principle 9 of the NICE charter, which refers to an aim to reduce health inequalities. The company response highlights that a DCEA allows them to provide quantitative evidence metrics for the impact on health inequalities via the slope index of inequality.

The EAG's response

The company response to issue 12 does not address the issue of reweighting of QALY benefits and costs as raised by the EAG. The EAG acknowledges that the application DCEA methods does provide unweighted quantitative information on the distribution of incremental net health benefits and the potential for the use of exa-cel to alter inequality in quality adjusted life expectancy via the slope index of inequality. However, the EAG must re-iterate that the distributions and health inequality examined in the DCEA undertaken by the company examines inequality by area level. Furthermore, the EAG maintain that the application of any weighting (i.e. as with the equity-weighted ICER presented by the company) requires a clear position statement from NICE and suitable reference case guidance.

1.5 Issue 13: Approach to distributional cost-effectiveness analysis

The company re-iterate their proposal that socio-economic deprivation is an adequate proxy for ethnicity. The company state that their external expert consultation supports this assessment, but do not provide further detail nor any analysis or supporting references for how adequacy was assessed.

The company state that their estimation of an equity-weighted ICER that is not part of standard DCEA methodology was informed by consultation with an expert.

The company state that their non-standard approach maintains the same ordinal ranking of alternatives as the standard approach.

The EAG's response

The EAG considers that presence of some association between two categorical variables is insufficient to assess whether one is a suitable proxy for the other. The EAG, under issue 12, highlighted that there is no need to use a proxy measure as ethnicity is measured directly. Hence the EAG suggested the alternative approach that the company could have applied DCEA methodology to estimate the distribution of net health benefits by ethnicity.

The EAG maintain that estimation of reweighted costs and health benefits in the form of an equity-weighted ICER requires a clear position statement from NICE and suitable reference case guidance. The EAG notes that the company response does not provide any further information or justification for departing from the standard way of presenting the results of a DCEA.

1.6 Issue 14: Input parameter used in the distributional cost-effectiveness analysis

The company states that they have aligned their base case with the EAG proposed inputs for the DCEA.

The EAG's response

The EAG note that in response to issue 15, the company has made further unnecessary alterations to the DCEA input parameters. The EAG proposed alternative approach under issue 15 was to recalculate the QALY shortfall, and no proposal was made to alter DCEA

inputs. It is unclear why the company have modified the share of the general population in each IMD quintile to reflect the burden of illness study instead of the actual share of the UK general population.

The EAG also note that, upon examining the company model submitted in response to technical engagement, the company has presented the results for an inequality aversion parameter of 11 and has not used the EAG preferred inequality aversion parameter of 3.5.

Issue 15: Discounting, Severity modifier and DCEA

The EAR outlines concerns regarding the appropriateness of applying application of a severity modifier, non-reference discount rate, and DCEA simultaneously. The company response raises several points justifying their approach.

- Firstly, it notes that that: "*The three modifiers applied are described independently in the NICE methods manual, and there is no reason to believe they are mutually exclusive."*
- Secondly, concerning the severity modifier, the company challenges the methodological validity of using discounted QALYs to calculate QALY shortfalls used to assess eligibility for the severity modifier. The company highlights that this approach tends to penalise conditions where quality of life deteriorates over an extended period or where there is a delayed mortality risk. The company further highlights that this approach is also inconsistent with the approach taken in the HST appraisal process which uses undiscounted QALYs.
- Thirdly, while the company acknowledges that the first criterion for the 1.5% discount rate overlaps with the severity modifier but highlights that the other two criteria (relating to curative potential and sustained benefits) are unrelated to the severity modifier. The company further argues that it is likely that the alternative 1.5% discounting rate was intended to be applied to advanced cell and gene therapies where costs are incurred upfront, but benefits are accrued over a longer period.

The EAG's response

The EAG is aware of no precedent in previous appraisals where a committee has considered the severity modifier, non-reference discount rate, and DCEA simultaneously. As discussed in the EAR the NICE methods guide offers no specific guidance on how or whether these

should be considered simultaneously. Indeed, DCEA is a non-reference case analysis that is not described in the NICE methods guide. It is therefore unclear how the simultaneous application of all three factors should be considered. Moreover, there are specific issues with combining all three factors simultaneously.

Regarding the second issue raised by the company, the ERG acknowledges the points raised by the company. However, the methods guide is clear that the 3.5% discount rate should apply to severity modifier shortfall calculations and makes no specific provisions for applying the 1.5% discount rate in circumstances where that is deemed to apply.

The EAG accepts that the second and third criteria listed under the non-reference discount rate are unrelated to disease severity. However, a technology must meet all criteria to qualify and therefore it is clear that the intention was to limit the application of the non-reference discount rate to only very severe conditions. Moreover, while the 1.5% is not strictly a modifier it does imply that health benefits and cost savings are valued relatively more favourably. The simultaneous application of the severity modifier and 1.5% may therefore double-count severity as a factor in decision-making.

Additional issues

Table 2 summarises the company and EAG responses to several additional issues described in the EAR.

Table 2 Response to additional issues

Issue from the EAR	Company Response	EAG response
Additional issue 16: Source used fpr baseline iron levels	The EAG considers the distribution of iron loading, derived from the Chart Review, to be broadly appropriate [1]. However, the EAG state that any apparent relationship in the Chart Review population is likely to be confounded by changes in the management of iron overload complications over time. On the basis described in key issue 7, we reiterate that baseline iron-level data from CLIMB THAL-111 fail to capture the transition of TD patients to higher iron levels over their lifetime and consider these data as unrepresentative of contemporary TDT populations.	The EAG reiterates the points raised in the EAR. There is no specific reason to expect iron levels to vary by age, and the data from the Chart review may be unrepresentative of the population eligible for exa-cel as it includes patients under the age of 12 and over the age of 35. The EAG reemphasises that the changes in the management of iron overload mean that the chart review may not fully reflect lifetime iron levels. The EAG also highlights that the inability of the model to reflect changes in iron overload reflects limitations of the model structure adopted and how iron overload risks are modelled which do fully reflect the complex dynamics observed in the real world, see Section 4.2.6.4 of the EAR for further discussion of this point.
Additional issue 17: Population weight used to inform cost of iron chelation agents	Not addressed in the company's response	Not applicable
Additional issue 18: Baseline osteoporosis and diabetes complication rates	Baseline osteoporosis and diabetes complication rates have updated based on CLIMB THAL-111.	The EAG confirms that the company has implemented this appropriately in their updated economic analysis and considers this matter to be resolved.

Additional issue 19: Risk of initial graft failure	Late mortality effects associated with the transplantation procedure are already captured by an SMR of 1.25 applied to functionally cured patients While it is possible to apply an instantaneous event rate due to busulfan conditioning in the model, this was intended to capture any mortality observed during the CLIMB THAL-111 trial observation period. As no mortality has been observed thus far, we have not included any in the model. Furthermore, late mortality effects associated with the transplantation procedure are already captured by an SMR of 1.25 applied to functionally cured patients, in line with that applied during the beti-cel appraisal (ID968). There are no relevant sources of near-term mortality rate that can be taken from the literature, as we have not been able to identify any evidence for the mortality impact of busulfan monotherapy in the TDT population. The majority of regimens in the literature being utilised within the context of allogeneic stem-cell transplant and comprising combinations of busulfan, cyclophosphamide, fludarabine, treosulfan and anti-thymocyte globulin have low or zero rates of transplant related mortality. It would therefore be impossible to separate out the relative contribution to mortality of busulfan monotherapy within these very different transplantation settings.	The EAG considers the 1.25 SMR applied to be quite separate from the acute mortality risks associated with myeloablative conditioning and does not capture this acute risk. The EAG, however, acknowledges the paucity of evidence to inform this parameter and that no mortality events were observed in the CLIMB THAL-111. In line with the committee recommendations in ID968, the EAG considers it likely that this value is not zero. The scenario provided using a 1.4% rate presented in EAR based on the value applied in the US ICER assessment indicates the potential impact on the ICER.
Additional issue 20: Iron normalisation period	Whilst acknowledging a lack of clear data relating to this issue, our assumption of 4 years is supported by the literature. Aloobacker *et al.* (2021) provide a useful summary of the data, such that it is. They observed a median duration of 47 months (n=149) of iron reduction treatment in patients treated with allo-	The EAG considers the evidence from Aloobacker et al and Angelucci *et al* relevant to understanding time to iron normalisation but disagrees with the company's interpretation of this evidence. The company's model assumes that all patients will achieve iron normalisation by 4 years A median of 47

	SCT between 2001 and 2012. We note that these patients were highly iron overloaded at baseline [10]. Angelucci *et al* looked at 48 patients treated with phlebotomy post-transplant; these patients had a median duration of 35 months (+/- 18months) to iron normalisation [11] In summary – the literature on this shows median rates of 14-17 months, 35 months and 47 months to iron normalisation. The paper with the longest time to iron normalisation still only gives 4 years and in this study patients were very iron loaded. In this context, we propose that 4 years to iron normalisation is a conservative estimate.	months as reported in Aloobacker et al indicates that approximately half of the patients will achieve iron normalisation at 4 years implying that the time for all patients to achieve iron normalisation will be considerably longer. The EAG also re-emphasises that the 5-year iron-normalisation period was based on assumptions accepted in ID 968. Evidence on iron normalisation in patients who achieve transfusion independence following betibeglogene suggests that there remained a number of patients with moderate to high levels at 48 months.
Additional issue 21: Ongoing risk of complications	The EAG state 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. Please see our response to key issue 7, where we describe how the majority of TDT-related complications are secondary to iron overload, and would be reversible following treatment with exa-cel. Based on our response to key issue 7, we re-state our position that exa-cel will restore patients to full or near-full health.	The short follow-up in CLIMB THAL-111 means it is impossible to establish the long-term complication and mortality risk in patients who have received exa-cel. The EAG maintains that the potential for ongoing complications in patients who achieve and maintain transfusion independence may impact overall mortality risks. As indicated the EAR evidence in HSCT patients indicates that very few patients developed a cardiac insufficiency which suggests any increased risk may be small.
Additional issue 22: Uncertainty in complication and infertility utility decrements	The company has removed infertility utility decrements from their base case.	The EAG confirms that the company has implemented this appropriately in their updated economic analysis and considers this matter to be resolved.

Additional issue 23: Removal of health state costs	We accept the EAG's proposal for removing health-state costs on the basis that Shah *et al*. (2021) does not separate out costs related to management of comorbidities already included in the model. Removing these costs altogether does, however, bias against exa-cel as the model will fail to capture other costs associated with TDT that are not explicitly captured by the model. These will include the routine monitoring of patients and their iron levels, as well as hospitalisations for conditions caused by TDT not captured in the model such as infection. Therefore, we have incorporated monitoring costs only via a micro costing approach, which includes blood tests, echocardiogram (echo) and MRI costs. These costs total £107.64 per month and are applied to TD and TR patients, replacing the original health state costs. No costs have been applied to the TI health state, as the model already includes additional monitoring costs over the iron normalisation period. Following iron normalisation, it is anticipated that patients will either no longer incur these monitoring costs, or they will be so infrequent as to have limited impact on the ICER. Frequencies for MRI and echo assessments were based on a weighted average of the frequencies cited in the Shah *et al* appendix (2021) [1]. All other frequencies for monitoring tests were obtained from the UKTS guidelines. All unit costs were obtained from NHS reference costs. Details of the micro	The EAG considers the approach adopted by the company to be reasonable. The EAG has examined the specific resource and unit costs applied and considers that the micro-costing approach adopted is face valid. The EAG is unable to provide a detailed critique of the resource use figures used as it was not able to consult necessary clinical advice. The committee may wish to explore the specific resource use assumptions adopted but notes that the impact on the ICER is small.

	costing have been provided in an Excel spreadsheet [12] .	

Updated modelling assumptions

In response to the issues noted in the EAR, and following the additional analyses undertaken by the company, an updated base-case cost-effectiveness model was presented.

The following EAG-preferred assumptions are incorporated within the company's revised model:

- Issue 10: Multiplicative age-adjustment.
- Issue 11: Use of eMIT costs to inform ICT acquisition costs.

The company also revise several assumptions in response to the additional issues raised by the EAG. The following assumptions were incorporated within the company's revised model:

- Issue 18: Baseline osteoporosis and diabetes complication rates based on CLIMB THAL-111.
- Issue 20: 5-years to iron normalisation.
- Issue 22: Removed infertility-related decrements.
- Issue 23: Revised health state costs based on micro costing approach.

Note that while the company did not accept issue 20 in their TE response, the assumption of 5-years to iron normalisation was included in the updated company base-case.

In addition, the company revised the following assumptions in response to key issues raised by the EAG:

- Issue 4: Set complication specific morality rates to zero. Revised SMR in transfusion dependent health state to 5. Revised SMR in transfusion reduced health state to 3.13.
- Issue 14: Updated the distribution of health opportunity cost shares in the DCEA to more recent estimates.

As outlined in Section 2, the EAG does not consider these changes to fully address the issues raised by the EAG.

Results

The results of the company's revised base-case are presented in Table 3 below. The results indicate that exa-cel is associated with increased costs (cost difference of [redacted]) but

higher accrued QALYs (QALY difference of [redacted]). The company's updated base-case ICER exclusive of severity reweighting is [redacted] per QALY gained. Inclusive of the severity modifier (1.2 multiplier) the ICER is [redacted] per QALY gained.

Table 3 Company updated base-case results (1.5% discount rate)

Technology	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	ICER (1.2 severity modifier)
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years						

The EAG performed additional scenario analyses on the company's updated base-case as presented in Table 4 below.

Table 4 EAG exploratory scenario analyses

Scenario	Technology	Total		Incremental		ICER	Severity weighted at ICER (1.2 multiplier)
		Costs	QALYs	Costs	QALYs		
Company base case	SoC	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Modelling no complications	*SoC*	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Costs and outcomes from exa-cel withdrawal	*SoC*	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Baseline iron levels based on CLIMB THAL-111	*SoC*	[redacted]	[redacted]				
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Frequency of blood	*SoC*	[redacted]	[redacted]				

transfusions based on Shah et al., 2021	*Exa-cel*						
6. 3.5% Discount rate	*SoC*						
	Exa-cel						
7. Align transfusion independence to the TI12 primary outcome in CLIMB THAL-111	*SoC*						
	Exa-cel						
8 (a). Relapse based on published values from Santarone et al. 2022	*SoC*						
	Exa-cel						
8 (b). Relapse based on US ICER report	*SoC*						
	Exa-cel						
10. Iron normalisation in patients with low iron levels	*SoC*						
	Exa-cel						
11 (a). SMR of 2.5 for TD patients	SoC						
	Exa-cel						
11 (b). SMR of 2 for TD patients	SoC						
	Exa-cel						
11 (c). SMR of 3.5 for TD patients	SoC						
	Exa-cel						
12. 1.4% mortality risk for myeloablative conditioning	SoC						
	Exa-cel						
13 (a). [redacted] utility decrement	SoC						
	Exa-cel						

13 (b). 0.1 utility decrement	SoC	[redacted]					
	Exa-cel	[redacted]					
13 (c). 0.15 utility decrement	SoC	[redacted]					
	Exa-cel	[redacted]					

Updated EAG base-case analysis

The EAG's base-case analysis is largely unchanged from that presented in the EAR. The only change relates to the incorporation of the health state costs based on the micro costing approach. The EAG base-case analysis incorporates the following assumptions:

- Scenario 1: No complications.
- Scenario 2: Costs and outcomes from exa-cel withdrawal.
- Scenario 5: Frequency of blood transfusions based on Shah et al., 2021.
- Scenario 6: Using a 3.5% discount rate.
- Scenario 7: Aligning the definition of transfusion independence to the TI12 primary outcome in CLIMB THAL-111.
- Scenario 11: Assuming an SMR of 2.5 for TD patients.
- Scenario 13: HRQoL decrement of [redacted] relative to the general population.

The cumulative impact of the EAG's preferred assumptions on the company's updated base-case both exclusive and inclusive of severity weighting are presented in Table 5 and Table 6.

Table 5 EAG's preferred model assumptions on the company's updated base-case

Preferred assumption	Cumulative ICER £/QALY	Severity weighted ICER (1.2 multiplier)
Company base-case	[redacted]	[redacted]
1. Modelling no complications	[redacted]	[redacted]
2. Costs and outcomes from exa-cel withdrawal	[redacted]	[redacted]
5. Frequency of blood transfusions based on Shah et al., 2021	[redacted]	[redacted]
6. Using a 3.5% discount rate	[redacted]	[redacted]

7. Aligning transfusion independence to the TI12 primary outcome in CLIMB THAL-111	[redacted]	[redacted]
11. Assuming an SMR of 2.5 for TD patients	[redacted]	[redacted]
13. HRQoL decrement of [redacted] relative to the general population	[redacted]	[redacted]

Table 6 EAG preferred base-case on EAG model structure

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Severity weighted ICER (1.2 multiplier)
SoC	[redacted]	[redacted]				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Additional scenario analysis on the EAG's base case

The EAG has conducted additional scenario analyses on the EAG base-case to address uncertainty, as presented in Table 7 below. This includes an analysis adopting the company's preferred model structure. As note in response to issue 4, the EAG does not consider the revisions to the economic model to have addressed the underlying issues with model and does not consider it suitable for decision-making.

Table 7 Results of scenario analyses on the EAG alternative base-case analysis

Scenario	Technology	Total		Incremental		ICER	Severity weighted at ICER (1.2 multiplier)
		Costs	QALYs	Costs	QALYs		
EAG base case	SoC	[redacted]					
	Exa-cel						
Company preferred model stucture	SoC						
	Exa-cel						
1.5% Discount rate	*SoC*						
	Exa-cel						
Relapse based on published values from Santarone et al. 2022	*SoC*						
	Exa-cel						
Relapse based on US ICER report	*SoC*						
	Exa-cel						
SMR of 3.5 for TD patients	SoC						
	Exa-cel						
1.4% mortality risk for myeloablative conditioning	SoC						
	Exa-cel						

DCEA analysis

The company's base-case incorporates an updated distribution of health opportunity cost shares as recommended by the EAG. However, in response to issue 15, the company also updated the general population share distributions by IMD based on a QALE shortfall calculation using data from the Vertex BoI study[2]. As highlighted in the response to issue 14,

issue 15 in the EAR addressed an alternative approach to calculating the QALY shortfall to account for IMD in relation to the severity modifier, not the DCEA inputs.

Additionally, the EAG identified an error in the model that resulted in the QALE shares being sourced from the wrong reference. This has been updated with the EAG preferred DCEA inputs. The results in Table 8 and Table 9 reflect the EAG's maintained preference for a general population share distribution of 0.20 for each IMD group based on ONS data[13], and an aversion parameter value of 3.5 based on more recent estimates from Robson et al., (2023).[14]

Table 8 EAG DCEA exploratory analysis at £20,000

	NHB at £20,000	
Scenarios	**Base case**	**EDE***
Company base-case	[redacted]	[redacted]
EAG preferred DCEA inputs on company base-case	[redacted]	[redacted]
EAG preferred DCEA inputs on EAG base-case	[redacted]	[redacted]
*Where EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality		

Table 9 EAG DCEA exploratory analysis at £30,000

	NHB at £30,000	
Scenarios	**Base case**	**EDE***
Company base-case	[redacted]	[redacted]
EAG preferred DCEA inputs on company base-case	[redacted]	[redacted]
EAG preferred DCEA inputs on EAG base-case on the EAG model structure	[redacted]	[redacted]
*Where EDE NHB is more negative than the unweighted NHB, it implies that health benefits are worth less if equity weighted as it increases inequality		

Severity modifier

The EAG has reproduced the shortfall analysis presented in the EAR for the revised company and EAG base-cases. The QALY shortfall associated with the condition based on the company's model was calculated considering the base case 1.5% discount rate and 3.5% discount rate applied in scenario analysis. The results of the shortfall analysis are presented in Table 1 below. The absolute QALY shortfall associated with the condition was between 12 and 18 when considering a 1.5% discount rate, indicating a severity modifier of 1.2 for the company's base case results. W a 3.5% discount rate was applied (as required by the methods), both the company and EAG base-case result in absolute and proportional QALY shortfalls that fall below the threshold of 12 and 0.85, respectively. This implies that a severity modifier of 1 should be applied.

Table 10 Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs achieved on SoC	Absolute QALY shortfall	Proportional QALY Shortfall
Company base-case (1.5% discount rate)			
34.51	17.81	16.70	48.39%
Company Scenario analysis (3.5% discount rate			
22.51	13.00	9.51	42.25%
EAG base case (3.5% discount rate)			
22.51	19.18	3.33	14.79%

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Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Centre (EAC) report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation

The feasibility assessment indicates whether the Managed Access team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access team.

Topic name: **Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia**
Topic ID: **4015**
Managed Access Lead: **Milena Wobbe**
Date of assessment(s): **08/05/2024**

Is Managed Access appropriate - Overall rating	Comments / Rationale
Committee judgement required	While the committee made a recommendation for managed access, it is unlikely that a period of further data collection could fully resolve all uncertainties. The uncertainties that would likely be resolved are: durability (although late relapsed would not be shown); the rates of complications in people who received exa-cel; the number of people who withdraw during the exa-cel treatment process before treatment is given; and effectiveness in an NHS population could be captured. However, uncertainties remain, mainly: the appropriateness of the 1.5% discount rate and specifically whether people return to full health after treatment with exa-cel; utility values in the exa-cel treatment arm; any potential longer-term relapse rate; life expectancy and mortality rates in the exa-cel population. Furthermore, it is highly unlikely that data on standard of care could be reliably captured. Conversations are ongoing with the company as to what may be feasible and what support for RWE collection could be offered. In the post marketing study, supported by the European Society for Blood and Marrow Transplantation (EBMT) Registry, comparisons are drawn between patients receiving exa-cel and patients receiving allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, this is not the comparative patient population data the committee would like to see to enable better decision making. It is imperative that committee discusses whether it could make a routine recommendation at the end managed access with the proposed data collection; it is unclear whether an overall 7 or 8 years of data would be sufficient to convince committee of lifetime benefits. The company are planning either 3 to 3.5 years of data collection within this period of managed access. Would this truly be sufficient enough to satisfy committee to recommend this exa-cel for routine commissioning, given the important remaining uncertainties that cannot be resolved through managed access?

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	Meets criteria to be a potential candidate for the Innovative Medicines Fund.
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Unclear	Some uncertainties, such as rate of complications of the exa-cel arm and the proportions of treatment withdrawals, can be addressed through further data collection. However, uncertainties relating to comparative data or the longer term treatment durability are unlikely to be resolved through a period of managed access.
Can data collection be completed without undue burden on patients or the NHS system	Yes	The ongoing RWE prospective observational cohort study would collect data from clinical practice, including in England. EBMT is an already established disease register. Clinics are resourced for data collection for EBMT and this is usually part of routine care, so unlikely to add further burden to the system.
Are there any other substantive issues (excluding price) that are a barrier to a MAA	Yes - Minor	While committee are aware of the issues surrounding the economic model, committee members would like to see an improved economic model when the technology is assessed again at the end of a managed access period. Potential equality issues with data collection during managed access. These would be minimised through engagement with patient groups during any managed access.

Further managed access activity	Rating	Comments / Rationale
pre-committee feasibility assessment update	Not applicable	
pre-committee data collection working group	Not applicable	
pre-committee patient involvement meeting	Not applicable	

Key questions for committee if Managed Access is considered	
1	Would committee require further data collection to decide on whether a 1.5% discount rate is appropriate (see DG2 in the uncertainties tab)?
2	Is the economic modelling and analyses provided suitable for making a managed access recommendation?
3	Would 3 or 3.5 years (registry, trial; company proposal) or 5 years (maximum) of managed access sufficiently resolve the key uncertainties to potentially enable a routine recommendation at the currently agreed price, given that some significant uncertainties are likely to remain at the end of a period of managed access?

Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for the managed access.

Date agreed with NHSE	19/04/2024

Is the technology a potential candidate for managed access?	
Rating	**Rationale**
Yes	Exa-cel is considered a promising innovative medicine as it would be expected to lead to significant clinical benefits and would addresses a high unmet need. It is therefore eligible to be considered for the Innovative Medicines Fund.

IMF prioritisation criteria	Supporting Evidence
Potential to address a high unmet need	Untreated transfusion dependent beta-thalassemia is fatal within the first few years of diagnosis if left untreated. Treatment involves regular blood transfusion. The only cure currently is allogeneic stem-cell transplant, which involves significant risk. Exa-cel is a gene therapy using a person's own stem cells, "correcting" them and then putting back into person's body. This is significantly less risky than allogeneic HSCT infusion. The patient population carries a high treatment burden and risk of worse health outcomes than the general population.
Potential to provide significant clinical benefits to patients	Exa-cel is modelled to have substantial clinical benefits, as measured by the quality adjusted life years (QALYs) gained compared with standard of care. Incremental QALYs are commercial in confidence and cannot be reported here
represents a step-change in medicine for patients and clinicians	88.9% of patients in the PES achieved transfusion independence for at least 12 consecutive months. As a gene therapy, exa-cel would be a significant step change in mechanism of action and patient experience.
new evidence could be generated that is meaningful and would sufficiently reduce uncertainty	See uncertainties tab

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
Medium	Some uncertainties that have been highlighted during the committee meeting can be addressed through further data collection. However, it is not clear whether SoC data can be collected, especially in a comparable patient population and with data of sufficient quality. The committee has also requested a new model structure, if at all possible, at the end of managed access. This is unlikely something that depends on further data collection. Furthermore, the company have suggested additional data collection for 3 years (EBMT registry) or 3.5 years (trial data). Questions remain on whether this is sufficient to satisfy the committee that the data collection is long enough.

Key Uncertainties

Issue	Key uncertainty	Company preferred assumption	ERG preferred assumption	Impact on ICER	Data that could sufficiently resolve uncertainty	Proposed primary data source	Likelihood data collection could sufficiently resolve uncertainty	Rationale / Notes
DG1	The durability of the treatment effect of exa-cel (relapse rate)	The company assumes that, once achieved, transfusion independence remains permanent	The EAG does not propose an alternative approach, but does provide 2 alternative scenarios. Uncertainty in long-term effects should be accounted for in decision-making.	Low	Long-term data on rate of thalassemia recurrence following treatment with exa-cel or SCT	CLIMB THAL-111 / CLIMB-131 trial / EBMT registry	Medium	While longer term (up to 5 years) efficacy data could be collected through a period of Managed Access, long-term data on very late relapses (as seen with allogeneic SCT) would not be captured over 5 years, the maximum period for managed access. However, further data collection would give more weight to the current evidence. The committee was satisfied with the clinical experts' joint view that the relapse rate would be low and if durability has been observed for two years post exa-cel treatment, this would likely last.
DG2	Whether people return to full health after exa-cel or whether complications persist	There is uncertainty with regards to surrogate markers of treatment efficacy and what these imply for long-term HRQoL and survival.	Questions company's assumptions	High	Comparative data of complications of individual patients pre- and post exa-cel transfusion	CLIMB THAL-111 trial / CLIMB-131 trial / EBMT registry	Medium	Disease-related end-organ damage/dysfunction as well as disease related therapies are captured in within the EBMT for the post-marketing authorisation study. It is important that this is captured both before and after exa-cel transfusion.

DG3	Utility values for exa cel for the transfusion-dependent and transfusion-reduced health states	The company has suggested a vignette study.	EAG is favouring EQ-5D, as collected in CLIMB THAL-111	Medium	Utility values collected in real world setting	EBMT registry	Low	Collecting utility values in real world is unreliable, with low update and poor data quality. Committee discussion centres around collecting more values in real world setting, rather than focussing on EQ-5D. The EBMT registry through the post-marketing authorisation study is capturing "health status" as an additional key variable. Please note: in the managed access proposal, updated after ACM1, the data source to collect QoL data is still "To be determined"
DG4	The rates of complications for exa-cel				SAEs related to exa-cel, mortality and survival data (with primary and contributory cause of death)	CLIMB-131, EBMT Registry	High	Complications likely possible to be captured for treatment arm. However, it must be noted that these are non-mandatory data fields.
DG5	The number of RBC transfusions per year for standard care	The company base-case uses the CLIMB THAL-111 trial to inform the frequency of RBC transfusions.	The EAG prefers to use the Shah Chart Review to inform the frequency of RBC blood transfusions.	Low	Contemporary UK data on RBC transfusions in TDT patients that would be eligible to receive exa-cel.	EBMT registry	Low	See DG10 for further assessment on collecting SoC data during a period of managed access.
DG6	The number of exa cel treatment withdrawals before the transfusion is given	The company stated that there is a time lag between cell cycle collection to infusion with exa-cel. This represents significant period of time which is not explicitly accounted for in the economic analysis; the model commences at the point of transfusion.	The EAG notes that it is common to utilise a decision tree framework in the modelling of gene-therapies to capture the alternative outcomes of patients who unable or unwilling to proceed to transfusion.	Low	Number of patients in the NHS who are in this position - this should be monitored in EBMT registry how many patients have had their cell cycle collection but no exa-cel infusion. A given time limit should be set after cell cycle collection and any patient who has not had their exa-cel infusion beyond that timeframe could be labelled as a withdrawal.	Vertex Connects™	High	"Vertex Connects™ is a secure order management portal used to facilitate steps throughout the exa-cel order management process for authorised treatment centre (ATC) staff. The system will track all the constituent actions required for each step of the order process following patient identification and evaluation: pre-mobilisation; mobilisation & collection of cells; drug product manufacturing and quality; conditioning, administration and engraftment. Anonymised metrics on pre-infusion patient withdrawals will be available via aggregate summary reports. "
DG7	Mortality and life expectancy for exa-cel	A standard mortality ratio of 3.45 was applied to patients who are transfusion dependent.	A standardised mortality rate of 2 should be used, as per NICE appraisal ID968 betibeglogene	Medium	Further contemporary data on mortality in patients treated with current exa-cel	EBMT registry	Low	In the trial, the upper age limit is 35 years. It is unlikely that an additional data collection of 5 years will completely resolve the uncertainty around mortality/life expectancy of people with TDT who received exa-cel. While date of death is recorded in EBMT, it is unclear whether the patients who have already died are a suitable comparative patient population because they are likely older than those who are due to/have received exa-cel and have also likely been offered different treatment in their lifetime than what is available today.

DG8	Generalisability of trial population (age)	The trial limits its population to ages 12-35	NICE recommendation likely for ages 12+	Unquantified	Data showing similar outcomes for people aged 35+ compared to younger patients	EBMT registry	Medium	The post-authorisation study, in theory, includes patients aged 12 and over with no upper age limit.
DG9	New model structure that more accurately models the interaction with iron levels, complications and mortality	The economic model uses a Markov modelling approach which does not track the outcomes of individual patients. This imposes several structural assumptions which impact significant on model outcomes.	The EAG considers the current model unsuitable for decision-making.	Unquantified	N/A	N/A	No further data collection possible / proposed	The committee urges the company to update their model structure during their time in managed access to accurately model the interactions with iron levels, complications and mortality. The company says that model structure is out of scope for managed access and as such should not be included in any managed access agreement.
DG10	SoC uncertainties: utility values, rates of complications, mortality and life expectancy			Unquantified	Up-to-date SoC arm data that follows patients who are comparable to those who receive exa-cel treatment	Systematic literature review, an extension to a current observational, retrospective UK database study of TDT clinical & economic burden, and most relevant and current evidence at time of managed access finalisation as options under consideration, with the final method(s) to be determined.	Low	Collecting SoC data during a period of managed access creates several issues. Identifying the correct patient population, guaranteeing data quality, resource for EMBMT to collect this data. The post-marketing authorisation study compares exa-cel outcomes with patients having received allo- HSCT, which is not the comparator/SoC committee need. Note that the data source to obtain SoC data in the managed access proposal is currently names as "SLR/single/multi-centre chart review (to be determined)" because Vertex are exploring the feasibility of conducting this literature review or single-/multi-centre chart review to derive data inputs for current SoC in TDT.

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	**Rationale/comments**
High	While the safety and efficacy study completes in 2024, the CLIMB-131 long term safety study would continue to collect relevant data.

CLIMB THAL-111 Clinical trial data	
Anticipated completion date	Aug-24
Link to clinicaltrial.gov	https://clinicaltrials.gov/ct2/show/NCT03655678
Start date	Sep-18
Data cut presented to committee	Sep-22
Link(s) to published data	N/A
Description of trial	This is a single-arm, open-label, multi-site, single-dose Phase 1/2/3 study in subjects with transfusion-dependent β-thalassemia (TDT). The study will evaluate the safety and efficacy of autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (hHSPCs) using CTX001 (exa-cel). n=45. Primary outcome measures are: - Proportion of subjects achieving transfusion independence for at least 12 consecutive months (TI12) - Proportion of subjects with engraftment (first day of 3 consecutive measurements of absolute neutrophil count [ANC] ≥500/µL on three different days) - Time to neutrophil and platelet engraftment - Frequency and severity of collected adverse events (AEs) - Incidence of transplant-related mortality (TRM) - All-cause mortality Secondary outcome measures include the change in HRQoL from baseline.

CLIMB-131 Clinical trial data	
Anticipated completion date	Sep-39
Link to clinicaltrial.gov	https://clinicaltrials.gov/ct2/show/NCT04208529
Start date	Jan-21
Data cut presented to committee	Sep-22
Link(s) to published data	N/A
Description of trial	This is a multi-site, observational study to evaluate the long-term safety and efficacy of CTX001 in subjects who received CTX001 in Study CTX001-111 (NCT03655678) or VX21-CTX001-141 (transfusion-dependent β-thalassemia [TDT] studies) or Study CTX001-121 (NCT03745287) or VX21-CTX001-151 (severe sickle cell disease [SCD] studies; NCT05329649). n=114. Primary outcome measures are: - New malignancies - New or worsening hematologic disorders - All-cause mortality - Serious adverse events (SAEs) occurring up to 5 years after CTX001 infusion - CTX001-related AEs Quality of life data will be collected up to 5 years post CTX001 infusion

Data collected in clinical practice

Is RWE data collection within managed access feasible?	
Overall Rating	**Rationale/comments**
High	The European Society for Blood and Marrow Transplantation (EBMT) registry is supporting Vertex in their post-marketing authorisation study

Data Source	EBMT Registry	
Relevance to managed access		
Existing, adapted, or new data collection	Existing	Further data would be collected through the EBMT
Prior experience with managed access	Low	The EBMT registry has not collected data for managed access previously
Relevance of existing data items	High	The registry is used as part of the post-marketing authorisation study and therefore the data items are extremely relevant, such as neutrophil recovery, mortality (and cause), haemoglobin measures, iron concentration measured, disease-related end-organ damage / dysfunction, and iron overload management.
If required, ease that new data items can be created / modified	Not applicable	
How quickly could the data collection be implemented	Normal timelines	
Data quality		
Population coverage	High	The registry receives data from approximately 80% of European transplant centres
Data completeness	High	
Data accuracy	High	
Data timeliness	Medium	Annual progress reports are planned. It is unclear whether these would be updated when needed for managed access oversight purposes.
Quality assurance processes	Yes	The EBMT has robust quality assurance processes in place.
Data availability lag	Low	The data collected would be made available approximately 12 months after data-cut off.
Data sharing / linkage		
New data sharing arrangements required?	Unclear	TBC - confirmation with company required

New data linkages required?	No	
If yes, has the governance of data sharing been established	Not applicable	
Analyses		
How easily could collected data be incorporated into an economic model	High	
Existing methodology to analyse data	Yes	
If no, is there a clear process to develop the statistical analysis plan	Not applicable	
Existing analytical capacity	High	
Governance		
Lawful basis for data collection	Yes	
Privacy notice & data subject rights	Yes	
Territory of processing	Yes	Data is collected In the UK, France, Germany and Italy
Data protection registration	Yes	
Security assurance	Yes	
Existing relevant ethics/research approvals	Yes	Existing register. Research ethics and governance established as part of existing study protocol
Patient consent	Unclear	All personal data under the responsibility of the EBMT are processed according to the EU GDPR. However, the company have highlighted that lack of patient consent to give access to their data after treatment after exa-cel might be a barrier.
Funding		
Existing funding	Yes	
Additional funding required for MA	No	
If yes, has additional funding been agreed in principle	Not applicable	
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?		Question not applicable. This is a approved research study, rather than service evaluation
Are any of the clinical assessments not validated for use or accepted clinical practice		Question not applicable. This is a approved research study, rather than service evaluation
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation		Question not applicable. This is a approved research study, rather than service evaluation
Additional considerations for managed access		

Are the clinical assessments and data collection comparable to current clinical practice data collection?		Question not applicable. This is a approved research study, rather than service evaluation
Burden		
Additional patient burden	No	
Additional clinical burden	No	According to the company: Patients will be routinely followed up by the transplant centres (as part of the transplant clinic for year 1 and the long-term effects monitoring clinics thereafter). These clinics are resourced for data collection for EBMT and this will be part of their routine care.
Other additional burden	No	

Other issues

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether any issues identified, taken as a whole, are likely to lead to a barrier to a Managed Access Agreement being agreed, or operationalised in the NHS. No assessment is made whether a Commercial Access Agreement is likely to be reached between the company and NHS England, which could be a substantive barrier to managed access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
Yes - Minor	The company highlight patients in England with TDT are disproportionately represented in ethnic minority groups and lower socioeconomic communities which may impact willingness to be part of managed access. In the event of a managed access recommendation the NICE managed access team would proactively engage with patient groups during the managed access period to minimise any barriers to access due to data collection.

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	Low	According to the company: Patients will be routinely followed up by the transplant centres (as part of the transplant clinic for year 1 and the long-term effects monitoring clinics thereafter). These clinics are resourced for data collection for EBMT and this will be part of their routine care.
	Expected overall additional system burden from data collection?	Low	Additional data collection would form part of the approved research protocol.
	Do stakeholders consider any additional burden to be acceptable	Not applicable	
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	Not applicable	

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?	No	The company considers the safety of the treatment to be a key uncertainty to be addressed through managed access Patients must be fit enough to undergo myeloablative conditioning with busulfan
	Is there a clear plan to monitor patient safety within a MA?	Yes	Data collection proposed with EBMT Registry is a mandated post-authorisation safety study (PASS). This will collect SAEs and mortality
	Are additional patient safety monitoring processes required		TBC

		Rating	Rationale / comments
Patient access after MAA	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Yes	Patients will be able to continue treatment once they are on the pathway. Agreement is built into MAA.
	If yes, have NHS England and the company agreed in principle to the exit strategy	Yes	

		Rating	Rationale / comments

Service implementation	Is the technology disruptive to the service	Unclear	Vertex has collaborated with the NHSE specialised commissioning team to put in place service specification for implementing exa-cel treatment. Some centres may lack some experience in thalassemia, due to the small population but work has been done to train staff and get the service ready. Uptake is uncertain.
	Will implementation subject the NHS to irrecoverable costs?	Unclear	
	Is there an existing service specification which will cover the new treatment?	Yes	Vertex has collaborated with the NHSE specialised commissioning team to put in place service specification for implementing exa-cel treatment. All but 1 centre is service ready.

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	
	If yes, are these different to what would be used if the technology had been recommended for routine use?	No	

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes	
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	No	
	Any issues from registry specific questions	No	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes	
	Any issues from registry specific questions	No	

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	Yes	Health inequalities in the affected population is high and not implementing this technology could worsen the inequality. The company highlight patients in England with TDT are disproportionately represented in ethnic minority groups and lower socioeconomic communities which may impact willingness to be part of managed access. In the event of a managed access recommendation the NICE managed access team would proactively engage with patient groups during the managed access period to minimise any barriers to access due to data collection

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Yes	

Position statement on using distributional cost-effectiveness analyses in NICE's technology appraisal and highly specialised technologies programmes

Summary

NICE has a set of principles universal to all its guidance and standards. Principle 9 is 'aim to reduce health inequalities'. It states that NICE guidance should support strategies that improve population health as a whole, while offering particular benefit to the most disadvantaged.

NICE defines health inequalities as 'differences in health across the population, and between different groups in society, that are systematic, unfair and avoidable'. Health inequalities come from a complex interaction between:

- external factors known as the 'wider determinants of health' and
- a person's biological, protected and other individual-level characteristics, which lead to varying health outcomes.

NICE has made a renewed commitment to addressing health inequalities in its 2021 to 2026 strategy.

Within the technology appraisal (TA) and highly specialised technologies (HST) programmes, decisions made by NICE evaluation committees take account of health inequalities as laid out in NICE's health technology evaluations manual, NICE's statutory duties and NICE's principles. The TA and HST evaluation committees have received qualitative information on health inequalities for a small proportion of topics. But the growth of quantitative techniques has shown that more guidance is needed on how to present quantitative evidence on health inequalities in TA and HST submissions.

This position statement provides clarity on how health inequalities can be presented in TA and HST submissions. Its aim is to:

- encourage submission and use of quantitative assessments of health inequalities to show the potential scale of effect for the eligible population
- support evaluation committees to carefully consider analyses showing the impact of new technologies on health inequalities, recognising the remit of the programmes
- exclude any consideration of a quantitative modifier using quality-adjusted life year (QALY) weights or estimates of health inequality impact that use an inequality aversion parameter.

This position statement has been developed through cross-department collaboration at NICE and engagement with committee members. It is also informed by NICE Listens health inequalities report, a deliberative public engagement done in 2022.

More work is being done to support evaluation committees and external stakeholders when considering health inequalities in NICE's TA and HST programmes. If needed, there may be a modular update with opportunity for stakeholder involvement and consultation.

Quantitative assessment of health inequalities in health technology assessments

NICE guidance aims to meet the needs of the entire population using NHS and Personal Social Services (PSS) services. But as laid out in the NICE principles, in some circumstances the needs of particular groups may sometimes override the needs of the broader population to ensure fairness and equity. NICE's methods, statutory duties, the NICE Principles and routine deliberative decision making, combined, provide the flexibility to take into account relevant considerations for individual evaluations. High-quality evidence on health inequalities may further support such consideration.

The NICE health technology evaluations manual does not include specific consideration of quantitative estimates of health differences or health inequalities between:

- different population groups or

- more and less socially disadvantaged groups who will be affected by the technology being evaluated.

Distributional cost-effectiveness analysis (DCEA) is a modelling approach that quantifies how costs and benefits vary across population groups. The method focuses on the distribution of health effects for a technology or intervention. It provides an assessment of the direction and size of the impact on health inequalities. It does so by considering the impacts on health inequalities in 3 parts:

- eligible population
- effects and uptake
- opportunity cost.

This position statement sets out how components of DCEA can be used in NICE's TA and HST programmes. It follows a report on quantifying the impact of health inequality in England (Cookson and Koh 2023), which outlines how DCEA could be used across NICE guidance-producing programmes. The report suggests potential uses of the DCEA, such as helping with:

- triaging topics to rapidly understand the likely direction and magnitude of health inequality impact
- considerations during decision making, either deliberatively or directly using aversion parameters and QALY weights
- developing supplementary delivery recommendations to increase adoption of new technologies in populations with high levels of health inequalities.

1. Impact of health inequalities on the eligible population

NICE supports using quantitative data to help evaluation committees understand the scale of health inequalities relevant to eligible populations in NICE's TA and HST programmes.

Evidence on health inequalities can be provided by companies or stakeholders as part of their submissions. Supporting materials could include:

- descriptive statistics around disease burden

- information on pertinent issues in care or research because of social or structural issues related to specific population groups
- any difficulties with access to care for the relevant population.

NICE recognises the potential value to committee of quantitative data on health inequalities relevant to the population in the evaluation. Evaluation committees would benefit from this information to help to frame deliberations on health inequalities and to add insight and nuance to decisions. Important context can be provided by data clearly showing:

- differences in health outcomes across populations
- that specific conditions either arise in a group that is already disadvantaged or are overrepresented in a disadvantaged group.

Stakeholders should also focus on the potential for the technology to reduce health inequalities.

Evaluation committees will consider how health differences are systematic, unfair and avoidable, and how they contribute to the health inequality of the relevant population or social group.

Health inequalities can be seen and measured in different ways. Submissions should justify and critically evaluate the sources of data and comparative groups. There should be a rationale for:

- the measure of health inequality
- the source of data, including an explanation on how well the data underlying the quantitative analysis aligns to the specific population of interest
- how alternative data might affect the estimates.

The evidence should show that there are significant differences in health outcomes or QALYs between different groups. Evaluation committees are aware that health outcomes are influenced by complex interactions between disease severity, current diagnostic and treatment options, clinical knowledge, research and development, health service design and delivery and personal

decisions. Information clarifying how social, economic and/or environmental factors disadvantage populations could support committee in ensuring health inequality considerations are fully included in their deliberations.

NICE aims to provide clarity to stakeholders about how these have been accounted for and what flexibilities or amendments have been considered or applied (see section 4).

2. Quantitative distributional analysis of the effects of the novel technology on health inequalities

DCEA quantifies how costs and benefits vary across social population groups. The differential treatment effect across subgroups should be considered by the evaluation committee in line with methods outlined for subgroup analyses in NICE's health technology evaluations manual.

Distributional analysis for health inequalities should only be submitted when health inequalities are likely to exist for the eligible population. Quantifying the direction and size of the impact on health inequalities using a distributional analysis across all evaluations would place a disproportional burden on NICE, the evaluation committees and stakeholders. Presenting distributional results should be limited to conditions in which there is an evidenced burden of health inequalities on the eligible population. This should be supported by quantitative evidence (see section 1).

A distributional analysis showing the health benefits by social population group should only be presented as supporting evidence of the benefit of the technology addressing health inequalities. Cost-effectiveness results by social group or deprivation group should not be part of the base-case analysis or presented as non-reference case scenarios.

Distributional analyses can account for differences in the proportion of the eligible population utilising the intervention within each population group. When health benefits are presented in different social population groups (for example, deprivation quintiles) a scenario should always be included in which utilisation is equal across groups. Justification should be provided for any

alternative scenarios presenting differences in utilisation across groups or technologies.

Assumptions to estimate differences in utilisation and the health effects of an intervention by deprivation or social population group will need to be made when a technology has not already been adopted in the NHS. This is likely to introduce uncertainty into any quantitative estimates. Evaluation committees should consider the reliability and generalisability of the evidence presented.

Health inequalities can occur because of differences in access to care or in health-seeking behaviour. The NHS is legally obliged to fund medicines and treatments recommended in NICE's TA and HST guidance. This is reflected in the NHS Constitution for England, which states 'you have the right to drugs and treatments that have been recommended by NICE for use in the NHS, if your doctor says they are clinically appropriate'. NICE's TA and HST recommendations cannot give advice on service delivery or guidance to support implementation for disadvantaged groups. The recommendations only recommend technologies as an option for use in the NHS. So, while differences in uptake may affect health outcomes and be a relevant consideration for the evaluation committee, it cannot be addressed by an evaluation committee's recommendation.

Evaluation committees should be aware of the remit of NICE's TA and HST programmes and consider how any variations in uptake modelled would be addressed by the new technology.

Considering how to support implementation of TA and HST recommendations for disadvantaged groups is outside the remit of this position statement. But better adoption of new technologies is being addressed as part of NICE's wider transformation programme and could be considered as part of NICE's ongoing work into reducing health inequalities.

3. Applying health inequality aversion weights to QALY benefits

Evaluation committees should not consider the application of health inequality aversion weights to the QALY benefits.

DCEA can be used to quantify equity-weighted estimates of QALY benefits that incorporate different levels of inequality aversion. Inequality aversion is the attitude towards inequality, in this case specifically health inequalities, and public preference for equality. This can also be explained as the willingness to forgo gains in total health if health inequalities are reduced.

The NICE reference case normally regards all QALYs as being of equal weight. But evaluation committees can consider other factors and specific decision-making modifiers when relevant. The modifiers should be morally and ethically supported by reason, coherence and available evidence. Modifiers are outlined in NICE's health technology evaluations manual.

The weighting of health benefits by social deprivation is an important social value judgement that needs to be carefully validated. A systematic review on how averse the UK general public are to inequalities in health between socioeconomic groups found significant variation in the strength of aversion (McNamara et al. 2020). The results of these studies are subject to experimental framing effects and biases. But they found a difference in public aversion to inequalities in life expectancy compared with quality of life. They also found that results vary depending on whether the groups in the study are labelled, and how they are labelled. So, how and what should be included when applying results to economic considerations of health inequalities is unclear. Published research studies vary in outcomes, are methodologically heterogeneous and do not explore specific types of health gain among different population groups. It is known that different methodologies can generate different estimates in inequality aversion attitudes (Hurley et al. 2020). Further work is needed to understand how social categorisation and societal value of aversion intersect when certain characteristics are considered.

On balance, NICE does not consider that there is a sufficiently robust evidence base to support using aversion weights in DCEA as part of evidence submissions to the TA and HST programmes. NICE will review this position if significant new evidence becomes available in the future.

4. Implications for committee decision making

NICE recently carried out deliberative public engagement on health inequalities. This position statement aligns with the NICE Listens health inequalities report, which highlighted the need for a holistic, deliberative case-by-case approach to considering health inequalities.

Evaluation committees are aware that there may be situations when a technology may increase or introduce inequalities. When evidence is available, evaluation committees should consider this in their decision making.

Evaluation committees should continue to consider what adjustments they can make in their deliberations when distributional analyses show that the eligible population under evaluation experiences health inequalities, and the technology reduces or mitigates inequalities. It should take into account the needs of and benefits to particular groups.

Evaluation committees should also consider making reasonable adjustments to avoid disadvantaging a relevant population. For example, by accepting a higher degree of uncertainty if evidence generation challenges exist. This is especially important when there are structural or social barriers to generating the evidence needed for the evaluation. This should be transparently documented to comply with the public sector equalities duty under the Equality Act 2010.

An evaluation committee can recommend a new technology for which the cost-effectiveness estimates are higher than the range normally considered an acceptable use of NHS resources. But when doing this, it must recognise the effects of healthcare displacement and opportunity cost in the NHS. Accepting higher cost-effectiveness estimates would displace more technologies, services and care, affecting people's health elsewhere in the

NHS. NICE does not have complete information about the costs and QALYs from all competing healthcare programmes, so it is not possible to know who and what is being displaced.

Although many studies have explored how healthcare expenditure affects population health, there is limited empirical evidence on the displacement of healthcare on health inequalities. Two published studies found that expenditure changes imposed greater health impacts on the most socioeconomically deprived (Love-Koh et al. 2020, Currie et al. 2019). But unpublished work referenced in Cookson and Koh 2023, found a broadly neutral distribution and no evidence that more deprived groups bear larger health opportunity costs. The results are highly uncertain and the effect on opportunity cost is complex and hard to estimate. More work is needed to fully understand this impact. If the evaluation committee make a recommendation when cost-effectiveness estimates are higher than the range normally considered an acceptable use of NHS resources, it should recognise the potential opportunity cost of doing so and provide a rationale for stakeholders.

Next steps

NICE plans to review this position statement if significant new evidence becomes available that might require a change on using DCEA as outlined in this statement.

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Single Technology Appraisal (STA)

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

Post ACM1 Analysis v2

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Authors	Nyanar Jasmine Deng, Research Fellow, CRD, University of York Mark Corbett, Research Fellow, CRD, University of York Eleonora Uphoff, Research Fellow, CRD, University of York Joseph Lord, Research Fellow, CRD, University of York Helen Fulbright, Information Specialist, CRD, University of York Susan Griffin, Professor of Health Economics, CHE, University of York Claire Rothery, Professor of Health Economics, CHE, University of York Robert Hodgson, Senior Research Fellow, CRD, University of York
Correspondence to	Robert Hodgson, Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD
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Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all depersonalised data (DPD) are highlighted in pink and underlined.

Committee Modelling Assumptions

Committee base-case:

- EAG base-case with company preferred model structure
- TD SMR of 5
- 0% relapse rate for exa-cel transfusion independence
- 3.5% discount rate
- Matza vignette utility values
- TI12 outcome for TI
- Include treatment withdrawals
- RBC transfusion frequency of 16.4
- No severity modifier

The cumulative impact of the committee's preferred assumptions on the company's updated base case is shown in Table 1.

Table 1 Committee preferred base-case

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
SoC	[redacted]	[redacted]			
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 and Table 3 report results for the following scenarios conducted on the committee base case:

1. Scenario 1 (optimistic case):
    - 1.5% discount rate
    - Excluding costs of treatment withdrawals but accounting for the impact of withdrawals on outcomes
2. Scenario 2 (pessimistic case):
    - EAG preferred utility values
    - 10% relapse rate
    - RBC transfusion frequency of Shah et al: 13.7

Table 2 Committee preferred base-case: Scenario 1 (optimistic case)

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
SoC	[redacted]	[redacted]			
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3 Committee preferred base-case: Scenario 2 (pessimistic case)

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
SoC	[redacted]	[redacted]			
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Additional scenario analysis on the committee base-case

Table 4 reports additional scenario analysis requested by the committee.

Table 4 Results of scenario analyses on the EAG alternative base-case analysis

Scenario	Technology	Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
Committee base-case	SoC	[redacted]	[redacted]			
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.5% Discount rate	SoC	[redacted]	[redacted]			
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred utility values	*SoC*	[redacted]	[redacted]			
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude treatment withdrawals	*SoC*	[redacted]	[redacted]			
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude costs of treatment withdrawal but still accounting for impact on outcomes	*SoC*	[redacted]	[redacted]			
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.19% relapse rate	SoC	[redacted]	[redacted]			
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10% relapse rate	SoC	[redacted]	[redacted]			

	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RBC transfusions from Shah et al (13.7)	SoC	[redacted]	[redacted]			
	Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]