Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission** from Vertex

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

3. **Clarification questions and company responses:**
   a. Main response
   b. List of updated economic model parameters

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Anthony Nolan & Sickle Cell Society joint submission
   b. British Society for Haematology
   c. National Haemoglobinopathy Panel
   d. Royal College of Pathologists
   e. UK Forum on Haemoglobin Disorders
   f. NHS England Haemoglobinopathy Clinical Reference Group

5. **External Assessment Report** prepared by Warwick Evidence:
   a. Main report
   b. Addendum
   c. Appendix with NICE-preferred prices

6. **External Assessment Report – factual accuracy check**

7. **Decision Support Unit Report on company model structure**

Post-technical engagement documents

8. **Technical engagement response from company**

9. **Technical engagement responses from stakeholders:**
   a. Anthony Nolan & Sickle Cell Society joint response
   b. Royal College of Pathologists & British Society for Haematology joint response
   c. UK Forum on Haemoglobin Disorders

d. NHS England Haemoglobinopathy Clinical Reference Group

10. External Assessment Report critique of company response to technical engagement prepared by Warwick Evidence:
   a. Main critique
   b. Additional works
   c. Response to company factual accuracy queries

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. Technical engagement responses and statements from experts:
   a. Funmi Dasaolu – patient expert, nominated by Anthony Nolan and Sickle Cell Society
   b. Toby Bakare - patient expert, nominated by Anthony Nolan and Sickle Cell Society
   c. Emma Drasar, Consultant Haematologist – clinical expert, nominated by Anthony Nolan and Sickle Cell Society

14. Responses to NICE technical team questions from clinical experts:
   a. Emma Drasar, Consultant Haematologist – clinical expert, nominated by Anthony Nolan and Sickle Cell Society
   b. Josh Wright, Consultant Haematologist – clinical expert, nominated by Anthony Nolan and Sickle Cell Society

15. External Assessment Group post-committee meeting 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 severe sickle cell disease [ID4016]

Document B

Company evidence submission

September 2023

File name	Version	Contains confidential information	Date
ID4016_Exa-cel_SCD_Document B_FINAL [CON DPD]	1.0	Yes	07/09/2023

Contents

Tables and figures

Tables

Figures

Abbreviations

Acronym	Definition
A&E	Accident and emergency
ACS	Acute chest syndrome
AE	Adverse event
AKI	Acute kidney injury
Allo	Allogeneic
APPG	All-Party Parliamentary Group
ASCQ-Me	Adult Sickle Cell Quality of Life Measurement Information System
ASH	American Society of Hematology
Beti-cel	Betibeglogene autotemcel
BMTS	Bone Marrow Transplantation Subscale
BoI	Burden of Illness
BSC	Best supportive care
BSH	British Society for Haematology
CD	Cluster of differentiation
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CNS	Central nervous system
CPRD-HES	Clinical Practice Research Database-Hospital Episode Statistics
CRISPR	Clustered regularly interspaced short palindromic repeats
CSR	Clinical study report
CSSCD	Cooperative Study of Sickle Cell Disease
D120	Day 120 analysis
DCEA	Distributional cost-effectiveness analysis
DNA	Deoxyribonucleic acid
DSA	Deterministic sensitivity analysis
EAC	Endpoint Adjudication Committee
EAG	Evidence Assessment Group
EBMT	European Group for Blood and Marrow Transplantation
EHA	European Haematology Association

EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D-5L	EuroQoL Questionnaire 5-Dimensions 5-Levels of Severity
EQ-VAS	EuroQoL-Visual Analogue Score
ESS	Effective sample size
EWB	Emotional well-being
Exa-cel	Exagamglogene autotemcel
F-cell	Erythrocytes expressing γ-globin (fetal haemoglobin)
FACT-BMT	Functional Assessment of Cancer Therapy-Bone Marrow Transplant
FACT-G	Functional Assessment of Cancer Therapy-General
FAS	Full analysis set
FDA	US Food and Drug Administration
FWB	Functional well-being
G-CSF	Granulocyte colony-stimulating factor
GP	General Practitioner
GvHD	Graft versus host disease
Hb	Haemoglobin
HbA	Adult haemoglobin
HbF	Fetal haemoglobin
HbS	Sickle haemoglobin
HbSS	Sickle cell anaemia
HCP	Health care professionals
HCRU	Healthcare resource use
HiQiP	National Healthcare Inequalities Improvement Programme
HLA	Human leukocyte antigen
HPFH	Hereditary persistence of fetal haemoglobin
HRQoL	Health-related quality of life
HSC	Haematopoietic stem cell
hHSPC	Human haematopoietic stem and progenitor cells
IA2	Second interim analysis
ICER	Incremental cost-effectiveness ratio
ICT	Iron chelation therapy
ICU	Intensive care unit

IMD	Index of Multiple Deprivation
IPD	Individual patient data
ITC	Indirect treatment comparison
IV	Intravenous
LDH	Lactose dehydrogenase
MAIC	Matched-adjusted indirect comparison
MBBRACE	Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRD	Matched-related donor
mRNA	Messenger ribonucleic acid
N/A	Not applicable
NHB	Net health benefit
NHP	National Haemoglobinopathy Panel
NHR	National Haemoglobinopathy Registry
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NRS	Numerical Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
PASS	Post-authorisation safety study
PES	Primary efficacy set
PPPY	Per patient per year
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PWB	Physical well-being
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Safety analysis set

SCD	Sickle cell disease
SCPC	Sickle cell-related pain crises
SCS	Sickle Cell Society
SCT	Stem cell transplant
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
STSTN	South Thames Sickle Cell and Thalassaemia Network
SWAY	Sickle Cell World Assessment Survey
SWB	Social/family well-being
SWF	Social Welfare Function
TA	Technology appraisal
TCD	Transcranial Doppler
TRM	Transplant-related mortality
UK	United Kingdom
UKTS	UK Thalassaemia Society
VBA	Visual Basic for Applications
VOC	Vaso-occlusive crisis
VTE	Venous thromboembolism
YFH	Years of life in full health

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 sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) who have β^S/β^S, β^S/β^0 or β^S/β^+, for whom a human leukocyte antigen (HLA)-matched related haematopoietic stem cell (HSC) donor is not available (1).

There is substantial variability in the definition of VOCs. In the broader scientific literature, VOC is typically used to refer to an acute pain crisis, whereas clinical trials often adopt a composite definition. A systematic literature review (SLR) including 39 studies confirmed the variability in definition of VOC; where VOC was defined it was most often used to mean acute pain events associated with healthcare visits. Several trials used complicated VOC or VOC to include a composite definition of acute pain and other acute pain complications requiring hospital attendance (2).

All references to VOCs throughout this document use a composite definition, which comprises any of the following:

- Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] nonsteroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions
- Acute chest syndrome
- Priapism lasting > 2 hours and requiring a visit to a medical facility
- Splenic sequestration

Note that the composite VOC definition was used in the pivotal clinical trial for this technology (see Section B.2 for details).

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	Individuals with sickle cell disease (SCD) where there is no human leukocyte antigen (HLA)-matched related donor	Patients with SCD 12 years of age or older for whom an HLA-matched related haematopoietic stem cell donor is not available	This population aligns with the proposed MHRA marketing authorisation
Intervention	Exagamglogene autotemcel (exa-cel)	Exa-cel	N/A
Comparator(s)	Established clinical management without exagamglogene autotemcel including: • Hydroxycarbamide • Blood transfusions (exchange and top-ups) • Best supportive care	• Best supportive care (including blood transfusions and chelating agents) • Hydroxycarbamide	N/A
Outcomes	The outcome measures to be considered include: • Changes to haematological parameters (haemoglobin levels) • Proportion of patients who have not experienced any severe sickle cell crisis for at least 12 consecutive months • Complications arising from sickle cell disease • Proportion with and time to engraftment	The outcome measures to be considered include: • Changes to haematological parameters (haemoglobin levels) • Proportion of patients who have not experienced any severe sickle cell crisis for at least 12 consecutive months • Complications arising from sickle cell crises/ disease • Proportion with and time to engraftment	N/A

	• Mortality • Adverse effects of treatment • Health-related quality of life	• 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 an NHS 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: <u>The technology is for people who would otherwise die or have a very severely impaired life.</u> • SCD is a chronic disease, characterised by unpredictable episodes of severe pain, chronic haemolytic anaemia, widespread organ damage, and shortened life expectancy, with a mean age at death of 40.2 year in a UK severe SCD cohort (3, 4). The disease affects multiple organs leading to acute and chronic complications such as ACS, stroke, priapism, splenic sequestration, osteonecrosis, renal failure, pulmonary hypertension, liver disease, bone damage, limited growth, increased susceptibility to infections, fatigue, and progressive cognitive decline. • Acute pain events, the hallmark clinical feature of SCD, reflect vaso-occlusion, impaired oxygen supply, and tissue injury from infarction and reperfusion (15, 30-32). These events are characterised by the unpredictable acute onset of severe pain which commonly manifests in the extremities, chest, back, or as dactylitis (severe pain of the hands and feet), or as priapism (15, 33). In the pivotal clinical trial of exa-cel, 94.8% of

			patients had received opioids at baseline, most commonly morphine, fentanyl, and oxycodone. • In summary, SCD 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 burden of frequent pain episodes and the associated substantial impact on HRQoL (5). <u>Exa-cel is likely to restore these patients to full or near-full health:</u> • Patient treated with exa-cel will experience improved survival, reduced risk of co-morbidities and they will no longer need to receive treatment, and experience the associated side-effects of hydroxycarbamide and transfusions, which are highly burdensome. Notably, 63.8% of patients in the pivotal trial had received hydroxycarbamide at baseline. In addition, by resulting in a functional cure, exa-cel will reduce the need for opioids and other strong analgesics to manage severe pain episodes. SCD patients treated with potentially curative therapies such as stem-cell transplant (SCT) or gene therapy experienced large positive effects in all HRQoL domains (6). At Month 24 in CLIMB SCD-121, EQ-5D had increased by 0.11, exceeding the minimal clinically important difference, and even exceeding general population norms (7). • Long-term survival following stem cell transplant in SCD 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 graft versus host disease [GvHD]) (8). • 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 (8). Patients with HPFH will experience few or no SCD symptoms, particularly with HbF levels of approximately 30% or more. By mimicking this, exa-cel will restore patients to near normal health (9-11). <u>The benefits are likely to be sustained over a very long period:</u> • The expected benefits of exa-cel as a one-time gene editing therapy include long-term amelioration of a life-long disease. Edits to the HSPCs are expected to be permanent and durable, and there is no known mechanism by which an edited HSC could revert to a wild-type sequence. 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. In CLIMB SCD-121 the mean proportion of Hb comprised by HbF increased to 36.8% at Month 3, and was maintained above 40% thereafter (See B.2.6). • Allele editing data in CD34+ cells of the bone

			marrow and peripheral blood were 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 (B 2.6). The stable, durable allelic editing observed is consistent with the stability of HbF production over time and indicative that the clinically meaningful effect of absence of VOCs will persist long-term. • 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 (12).
Subgroups to be considered	NR	None	N/A
Special considerations including issues related to equity or equality	NR	SCD predominantly affects individuals of African or Caribbean heritage, who disproportionately experience health inequalities and are overrepresented in lower socioeconomic groups that are more likely to have suboptimal clinical outcomes, with significant variations in care depending on clinical proficiency or the patient's locality, inadequate or non-existent community care, and chronic underinvestment in appropriate service resources. The 2021 'No One's Listening' report found	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. 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.

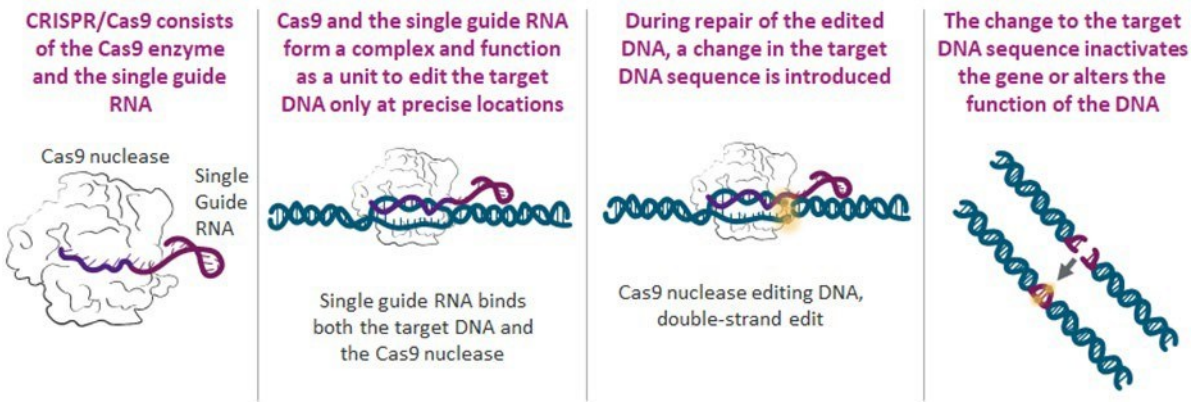
		that patients in the UK with SCD are regularly treated with disrespect, not believed or listened to, and not treated as a priority by healthcare professionals (13).	

Key: Exagamglogene autotemcel: exa-cel; HbF: fetal haemoglobin; HLA: human leukocyte antigen; HRQoL: health-related quality of life; N/A: not applicable; NR: not reported; SCD: sickle cell disease.

B.1.2 Description of the technology being appraised

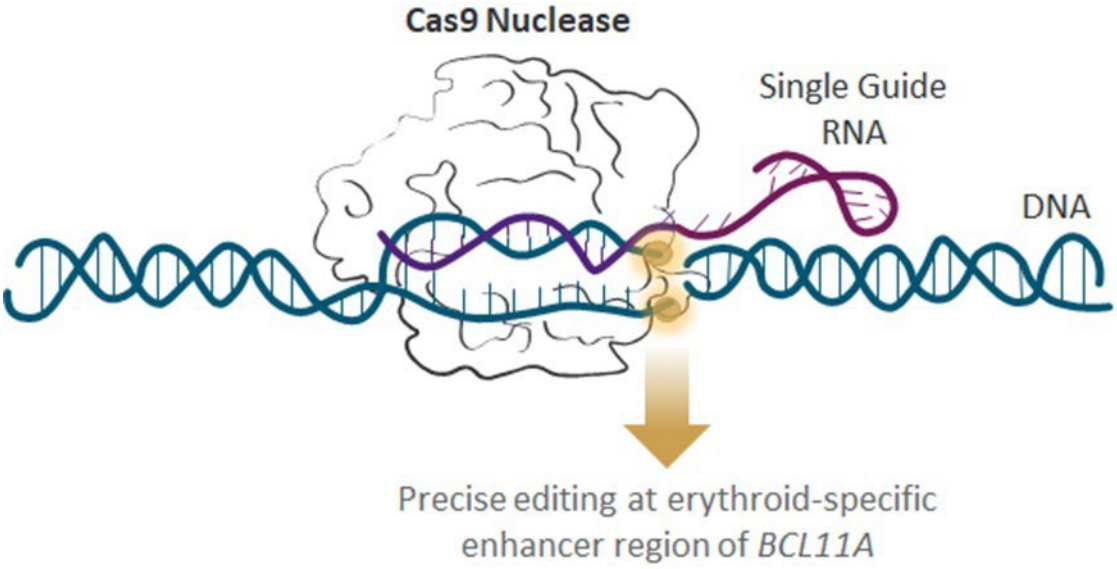
Exagamglogene autotemcel (exa-cel), formerly known as CTX001, is a cellular product consisting of autologous $CD34^+$ human haematopoietic stem and progenitor cells (hHSPCs) modified by non-viral, *ex-vivo* CRISPR/Cas9-mediated gene editing to restore fetal haemoglobin (HbF) production through the editing of a non-coding region in the *BCL11A* gene (Figure 1 and Figure 2) (14). By reactivating the production of HbF, exa-cel mimics hereditary persistence of fetal haemoglobin (HPFH), a naturally occurring genetic variation identified in some patients that causes continued expression of HbF into adulthood (15, 16). Patients with compound heterozygosity for SCD and HPFH will have raised levels of HbF with a pancellular distribution (i.e. all red blood cells (RBCs) contain HbF) and they will experience few or no SCD symptoms. Generally, higher levels of HbF correlate with fewer symptoms in SCD patients; patients with HbF levels of approximately 30% or more experience a mostly benign clinical course of SCD (9-11). Both high levels of HbF and pancellularity of HbF will have an anti-sickling effect in SCD, reduce haemoglobin polymerisation and reduce clinical complications (17, 18).

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) (19, 20).

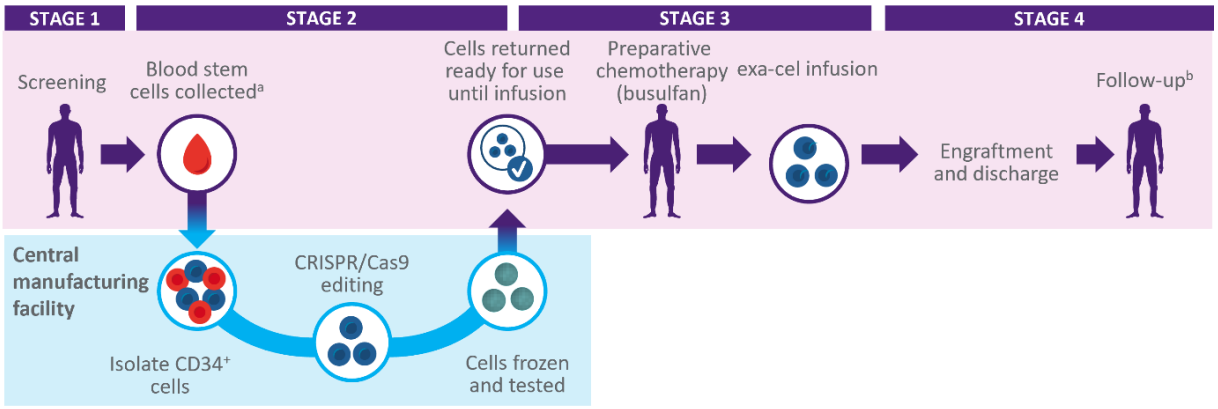
Figure 2: Exa-cel mechanism of action



Key: DNA: deoxyribonucleic acid; RNA: ribonucleic acid.
Notes: In exa-cel, CRISPR/Cas9 mediated gene editing only occurs at the erythroid-specific enhancer region of the BCL11A gene using a specific single-guide RNA and Cas9 nuclease. Precise editing confers lineage specificity and avoids pleiotropic effects. The goal of this genetic modification is to reactivate the expression of γ-globin mRNA in erythroid precursors which increases HbF protein levels in adult erythroid cells.
Source: Frangoul *et al*., (2020) (14)

Following stem cell mobilisation, the patient's HSPCs are collected by apheresis. These HSPCs are used to manufacture exa-cel via gene editing using the CRISPR/Cas9 system 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) (14). 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), graft rejection and increased mortality that is associated with allogeneic stem cell transplantation (hereafter referred to as allo-SCT) (21, 22).

Figure 3: Exa-cel treatment process schematic



Key: CRISPR, clustered regularly interspaced short palindromic repeats; HSPCs, haematopoietic stem and progenitor cells
[a] In the CLIMB SCD-121 trial plerixafor alone was used for cell mobilisation; cells were collected through apheresis.
[b] All patients will receive routine long-term follow-up by treating clinicians.
Source: Frangoul *et al*., (2020) (14).

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

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 red blood cells, thereby potentially ameliorating effects of sickle haemoglobin (HbS) in SCD and preventing HbS polymerisation. Thus, exa-cel allows SCD patients to achieve a disease-free state by addressing the underlying cause of the disease.
Marketing authorisation/CE mark status	A regulatory submission was made to the MHRA on 29 December 2022. Regulatory approval is 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 sickle cell disease in patients 12 years of age and older with recurrent VOCs who have β^S/β^S, β^S/β^0 or β^S/β^+, for whom a HLA-matched related HSC donor is not available.
Method of administration and dosage	To manufacture exa-cel, isolated $CD34^+$ HSPCs from the patient are edited *ex vivo* using CRISPR/Cas9 technology delivered via electroporation. Exa-cel is administered as a one-time, single dose intravenous infusion. The minimum cell dose is 3.0×10^6 $CD34^+$ cells/kg and the maximum cell dose is 20×10^6 $CD34^+$. The target $CD34^+$ cell collection is $\geq 15 \times 10^6$ $CD34^+$ cells/kg to allow for exa-cel manufacture. An additional 2×10^6 $CD34^+$ cells/kg will be collected as backup for rescue therapy.
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)	

Key: HbF: fetal haemoglobin; HbS: sickle haemoglobin; HLA: human leukocyte antigen; HSC: haematopoietic stem cell; MHRA: Medicines and Healthcare products Regulatory Agency; SCD: sickle cell disease; VOC: vaso-occlusive crisis.

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

B.1.3.1. Disease overview

SCD is a life-long disease characterised by unpredictable episodes of severe pain, chronic haemolytic anaemia, widespread organ damage, and shortened life expectancy. It is a multi-system disorder associated with acute complications, including acute pain events, acute chest syndrome (ACS), splenic sequestration and stroke, as well as chronic end-organ damage (23). Chronic organ complications are the main cause of morbidity and mortality in SCD patients from around the third decade of life (24). Although survival estimates have improved in the last few decades, life expectancy for patients with severe SCD is reduced compared to an age, sex and ethnically matched population (4, 25). In a longitudinal, retrospective study of disease burden in UK SCD patients, the mean age at death for SCD patients who experienced at least 2 VOCs per year for two consecutive years was 40.2 years (n=41) (3, 4).

SCD is an umbrella term describing a group of inherited diseases characterised by a mutation in the *HBB* gene encoding β-globin, which results in the expression of abnormal, sickle haemoglobin (HbS) (23, 26). The polymerisation of deoxygenated HbS forms rod-shaped structures, causing RBCs to become rigid, fragile and deform into a characteristic sickle shape which results in a range of acute and chronic complications (23, 24).

Individuals who inherit two *HBB* alleles carrying the single amino acid substitution of glutamic acid with valine at position 6 on the β-globin gene have the most common and severe form of SCD, known as sickle cell anaemia (often denoted as HbSS or β^S/β^S). HbSS is the most common subtype in England (23, 27).

Other relatively common genetic mutations in SCD are compound heterozygous states leading to HbSβ-thalassemia, which can be divided into two groups (23):

- HbS/β^0, a severe condition phenotypically similar to HbSS, in which the allele encoding HbS is combined with a mutant *HBB* allele from which no β-globin is

produced (23). Clinically, HbS/β^0 is very similar to HbSS, except for the presence of microcytosis, i.e., the presence of abnormally small erythrocytes (23, 28).

- HbS/β^+, in which there is some expression of normal adult haemoglobin (HbA) in addition to HbS; therefore individuals generally have a more benign course of disease compared to HbSS. Of note, severity is variable and some individuals will have recurrent VOCs with a similar course to HbSS (29).

There are additional compound heterozygous states causing SCD including HbSC (in which the allele for HbS is inherited in combination with the allele for HbC) and several other less common types.

At present, there is no universally accepted severity classification for SCD and establishing a classification system based solely on genotype is complicated due to the high heterogeneity of the disease, as well as the non-linear relationship between genotype and phenotype (30). The severity of SCD can be characterised phenotypically as patients with recurrent acute pain events, particularly those requiring hospitalisation, which is associated with a high risk of mortality (31, 32).

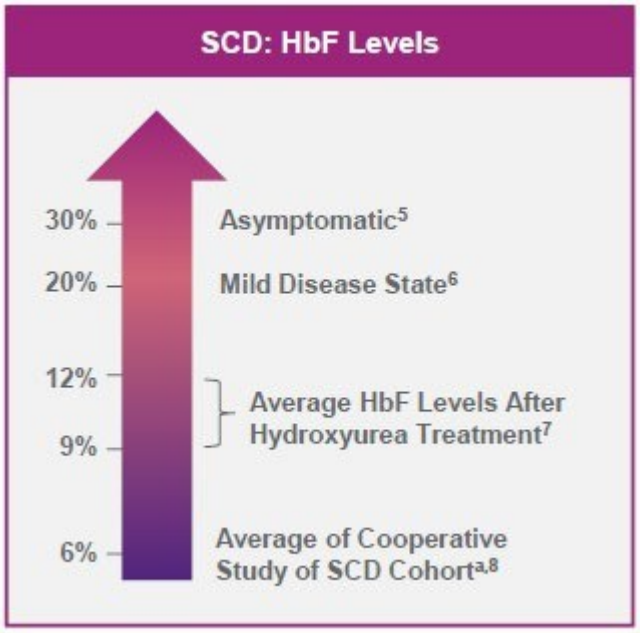
There are an estimated 14,200 patients with SCD who reside in the UK, of which approximately 11,580 are 12 years of age or above (33). This prevalence equates to less than 2 in 10,000 people, and therefore satisfies the MHRA's designation of an orphan condition (1).

Treatment options for SCD are limited to either established therapies, such as hydroxycarbamide and RBC transfusions, or the potentially curative allo-SCT (23, 34). Only approximately 10% of SCD patients are receiving hydroxycarbamide in England according to the NHR, although this figure is likely to be far higher in those experiencing frequent acute pain events (35). This limited use is partially explained by the poor adherence, frequent monitoring, and potential risks such as teratogenesis, malignancy, neutropenia, and thrombocytopenia associated with hydroxycarbamide. There are also concerns about the use of hydroxycarbamide in relation to fertility (36-39).

There are several risks associated with allo-SCT including infections, GvHD, graft rejection and increased mortality, and these risks plus the lack of HLA-matched donors partially explain the relatively low usage in SCD patients (21, 22).

Exa-cel reactivates the production of HbF in erythroid cells, mimicking the activity of HPFH, a naturally occurring genetic variation identified in some SCD patients which causes continued expression of HbF into adulthood. Published literature has demonstrated that both increases in HbF and pancellularlity of HbF inhibit the polymerisation of sickle haemoglobin which has a protective effect, ameliorating the clinical phenotype of SCD (Figure 4) and decreasing mortality (10).

Figure 4: HbF levels in SCD



Abbreviations: CSSCD: Cooperative Study of Sickle Cell Disease; HbF : fetal haemoglobin.
Note: Reference in the above diagram refers to a largely asymptomatic disease state.
Sources:
[a]Modelling for risk factors cohort (n=893).
[5]Ngo *et al.* (2012) (9).
[6]Alsultan *et al.* (2012) (11).
[7]Fitzhugh *et al.* (2015) (40).
[8]Platt *et al.* (1991) (41).

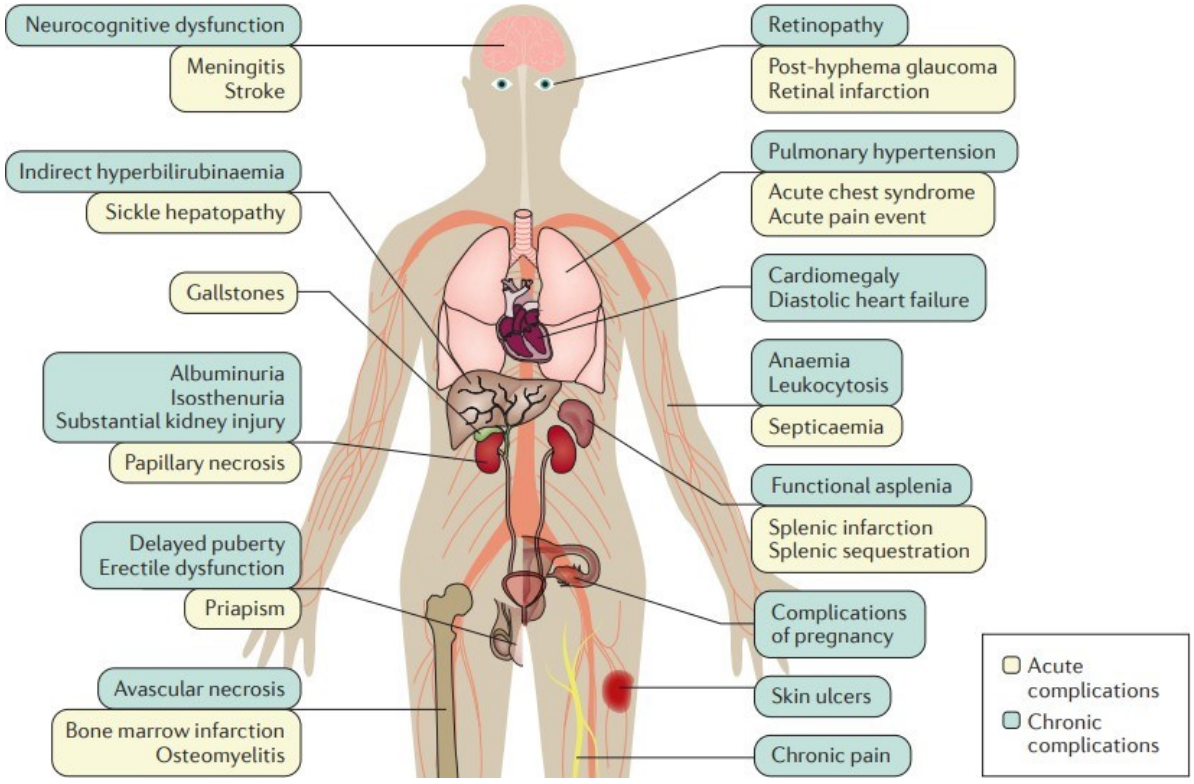
B.1.3.2. Burden of disease

B.1.3.2.1. Clinical burden

SCD is a chronic disease characterised by recurrent acute pain events, chronic haemolysis, anaemia, progressive tissue injury and organ dysfunction. The disease affects multiple organs leading to acute and chronic complications such as ACS,

stroke, priapism, splenic sequestration, osteonecrosis, renal failure, pulmonary hypertension, liver disease, bone damage, limited growth, increased susceptibility to infections, fatigue, and progressive cognitive decline (Figure 5) (11, 12).

Figure 5: Acute and chronic complications of SCD



Key: SCD: sickle cell disease.
Notes: The most common acute complication of SCD is pain which requires immediate medical attention. Chronic complications including organ dysfunction develop as SCD patients age and can contribute to an early death.
Source: Kato et al. (2018) (23).

To better understand the clinical and economic burden of SCD in the UK, a retrospective Clinical Practice Research Database-Hospital Episode Statistics (CPRD-HES) longitudinal study of the burden of illness (BoI) in a SCD cohort (n=1,117) was conducted over a 10-year period from 1 July 2008 – 30 June 2018 (4). Median follow-up was [redacted] years in the severe SCD cohort, and [redacted] years in the matched control cohort. The study population comprised SCD patients who had experienced at least 2 VOCs in at least 2 consecutive years where VOC was defined as SCD with acute pain crisis, ACS or priapism. This study provides data on a population aligned to the pivotal CLIMB SCD-121 eligibility criteria (4).

a. Acute SCD complications

A wide variety of acute complications occur in SCD, reflecting the complex pathophysiology of vaso-occlusion, infection and anaemia. Acute pain events, the hallmark clinical feature of SCD, reflect vaso-occlusion, impaired oxygen supply, and tissue injury from infarction and reperfusion (24, 42-44). These events are characterised by the unpredictable acute onset of severe pain which commonly manifests in the extremities, chest, back or as dactylitis (severe pain of the hands and feet), or as priapism (24, 45).

Infections are an important contributor to morbidity and mortality in patients with SCD (43). Notably, patients with SCD are at a higher risk of bacterial infections than healthy individuals without SCD, and this risk is highest in the first five years of life (44, 46). As a result of sickling and hypoxic injury to the spleen, many infants with SCD lose splenic function and experience functional asplenia, which leaves patients at risk of life-threatening infections, including pneumonia, sepsis, and meningitis (24, 46).

In addition, over 50% of patients with SCD will experience an acute anaemic event at some point during their lives and these often need emergency blood transfusion and can be fatal (23). Acute anaemia is defined as a decrease in haemoglobin of >2 g/dL below baseline and is associated with symptomatic anaemia, manifesting as fatigue, shortness of breath, palpitations, and pallor (47-49). Anaemia may be caused by splenic sequestration (see Section B.1.3.2.1.a), aplastic crises, and increased haemolysis (23). Delayed haemolytic transfusion reactions are a complication of blood transfusion and can lead to profound acute anaemia and may have a severe or life-threatening course (50).

In a UK cohort of severe SCD patients (n=1,117), the most common acute clinical complications observed over the median [redacted] years follow-up period include ACS (62.4%), infections (21.6%) and gallstones (19.4%) (Table 3) (3, 4).

Table 3: Most common acute complications of SCD

	Severe SCD Cohort N = 1,117		Matched General Population N = 5,585	
	(N)[a,b]	(%)[a,b]	(N)[a,b]	(%)[a,b]
Median Follow-Up Time Q1-Q3 (years)	[redacted]	-	[redacted]	-
Acute complications over the study period				
Acute renal failure	142	12.71	39	0.70
Cerebral vasculopathy	22	1.97	-	-
Gallstones	217	19.43	49	0.88
Infections (any)	241	21.58	24	0.43
Leg ulcers	71	6.36	7	0.13
Pulmonary embolism	61	5.46	17	0.30
Strokes	27	2.42	11	0.20
VOCs (any)	1,117	100	-	-
Acute pain crises	1,105	98.93	0	0
Acute chest syndrome	697	62.40	0	0
Priapism	58	5.19	-	-

Key: SCD: sickle cell disease; VOC: vaso-occlusive crisis.
Notes: [a]Prevalence calculated based on the number of patients with acute complications during follow-up; [b]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.
Source: Udeze *et al*., (2023) (3).

As highlighted in B.1.1, the pivotal trial for exa-cel uses a composite endpoint to define VOCs, defined as occurrence of any of the following events:

- Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or IV NSAIDs) or RBC transfusions;
- ACS;
- Priapism lasting > 2 hours and requiring a visit to a medical facility;
- Splenic sequestration

Further detail is provided on each of these acute complications below.

Acute pain event

Life-threatening acute pain events are experienced by patients with SCD due to the cycle of blood vessel occlusion, impaired oxygen supply, and tissue injury from

infarction and reperfusion (24, 42-44). These events are often accompanied by acute onset of severe pain and commonly manifest in the extremities, chest, back or as dactylitis (severe pain of the hands and feet) (24, 45).

Acute pain events can be triggered by illness, dehydration, stress, or wind speed, or pain itself, however, they may also occur unpredictably and without warning (51-53). A small subset of patients experience more frequent and more severe VOCs, accounting for most hospitalisations due to pain, while a substantial portion of patients have a relatively low frequency of VOC pain events (53).

The management of these episodes varies; some patients seek medical help, where others manage acute pain events at home (54). In the UK analysis of the Sickle Cell World Assessment Survey, which sampled 299 patients and 30 healthcare professionals (HCPs) in the UK, 42% of severe pain crises were managed at home (55, 56). The most commonly reported motivations for doing so included poor experience at hospital (56%) and lack of understanding of disease from medical professionals (40%) (56).

In the UK analysis of SWAY, 81% of patients self-reported ≥2 severe pain crises per year, providing further support for the idea that a substantial number of severe pain crises are managed at home, despite being defined as ‘severe’ by the patient (56).

Importantly, severe acute pain events are a marker of SCD severity and pose a risk of premature mortality (31, 57). An analysis of the UK Hospital Episodes Statistics (HES) database reported an association between having 3 or more acute pain events per year and an increased risk of several other SCD complications (58). The risk of priapism, osteomyelitis and ACS were increased ≥5-fold in SCD patients experiencing ≥3 VOCs in the past year compared with those experiencing no VOCs. For gallstones, avascular necrosis, sepsis, cardiomegaly, pulmonary hypertension, central nervous system (CNS) complications, leg ulcers, cellulitis, hyposplenism, liver complications, and acute kidney injury, the risk was between ≥2 and ≤5-fold higher in patients with ≥3 VOCs in the past year compared with those experiencing no VOCs (58). A similar finding was reported in a recently published analysis of CPRD-HES data, with risk of pulmonary embolism and gallstones increased fourfold in those with ≥2 VOCs per year

compared to those with <2 VOCs per year, and risk of leg ulcers increased eightfold (3).

Acute chest syndrome

Acute chest syndrome (ACS) is one of the main severe outcomes of acute pain events and is responsible for up to 25% of SCD-related deaths (59, 60). ACS is defined as the presence of a new pulmonary infiltrate and associated with pneumonia-like symptoms, pain, and fever (44). In adults, ACS tends to be a more severe illness marked by severe hypoxia, a higher requirement for transfusion and higher mortality (61). It can be considered as a form of acute lung injury that can progress to acute respiratory distress syndrome prior to, albeit infrequently, acute multi-organ failure (61).

ACS is relatively common and is a major cause of morbidity and mortality, requiring immediate intervention regardless of the patient's age (44). In an analysis of the UK HES database between 2008 and 2018, 27% of 15,076 patients experienced an ACS event (62). In a UK SCD population more closely matched to the indication under review in this appraisal, ACS occurred in 62.4% of patients, with a median follow-up of [redacted] years (n=1,117) (3, 4).

ACS may progress very rapidly, worsening within 24 hours from mild hypoxaemia to acute respiratory failure (63). The risk of respiratory failure and mortality associated with ACS is high: in a multi-centre study capturing 671 ACS episodes occurring in 538 children and adults with SCD, 13% of patients developed respiratory failure and required mechanical ventilation for a mean of 4.6 days (64). Further, 18 patients (3%) died, mostly from bronchopneumonia and pulmonary emboli (6 cases each) and infection was a contributing factor in 56% of the deaths (64). In a more recent study of adults with SCD, mechanical ventilation was needed in 4.6% of 24,699 hospitalisations with ACS and 1.6% of patients died in hospital (65). ACS is also the most common cause of intensive care unit admission in patients with SCD, with a mortality rate in the intensive care unit as high as 25% (66, 67).

Patients with ACS should therefore be hospitalised and carefully monitored, reflecting a substantial resource use associated with this acute complication (63).

Priapism

Priapism, a common complication of SCD, is defined as a painful or painless, purposeless and persistent state of penile erection, which may follow or occur in the absence of sexual stimuli (68). Priapism is expected to affect 35-90% of male patients with SCD over the course of their lifetime, with a majority of first episodes occurring before the age of 20 years (69). It is a complication that causes significant embarrassment and discomfort, and is often poorly discussed with patients (68). In sustained episodes, emergency treatment is required to prevent permanent erectile dysfunction (70).

A study combining a cross-sectional survey and focus group discussions with young adult (aged 18–40 years) men in Nigeria reported the prevalence of priapism was more than 15-fold higher among 353 men with SCD (31.72%) than 250 control men without SCD (2%) (71). In a Brazilian cross-sectional study of 64 men with SCD aged 2 to 69 years, the prevalence of priapism was 35.9% and boys as young as 2 years of age were affected (72). Cold was the major precipitating factor (72).

Piel *et al.,* (2021) analysis of HES data reported that 7.3% of a UK SCD cohort experienced priapism between 2009-2018 (73). Priapism occurred in 5.2% of a UK severe SCD cohort with a median follow-up of [redacted] years (n=1,117) (4). Both of these studies only measured patients with priapism who presented to hospital. The rates within the community are likely to be much higher and reflect the levels reported above (71, 72).

Splenic sequestration

Splenic sequestration is a complication of SCD that predominantly affects young children. In children with SCD, abnormal sickle RBCs become trapped in the spleen. Typically, this self-resolves or results in the formulation of isolated areas of congestion and fibrosis. With repeated episodes of auto-infarction and scarring, the spleen in children with SCD gradually becomes loses function and decreases in size (74). Resulting functional asplenia leaves patients at risk for life-threatening infections, including pneumonia, sepsis, and meningitis (24). However, in some cases, the localised obstruction expands, causing the spleen to rapidly fill with RBCs and a large

percentage of blood volume to become trapped in the spleen, leading to a sequestration crisis (74).

Acute splenic sequestration is a leading cause of mortality in infants with SCD and is characterised by a rapid swelling of the spleen and a sudden decrease in Hb levels (23). Splenectomy may be required to prevent recurrence of splenic sequestration, which in turn places the patient at risk of infectious complications due to the important role the spleen plays within the immune system (74). In the aforementioned UK BoI study, a total of [redacted] patients ([redacted] %) were identified with splenectomy at baseline from the overall severe SCD cohort (4). A systematic review involving six studies of SCD patients in Africa reported a prevalence of <10% for acute splenic sequestration crisis (75).

b. Additional complications

SCD is associated with a range of acute and chronic complications, affecting multiple organs. End-organ damage arises due to repeated vaso-occlusion, infarction, and chronic haemolytic anaemia, and chronic organ complications become the main cause of morbidity and mortality in patients with SCD around the third decade of life (24). Patients with HbSS are usually anaemic with a haemoglobin level of 6-9 g/dL and this leads to fatigue. Almost every organ system can be affected by SCD, including the nervous, musculoskeletal, urogenital, and gastrointestinal systems (Table 4) (25).

In addition, the risk of pregnancy-associated morbidity in women with SCD is high, with maternal complications including VOCs, venous thromboembolism (VTE), prenatal haemorrhage, toxemia, chorioamnionitis, and cardiomyopathy. Risks to the foetus/infant include abortion, premature delivery, low birth weight, growth retardation, and perinatal mortality (76). Pregnancy in women with SCD is also associated with maternal and fetal mortality rates as high as 11.4% and 20.0%, respectively (76). These high mortality rates are particularly critical considering the poor pregnancy outcomes experienced by Black women in the UK. According to the Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries (MBRRACE) UK Report (2022), the risk of maternal mortality in 2018-2020 was 3.7 times more likely amongst women from Black ethnic backgrounds compared to White women (77).

Table 4: Most common chronic clinical complications of SCD

	Severe SCD Cohort N = 1,117		Matched General Population N = 5,585	
	(N)	(%)	(N)	(%)
Median Follow-Up Time Q1-Q3 (years)	[redacted]	-	-	-
Chronic complications over the entire study period				
Bone and joint problems	288	25.8	-	-
Cardiopulmonary complications (any)	337	30.2	45	0.81
Cardiomegaly	262	23.5	22	0.39
Pulmonary hypertension	114	10.2	-	-
Heart failure	71	6.4	27	0.48
Chronic pain	172	15.4	-	-
Pregnancy complications related to SCD	148	13.3	0	0
Hyposplenism	138	12.4	0	0
Liver complications (any)	87	7.8	55	0.98
Hepatitis	58	5.2	-	-
Mental health problems	176	15.8	762	13.64
Neurocognitive impairment	56	5.0	46	0.82
Retinal disorders or retinopathy	207	18.5	106	1.90
Renal complications (any)	62	5.6	51	0.91

Key: SCD: sickle cell disease.
Notes: 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.
Source: Udeze *et al*., (2023) (3).

Further detail on additional complications of SCD are provided below.

i. Stroke and other neurological complications

Neurologic complications in SCD include ischaemic or haemorrhagic stroke, silent ischaemic stroke, cognitive impairment, acute and chronic headaches (24, 78, 79).

Patients with SCD may experience transient ischaemic attacks, and ischaemic or haemorrhagic strokes and these may be associated with subsequent seizures and cognitive and behavioural changes (78). It is estimated that with no preventative

measures, approximately 11% of children with SCD experience an ischaemic stroke and as many as 39% have silent cerebral infarcts, which are associated with substantial cognitive impairment (79). However, improved management, including primary and secondary stroke prevention, has substantially improved the mortality associated with stroke amongst children (78, 79). For instance, children with SCD are offered annual trans-cranial doppler screening to determine risk of stroke and long-term transfusions or hydroxycarbamide if identified as high risk (46). Haemorrhagic strokes and cerebral aneurysms are more common in adults and adults are at a considerable risk of morbidity and mortality from neurologic complications (78, 79).

Moreover, in adults with SCD, cognitive impairment is more severe in those with HbSS or HbSβ^0 than in patients with HbSC disease or HbSβ^+, a difference evident even after excluding patients with a history of stroke (80). Historically, by 45 years of age, one in four adults with SCD experienced a stroke, although these rates are likely to be lower now, following the introduction of trans-cranial doppler (TCD) stroke screening (81).

ii. Hepatic complications

Hepatic complications are common and range in severity from liver dysfunction to liver failure (82). Approximately 20% of SCD patients develop acute complications from gallstones by adulthood (23). In a single-centre study conducted in the UK, 26% of 134 SCD patients with gallstones developed serious complications and 25% underwent a cholecystectomy during the 11-year study period (83).

Severe liver complications of SCD include acute hepatic crisis, intrahepatic cholestasis, and acute hepatic sequestration (84). The prevalence of severe liver complications in adults is approximately 10% (84). An acute hepatic crisis is usually associated with right abdominal pain, liver enlargement and jaundice. Sickle cell intrahepatic cholestasis is a severe form of an acute hepatic crisis and may rapidly progress to multi-organ failure (84). Hepatic sequestration, similar to splenic sequestration, results from liver congestion with RBCs and may lead to acute hepatomegaly and anaemia (50).

iii. Cardiopulmonary complications

Cardiopulmonary complications are a leading cause of morbidity and mortality in patients with SCD, with one large retrospective study reporting that such complications were responsible for 45% of deaths for adults with SCD (85).

Chronic cardiac complications of SCD include increased cardiac output at rest, cardiomegaly, and myocardial ischaemia (86, 87). The pathophysiology of SCD puts the patient's cardiovascular system under sustained stress, culminating in the development of pulmonary hypertension, left ventricular diastolic heart disease, dysrhythmia, and sudden death (86).

Chronic pulmonary complications in SCD include pulmonary hypertension, asthma and recurrent wheezing, sleep-disordered breathing, and pulmonary function abnormalities (88). Pulmonary hypertension is associated with considerable mortality in patients with SCD. In a long-term US-based prospective registry of patients with SCD and pulmonary hypertension, 5-year mortality rates were 31.7% in patients with pulmonary hypertension compared with 15.9% in SCD patients with no pulmonary hypertension (89).

iv. Bone and skin complications

Bone and joint problems were also frequently reported by SCD patients during the aforementioned UK BoI study follow-up (25.8%). Avascular necrosis is a common skeletal complication and may simultaneously affect several joints, although the femoral head is the most common site where this may rapidly progress to femoral head collapse and pain in the joint, requiring total hip arthroplasty (90).

Avascular necrosis of a joint, amongst other SCD-related complications, can result in daily chronic pain defined as pain present on most days lasting over three months (70). A study by Smith *et al*., (2008) found the prevalence of chronic pain increases with age, and by adulthood, over 55% of SCD patients experience pain on over 50% of days; with 29% of patients experiencing pain on more than 95% of days (91). An additional study of adult patients with SCD reported that 92% of patients experienced chronic pain lasting from six months to two years (92).

v. Sickle cell nephropathy

Sickle cell nephropathy, which accounts for up to 18% of mortality in patients with SCD, begins in childhood and can advance in adulthood to albuminuria, chronic kidney disease (CKD) and end-stage renal disease (24, 93, 94). CKD disproportionately affects patients with SCD and is associated with a considerable burden (95).

CKD from sickle cell involves damage to multiple structures within the kidney. The haemodynamic changes that occur with chronic anaemia, renal hypoxia that results from recurrent vaso-occlusion and haemolysis-related endothelial dysfunction can lead to functional and structural changes which may progress to CKD (96). In a study of Ghanaian SCD patients, CKD was present in 39.2%, with proteinuria and CKD most common in the HbSS genotype (97).

SCD patients are predisposed to recurrent subclinical and clinical acute kidney injury (AKI), which affects between 4% and 10% of hospitalised patients with SCD (94). In a French retrospective analysis of 138 ICU admissions among 119 SCD patients, the presence of AKI was associated with an 11.5-fold increase in the odds of complicated outcome, defined as requirement for vital support or death (98).

vi. Multi-organ failure

Organ damage arises due to repeated vaso-occlusion, infarction, and chronic haemolytic anaemia (24). Almost every organ system can be affected, including the nervous, musculoskeletal, urogenital, and gastrointestinal systems (25). A retrospective analysis of all adult sickle cell patient admissions (aged ≥16 years) to a single ICU in the UK found that one of the most common reasons for admission was multi-organ failure (99). Over an 8-year period spanning from 2000 to 2007, 38 patients were admitted a total of 46 times to the ICU, with 17% of these patients admitted due to multi-organ failure (99). In addition, a prospective evaluation over 7 years of 104 adult SCD patients in the Netherlands found that 62% of patients developed a new form of organ damage or complication since baseline analysis (100).

c. Mortality

Although survival estimates have improved over the past few decades, life expectancy for patients with SCD is reduced compared to that of the general population,

underscoring the morbidity and mortality associated with SCD. In a longitudinal, retrospective study of disease burden in UK SCD patients, the mean age at death for SCD patients who experienced at least 2 VOCs per year for two consecutive years was 40.2 years (n=41) (3). This mortality rate was around 5 times higher than the rate in an age, sex and ethnically matched population (overall mortality rate per 100 person-years 0.78 vs 0.16) (16,18).

Furthermore, a cohort analysis of 712 adult SCD patients (not selected for severity) registered at a single London hospital by Gardner *et al.,*(2015) reported a median age at death of 42 years (n=43) (57), while an analysis of the UK HES database from 2009 to 2018 by Piel *et al*, (2021) found the mean age at death for patients with SCD in England to be 46.7 years (73). In the sub-cohort with 4+ hospital admissions due to sickle cell crises over the two base years 2009, and 2010, the mean age at death was 39.7 years (73).

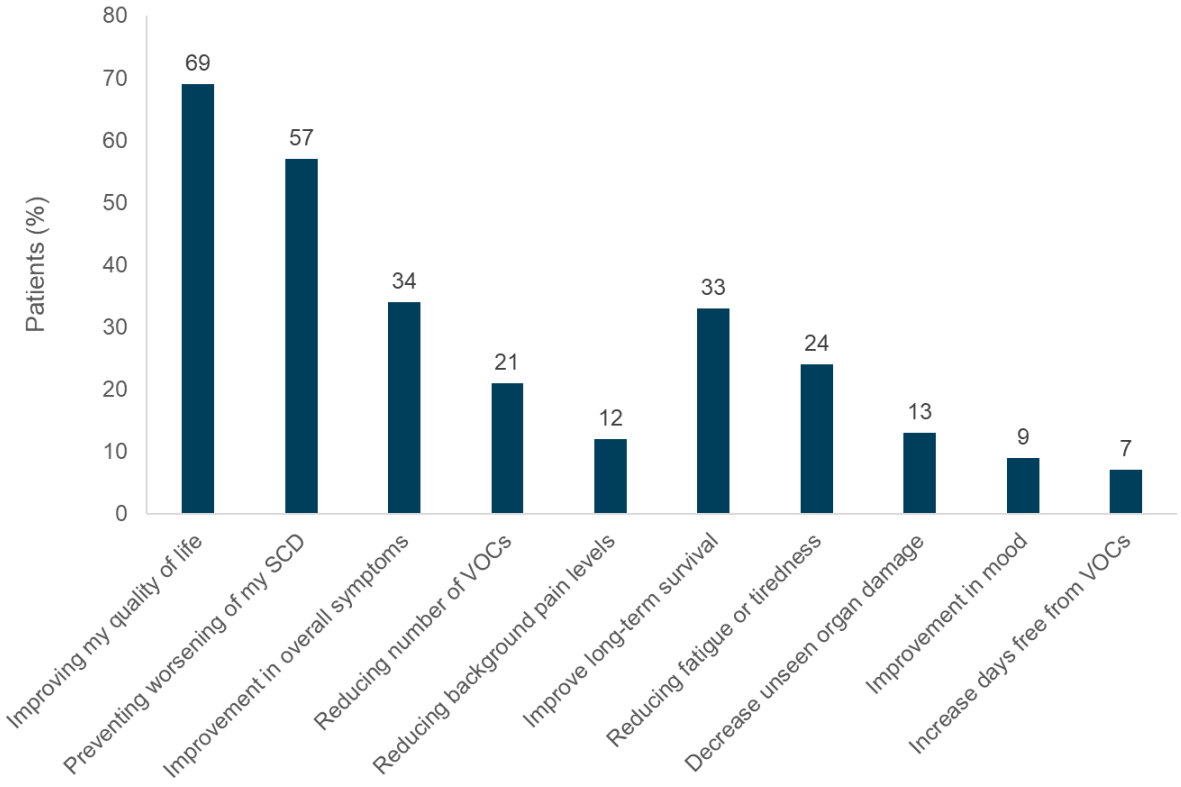
Importantly, higher rates of acute pain events (and consequently higher rate of hospitalisation and ACS) are linked with increased mortality risk (31). For example, patients with an average of 3+ acute pain events per year across their lifetime have been shown to have worse survival outcomes compared to those with 1-<3, or 0-<1 (32). UK data also showed that mean survival was significantly lower in those with more than one hospital admission in the previous two years (41, 57). In contrast, mortality rates are lower amongst patients who receive therapies that reduce the frequency of acute pain events, highlighting a key unmet need for treatments that can effectively prevent acute pain events (101). In a retrospective analysis of CPRD data conducted between 2008 – 2018, mortality rate was >2x higher in SCD patients with ≥2 VOCs per year (0.99 per 100 patient years) relative to those with <2 VOCs per year (0.47 per 100 patient years) (3). SCD patients with ≥2 VOCs were included in the CLIMB SCD-121 and CLIMB-131 studies, therefore these patients are expected to have a high mortality rate.

B.1.3.2.2. Humanistic burden

Individuals with SCD face significant risk, adversity and uncertainty, although many show remarkable resilience to the impacts of the disease by establishing successful coping strategies and managing their potentially debilitating condition in an adaptive

manner (102). According to the UK analysis of the SWAY survey, the most cited treatment goal for both patients and HCPs was improvement in health-related quality of life (HRQoL) (69% of patients versus 80% of HCPs) (55). Treatment goals for patients can be found in Figure 6 below.

Figure 6: Top 10 ranked patient treatment goals (n=299)



Key: HCP: healthcare professional; SCD: sickle cell disease; VOC: vaso-occlusive crises.
Notes: Patients and HCPs were independently selected; no matching was conducted. Patients and HCPs were asked: Other than a cure for SCD, what are your 3 most important treatment goals?'
Sources: Inusa *et al.,* (2020) (103).

The international SWAY survey cohort (n=2,145) reported similar treatment goals and highlighted the importance of preventing the worsening of SCD (43%), reducing the number of severe VOCs (30%) and improving overall symptoms (29%) (54). However, the most common patient-reported treatment goal in the international cohort was also improvement in HRQoL (55%) (54), emphasising the need for therapies which can provide a lasting alleviation of SCD burden on patients' lives.

SCD severely impairs all aspects of HRQoL including physical, mental, and social functioning. Patients with SCD report impaired HRQoL related to physical well-being,

with the physical functioning domain being worse than or comparable to that of patients with other chronic diseases or cancer (23, 104).

Clinical experts consulted by Vertex highlighted that patients suffer a huge reduction in their ability to perform tasks on a day-to-day basis throughout their lives as a result of SCD (12). The UK SWAY cohort reported that SCD has a high impact on activities of daily living, ranging from impact on daily activities (43%) to family or social life (47%) (56). A global longitudinal study in adult SCD patients (n=142) across the EU and US found that 80% of surveyed participants experienced problems with their usual activities (5).

Furthermore, SCD also has negative impacts on psychological health. Psychological complications in patients with SCD are multifactorial, arising from the impact of pain and symptoms on their daily life (105). Patients with SCD experience severe psychological impact. The physical complications of SCD adversely influence the mental health of patients and can cause anxiety and depression, which can adversely impact physical health (106). In the UK cohort of SWAY, over two thirds of patients (69%) reported a high impact on emotional well-being, while 78% reported a higher impact in terms of frustration with having to put up with symptoms and 71% reported they were concerned about worsening disease (56). Patients reported a higher emotional impact with increased frequency of pain crises, as shown in Table 5 below. Patients also reported that SCD has a high impact on relationships with family/spouse (48%), daily activities (e.g. housework) (44%) and sexual desire/activity (44%). Nearly three-quarters of all patients (72%) reported a desire to receive additional support, and 29% of all patients received professional emotional support (e.g. psychiatrist, psychologist, counselling) (56).

Table 5: Impact of severe pain crisis burden on emotional wellbeing

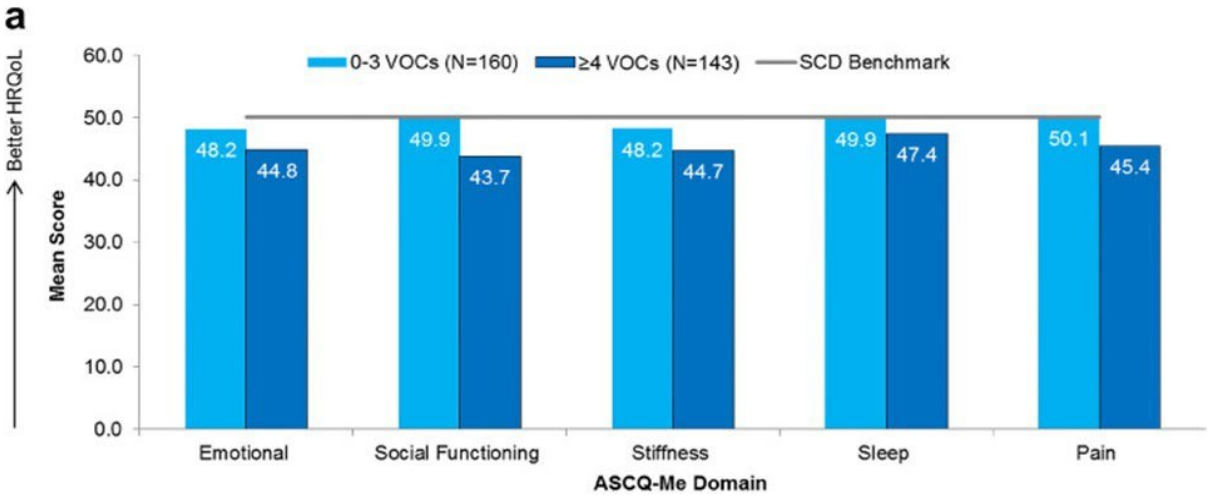
Number of self-reported severe pain crises in previous 12 months	Patients reporting high impact (%) (5-7)
0-1	52%
2-4	66%
5-10	77%
11+	86%

Notes: Impact statements were asked using a 7-point Likert scale with high agreement and satisfaction scores = 5-7.

Source: Inusa *et al.,* (2020) (56).

Further support for this comes from a US online survey of 303 SCD patients, which demonstrated that more frequent SCD-related pain crises were associated with worse HRQoL across the emotional, social functioning, stiffness, sleep, and pain domains of the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) instrument (Figure 7) (107). Both acute and chronic pain pose a substantial burden on patients with SCD due to delays in seeking care, stigma, discrimination, and negative provider attitudes (51, 108, 109).

Figure 7: HRQoL according to SCD-related pain crisis frequency



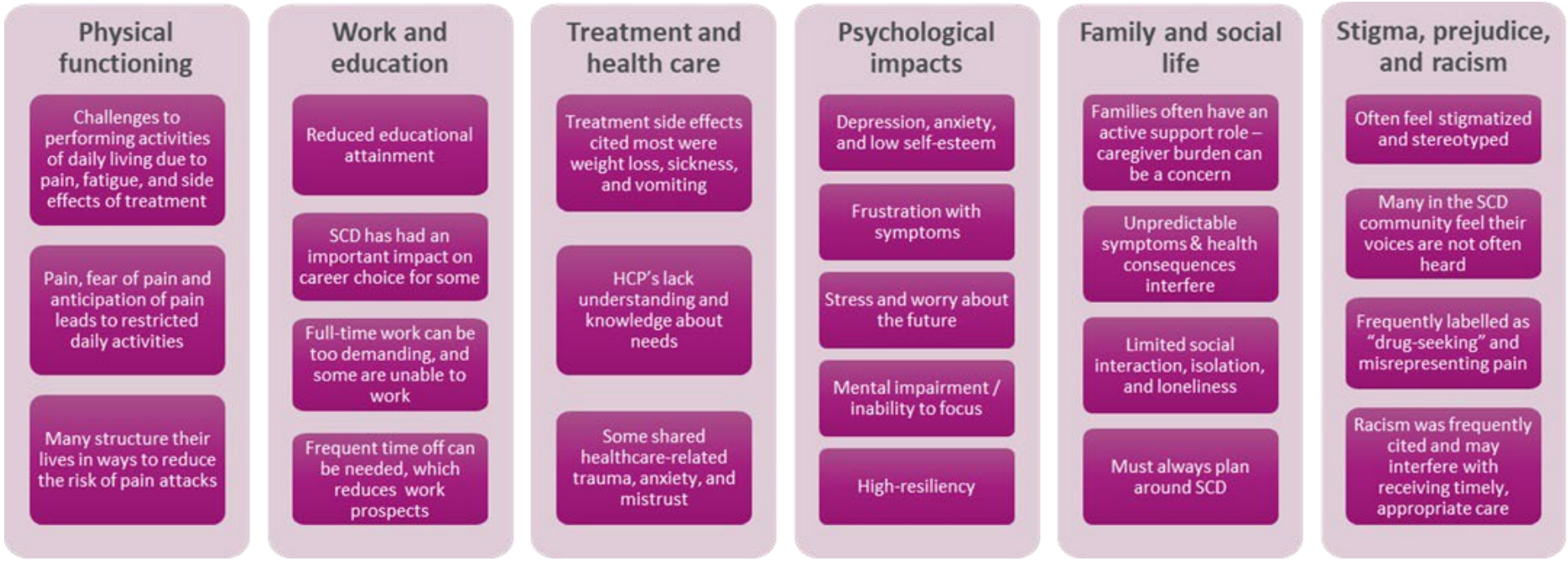
Key: ASCQ-Me: Adult Sickle Cell Quality of Life Measurement Information System; HRQoL: health-related quality of life; SCD: sickle cell disease; VOCs: vaso-occlusive crises.
Notes: Higher ASCQ-Me impact scores indicate better functioning. The grey bar in the figure indicates the "benchmark" average score of 50. VOC refers to a sickle cell disease-related pain crisis.
Source: Rizio *et al.* (2020) (107).

Furthermore, in a series of interviews and focus group discussions conducted by QC Medica, SCD patients in the UK and US reported that the disease impacts almost all aspects of daily life (110). Notable concepts mentioned in these discussions are illustrated below in Figure 8, highlighting that almost every aspect of patients' lives are adversely affected by SCD. Individuals living with SCD often reported profound impact of the disease on their daily lives and structured their lives in a way to reduce the risk of pain attacks. The unpredictability of SCD symptoms and consequences had adverse effects on the patients' educational attainment, work prospects, and social lives. Patients often cited loneliness/isolation, experiencing depression and low mood, anxiety, and fear of living in pain (5, 110).

In a global longitudinal study of adult SCD patients (n=142) across the EU and US, 61.3% of participants reported experiencing ≥4 severe pain episodes in the past year. Moreover, 69.3% of participants reported managing ≥4 pain episodes at home in the past year. Similarly to the QC Medica interviews and discussions, participants reported impact to numerous aspects of daily life experiencing problems with pain and discomfort (90%), anxiety and depression (74%), mobility (71%) and self-care (47%) (5).

In addition to the significant burden imposed on patients, caregivers also experience negative impacts on their physical, mental, and social well-being (111, 112). Caregivers of patients with SCD have been shown to have a lower quality of life compared to the general population. In an online survey of caregivers for patients with SCD in the UK (n=43), the mean (range) EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) utility score was 0.62 (0.29), with a utility decrement of 0.23 when compared with age- and gender-matched population norms (111). Furthermore, patient caregivers experience high levels of productivity and economic losses, with the annual mean productivity loss per caregiver in the UK estimated to be £5,391 when using the 2022 average hourly wage rate (111).

Figure 8: Summary of the impact of SCD on patient lives



Key: HCP: healthcare professional; SCD: sickle cell disease.
Source: Vertex data on file (110).

B.1.3.2.3. Societal and economic burden

The healthcare resource use (HCRU) and costs associated with SCD are substantial. A 10-year cohort analysis of HCRU and costs for SCD patients in England by Jobanputra *et al*. (2021) reported a total of 6,219 hospital admissions relating to a primary diagnosis of SCD in 2018, at a total cost to the NHS of £38.5 million (113). A longitudinal, retrospective study of disease burden in UK SCD patients found that SCD patients with recurrent VOCs had significantly higher HCRU compared to a cohort of matched patient controls (3). Extrapolation of annual HCRU costs suggests that SCD patients with recurrent VOCs incur substantial costs over lifetimes; by age 50 the expected lifetime cost per patient in this population is approximately 18.6 times that of the matched general population. In addition, SCD patients with recurrent VOCs averaged 7.59 inpatient hospitalisations, of which 4.61 were for <1 day, 9.60 outpatient visits, and 31.06 prescriptions, all per year. A full list of results from the BoI study can be found below in Table 6 (4).

Table 6: HCRU associated with managing SCD in the UK

Rate per patient per year. Mean (SD)	**SCD (N=1,117)**	**Matched controls (N=5,585)**
Primary care visits*[1]	6.98	4.12
GP Visits PPPY*[1]	4.94 (5.37)	2.93 (3.50)
Nurse visits PPPY*[1]	2.04 (3.20)	1.19 (2.28)
Prescriptions*[1,2]	31.06 (60.62)	7.58 (27.77)
Hospitalisations (any) *[2]	22.17 (26.62)	2.63 (5.99)
A&E hospitalisations*[2]	4.97 (10.59)	0.53 (1.62)
Outpatient visits*[2]	9.60 (10.69)	1.78 (4.18)
Inpatient hospitalisations*[2]	7.59 (14.50)	0.32 (2.71)
Inpatient hospitalisation < 1 day*[2]	4.61 (13.10)	0.21 (2.62)
Inpatient hospitalisation ≥ 1 day*[2]	2.98 (3.64)	0.11 (0.34)

Key: A&E: accident and emergency; CPRD: Clinical Practice Research Database; GP: general practitioner; HES: Hospital Episode Statistics; HCRU: healthcare resource utilisation; PPPY: per patient per year; SD: standard deviation.
Notes: *P<0.05 between SCD patients and matched controls (z-test). [1]Captured from CPRD. [2]Captured from HES.
Source: Table 12, Vertex BoI study (4).

Furthermore, HCRU and associated costs increase in SCD patients with a high VOC burden. The study by Jobanputra *et al*., (2021) reported the cost of treating SCD patients with high crises, who were defined as patients with four or more hospital admissions for sickle cell crisis over any two-year period, was found to be disproportionately greater compared to the rest of the SCD patient cohort. These patients represented only 16% of the admitted patient population but accounted for more than 50% of hospital expenditure on SCD patients (113). The mean annual cost of treating high crises patients was estimated at £17,200, more than £12,000 per year higher than for the remainder of the tracked SCD cohort (mean: £4,400) (113).

A longitudinal, retrospective study of disease burden in UK SCD patients, stratified analysis of patients by annualised number of VOCs suggested an association between the number of VOCs and level of HCRU, similar to that found in other retrospective studies (Table 7) (114-116). The mean total HCRU cost per patient per year (PPPY) increased with the number of VOCs (£[redacted] PPPY for patients with >0 - <2 VOCs PPPY, and £[redacted] PPPY for patients with ≥2 VOCs during follow-up) (4).

Table 7: HCRU associated with managing SCD in the UK, by annualised number of VOCs during follow-up

	Annualised number of VOCs during follow-up					
	>0 - <2 (n=421)	≥2 - ≤4 (n=[redacted])	>4 - ≤6 (n=[redacted])	>6 - ≤8 (n=[redacted])	>8 - ≤10 (n=[redacted])	>10 (n=[redacted])
GP Visits PPPY*[1]	4.14 (4.27)	4.82 (5.58)	5.58 (5.31)	5.62 (5.73)	6.33 (5.99)	6.24 (7.27)
Nurse visits PPPY*[1]	2.01 (2.41)	2.10 (4.80)	2.07 (2.17)	2.37 (3.24)	2.21 (1.79)	1.16 (1.87)
Prescriptions*[1,2]	27.57 (53.90)	31.05 (64.53)	33.06 (68.78)	28.29 (39.63)	41.49 (76.71)	38.81 (67.24)
Hospitalisations (any) *[2]	13.52 (12.34)	17.01 (10.64)	22.08 (13.96)	24.13 (11.74)	28.28 (10.85)	63.66 (60.58)
A&E hospitalisations*[2]	1.58 (1.54)	2.91 (3.00)	4.88 (4.66)	5.67 (3.24)	7.18 (5.63)	21.58 (26.43)
Outpatient visits*[2]	8.26 (7.46)	9.44 (8.24)	10.49 (10.32)	9.30 (8.28)	11.15 (8.75)	13.36 (22.41)
Inpatient hospitalisations*[2]	3.68 (7.41)	4.67 (4.22)	6.70 (5.40)	9.16 (4.98)	9.95 (4.41)	28.72 (35.20)

Inpatient hospitalisation < 1 day*[2]	2.63 (7.26)	2.52 (4.09)	3.41 (5.63)	5.01 (5.48)	4.55 (4.50)	18.75 (34.13)
Inpatient hospitalisation ≥ 1 day*[2]	1.05 (0.71)	2.15 (1.00)	3.29 (1.31)	4.15 (1.93)	5.40 (2.19)	9.97 (7.13)

Key: A&E: accident and emergency; CPRD: Clinical Practice Research Database; GP: general practitioner; HES: Hospital Episode Statistics; HCRU: healthcare resource utilisation; PPPY: per patient per year; SD: standard deviation; VOC: vaso-occlusive crisis.
Notes: *P<0.05 between SCD patients and matched controls (z-test). [1]Captured from CPRD. [2]Captured from HES.
Source: Table 33, Vertex burden of illness study (4).

B.1.3.3. Clinical care pathway

Formal treatment guidelines used to inform some aspects of the management of SCD in the UK come from the British Society for Haematology (BSH) guidelines (61, 117-119). Whilst the National Institute for Health and Care Excellence (120) do not provide full guidelines on the treatment of SCD, they provide guidance for managing acute painful sickle cell episodes in hospital (CG143) published on 27 June 2012 (updated in October 2022) (121). There are no NICE guidelines published on appropriate treatment or chronic management of SCD, however two technology appraisals (TA) have been initiated by NICE, one of which is still ongoing as summarised in Table 8. Following publication of NICE's final TA guidance for crizanlizumab, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recently recommended revoking the conditional marketing authorisation for crizanlizumab after preliminary results from the pivotal STAND trial indicated that after one year of treatment, crizanlizumab did not reduce the number of painful crises compared to placebo (122).

Table 8: Summary of NICE technology appraisals in SCD

Title	Outcome	Rationale
TA743: Crizanlizumab for preventing sickle cell crises in sickle cell disease.	Recommended with a managed access agreement.	Despite a reduction in the number of VOCs, there was uncertainty in the results given the short trial duration, limited numbers of patients who received the licensed dose, and the plausibility of the ICER. However, unmet need & potential to address health inequalities resulted in a recommendation with data collection through a managed access agreement.
ID1403 [GID-TA10505]: Voxelotor for treating sickle cell disease.	Not recommended according to NICE final draft guidance published on 28 July 2023.	Key issues behind negative guidance include proposed positioning, comparators, uncertainty around reduction of long-term SCD complications, uncertainty around utility benefit evidence, and model data did not reflect target population.

Key: ICER: Incremental cost-effectiveness ratio; VOC = vaso-occlusive crisis
Source: NICE TA473 and GID-TA10505 (123, 124).

B.1.3.3.1. BSH guidelines

BSH have developed three clinical practice guidelines on the management of SCD, including for hydroxycarbamide, ACS and RBC transfusions (61, 117-119). Key recommendations made in these documents are summarised below.

- Hydroxycarbamide should be offered to adults and children with HbSS or HbS/β^0 genotypes who have sickle cell pain which interferes with daily activities and quality of life (119).
- Guidelines recommend that the risks and benefits for the use of hydroxycarbamide are discussed with all patients or parents of children to enable informed joint decision-making between both provider and patient (119).
- BSH guidelines for RBC transfusions recommend that Hb concentration and/or percentage of HbS should be carefully considered to ensure maximal oxygen delivery to tissues without a detrimental increase in overall blood viscosity (117).
- The choice of transfusion method, i.e., simple (top up) or exchange, should be based on clinical judgement of individual cases, taking into account the indication for transfusion, the need to avoid hyperviscosity and minimise

alloimmunisation, maintenance of iron balance, venous access issues and available resources (117).

- The potential benefits and risks should be weighed up when considering transfusion, particularly long-term regimens (118).

- The indications for transfusion in SCD can be broadly categorised into conditions in which correction of anaemia is the main goal and those where reduction of HbS may be more appropriate. In both categories, transfusion is either performed acutely, as part of management of an acute complication of SCD, or electively for the prevention or management of disease complications (118).

- Early recognition of ACS is vital, and patients should be monitored for predictors of severity which included worsening hypoxia, increasing respiratory rate, decreasing platelet count, decreasing Hb concentration, multilobar involvement on chest X-ray and neurological complications (61).

- Patients with ACS should be treated aggressively irrespective of their SCD genotype. Early simple (top up) transfusion should be considered early in hypoxic patients, but exchange transfusion is necessary if there are severe clinical features or evidence of progression despite initial simple transfusion (61).

- BSH guidelines recommend hydroxycarbamide for the prevention of recurrent ACS in adults, with chronic transfusion recommended should hydroxycarbamide prove ineffective (61).

- In children, stem cell transplantation should be considered if hydroxycarbamide proves ineffective in preventing recurrent ACS (61).

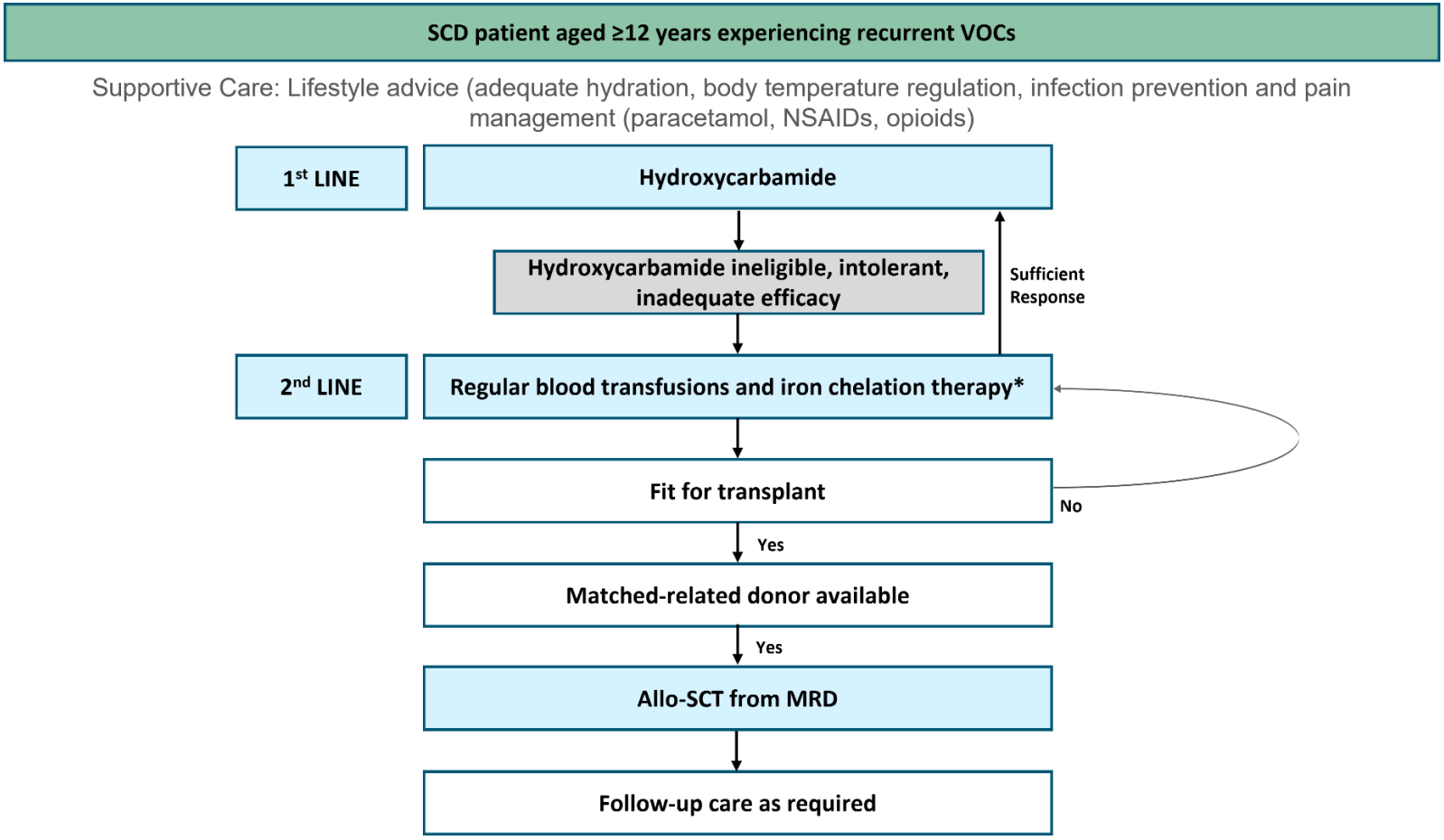
B.1.3.3.2. NICE guidelines

NICE has published one clinical guideline (CG143) in SCD for the management of acute painful sickle cell episodes in hospital (121). However, additional NICE

guidelines published on recommended treatment pathway, or chronic management of SCD do not exist, perhaps owing to the limited treatment options available.

In the absence of any formal NICE guidelines that define the treatment pathway for patients with SCD, Vertex explored the topic with clinical advisors. The UK pathway for SCD based on these discussions is depicted below in Figure 9. As described earlier in this section, the CHMP has recommended revocation of the crizanlizumab conditional marketing authorisation after a negative Phase 3 readout (122).

Figure 9: Treatment pathway for severe SCD patients in the UK



Key: MRD: matched-related donor; NSAIDs: Non-steroidal anti-inflammatory drugs; SCD: sickle cell disease, SCT: stem cell transplant.
Notes: If the patient is not eligible for allo-SCT, they remain on current treatment.
In this context, severe SCD is defined by the presence of recurrent pain and ACS. Recurrent VOCs are defined as ≥2 VOCs experienced per year.
Specific criteria for allo-SCT eligibility for adults and paediatric patients are detailed in B1.3.3.3.
*Regular blood transfusions and iron chelation therapy can be used alongside treatment with hydroxycarbamide.
Sources: BSH guidelines (61, 117-119); Vertex haemoglobinopathies advisory board (125); NHS clinical commissioning policy: Allogeneic haematopoietic stem cell transplantation for adults with sickle cell disease (126).

B.1.3.3.3. Recommendations on allo-SCT

The NHS commissioning policy considers allo-SCT for adults and children who have an HLA matched related (sibling) donor:

- Adults are eligible if they have recurrent severe pain or other acute complications despite supportive care (hydroxycarbamide or transfusion), clinically significant neurologic vascular event, regular transfusion therapy to prevent severe sickle complications and/or established end organ damage relating to SCD (127).

- Children are eligible if they experience ≥4 VOCs per year requiring hospitalisation or impacting schooling despite hydroxycarbamide, recurrent ACS despite hydroxycarbamide, CNS disease, or suboptimal medical care (128).

B.1.3.3.4. Other Relevant Guidelines

A summary of other relevant guidelines for SCD is shown in Table 9 below.

Table 9: Summary of other relevant guidelines for SCD

Title	Key Recommendations		
	Hydroxycarbamide	**Blood Transfusions**	**HSCT**
Sickle Cell Society (SCS): Standards for the clinical care of adults with sickle cell disease in the UK (2018)	Consider hydroxycarbamide in adults with HbSS or HbS/β^0 genotypes with symptomatic chronic anaemia or proteinuria unresponsive to angiotensin-converting enzyme inhibitors or angiotensin receptor blocker treatment. Individuals should be counselled regarding the need for contraception while taking hydroxycarbamide.	Transfusion history should be obtained in all SCD patients requiring transfusion. Centres should consider transfusion reactions in patients presenting unwell following a transfusion.	Protocols for allo-SCT in adults with SCD should be agreed nationally.
SCS: Sickle cell disease in childhood: standards and	Hydroxycarbamide should be offered to all children with HbSS or HbS/β^0 genotypes aged	Urgent RBC transfusion should be used in patients with	All patients or families with a child with SCD should be

recommendations for clinical care (2019)	9-42 months regardless of clinical severity. Hydroxycarbamide should be offered to all children older than 42 months who have recurrent episodes of acute pain, who have had two or more episodes of ACS, who are at high risk of progressive organ damage caused by SCD or whose lives are significantly affected by SCD symptoms.	rapidly progressive ACS, acute neurological symptoms or those who are severely unwell. Long-term transfusion regimens should be used after a cerebrovascular event to prevent recurrence and should be considered if cerebral artery velocities are abnormal on TCD scans. Iron chelation should be considered in all children on regular RBC transfusions.	offered SCT as a treatment option; should not depend on family having an available donor at the time. Transplants from any other donor than an HLA-identical family member should be undertaken only in exceptional circumstances and as part of a clinical trial.
National Haemoglobinopathy Panel Guidelines (2022)	National Haemoglobinopathy Panel Guidelines (2022) include publications of (129): • National Acute Sickle Pain Action Plan aiming to provide a guide for NHS trusts to assist implementation of care improvement initiatives. • Guidelines for the use of voxelotor in the treatment of haemolytic anaemia due to SCD. • Guidelines for the use of crizanlizumab for preventing sickle cell crises in SCD.		
Regional Guidelines from Haemoglobinopathy Coordinating Centres across England	A total of ten Haemoglobinopathy Coordinating Centres have been established across England to build care networks ensuring patients with haemoglobinopathies have access to expert clinical management. Regional guidelines provided on the South Thames Sickle Cell and Thalassaemia Network website are for information purposes only are not intended to inform individual clinical decisions (130).		

Key: Allo-SCT: allogeneic stem cell transplantation; SCD: sickle cell disease; SCS: Sickle Cell Society; SCT: stem cell transplant; TCD: transcranial Doppler.
Source: SCS Guidelines (131, 132); NHP Guidelines (129); STSTN Guidelines (130).

B.1.3.3.5. Unmet needs with current treatment

Treatment options for SCD are limited to either established therapies, such as hydroxycarbamide and transfusions, or the potentially curative allo-SCT (23, 34). Although allo-SCT can provide a cure for SCD, the procedure involves serious risks

and remains a treatment option for only a small subset of affected individuals, specifically those with a matched-related donor (21, 133). The total number of patients with all haemoglobinopathies to undergo allo-SCT in the UK in 2021 was just 36, including 24 SCD patients, the majority of which are likely to have been paediatric (134). In 2020, 25 allo-SCT were carried out for all haemoglobinopathies, SCD plus transfusion dependent thalassaemia (134). There are several risks associated with allo-SCT including infections, GvHD, graft rejection and increased mortality, and these risks plus the lack of HLA-matched donors partially explain the limited use in SCD (21, 22). Exa-cel uses the patient's own HSPCs, removing the risk of graft rejection, GvHD and increased mortality associated with allo-SCT as highlighted in B.1.3.1 (21, 22).

Hydroxycarbamide was initially approved over 50 years ago as an antineoplastic treatment for use in a range of cancers, most prominently chronic myeloid leukaemia (135). Hydroxycarbamide has been shown to improve anaemia, reduce some long-term outcomes, and improve survival in some SCD patients (36, 119, 136). However, it is not suitable for all patients and is associated with a number of issues including poor adherence, frequent monitoring, and potential risks such as teratogenesis, malignancy, neutropenia, and thrombocytopaenia (34, 36-39). Data from the three most recent National Haemoglobinopathy Registry (137) annual reports (2018/2019 – 2020/2021) indicate that approximately 10% (range: 9.6% - 10.3%) of SCD patients are receiving hydroxycarbamide in England (35). Notably, in the indication under review for this appraisal for patients experiencing recurrent acute pain events, this rate is expected to be higher, agreed as ~30% in the crizanlizumab appraisal (138).

RBC transfusions are used to manage acute and chronic complications of SCD. Despite their limited benefit, RBC transfusions are associated with risks that limit their long-term use, including iron overload, alloimmunisation, and delayed haemolytic transfusion reactions (23, 24, 139). Individuals with SCD are among the most alloimmunised groups among chronic transfusion patients, leading to an increased frequency of haemolytic transfusion reactions (117, 140). Alloimmunisation occurs in approximately 30% of transfused SCD patients, compared to 2-5% of all transfused patients (141). Data from the three most recent NHR annual reports indicates that 5-6% of SCD patients are receiving transfusions (35).

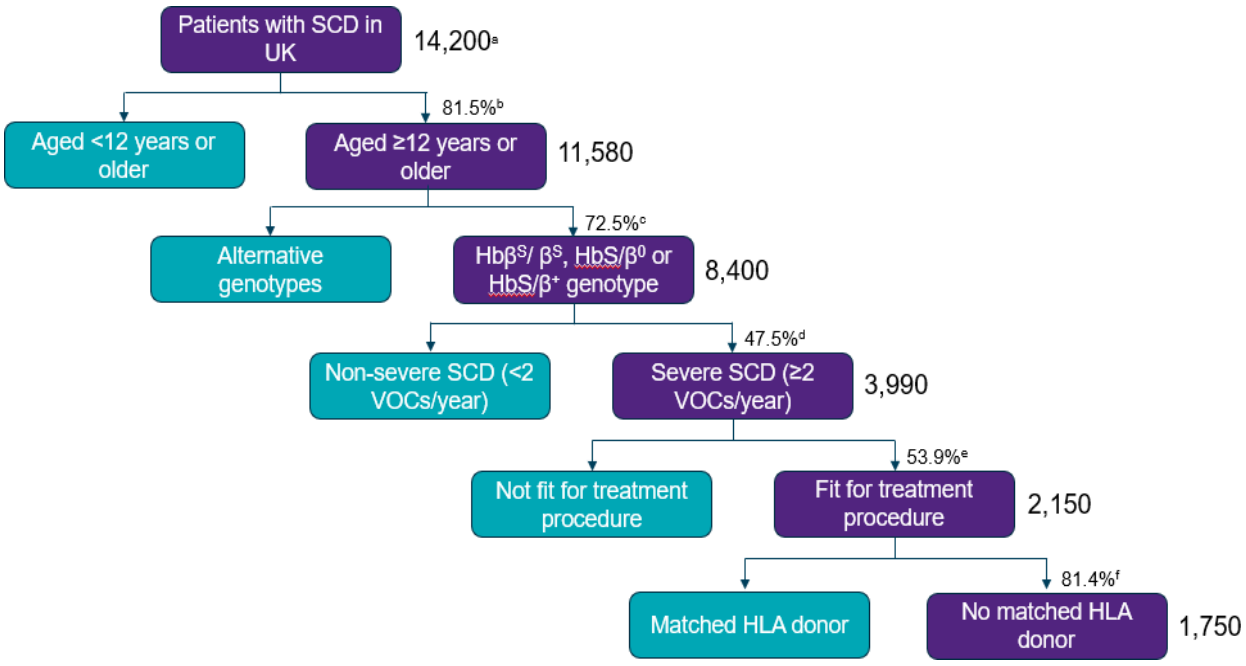
Crizanlizumab, the first SCD therapy to be made available in England for 20 years, is recommended by NICE through a managed access agreement (138). Based on clinical expert feedback, our understanding is that its usage is limited in clinical practice (12). In addition, results did not meet the primary endpoint of the Phase III STAND trial of crizanlizumab, which has resulted in the EMA recommending revocation of the conditional approval for market authorisation (122).

B.1.3.4. Proposed positioning of exa-cel in the SCD treatment pathway

As stated in Section B.1. there were an estimated 14,200 patients with SCD in the UK in 2021. Of these, 11,580 patients were 12 years of age and older, of whom an estimated 72.5% have a genotype corresponding to β^S/β^S, β^S/β^0 or β^S/β^+ (33). More than 80% of these patients do not have an HLA-related matched HSC donor, and a further 47.5% are estimated to experience recurrent VOCs (≥2 VOCs per year) (114, 116, 142, 143).

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

Figure 10: Epidemiological cascade for SCD in the UK

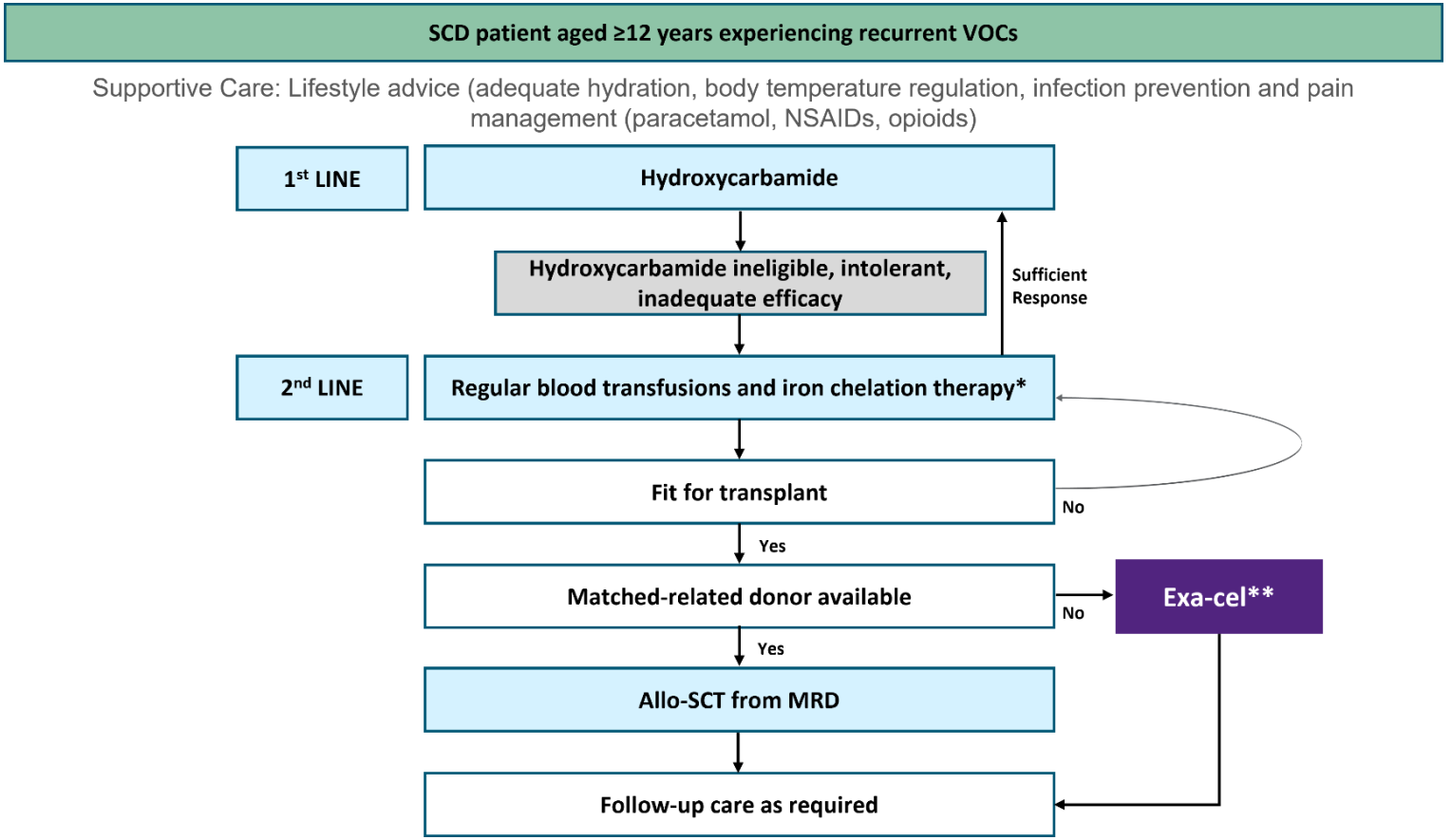


Key: Hb: haemoglobin; HLA: human leukocyte antigen; SCD: sickle cell disease; VOC: vaso-occlusive crisis.
[a]Based on data collected by the National Haemoglobinopathies Registry in 2020/21 (33).
[b]Based on data collected by the National Haemoglobinopathies Registry in 2020/21 (33).

[c]Based on data collected by the National Haemoglobinopathies Registry in 2020/21 (33).
[d]Based on data from Shah et al. (2020), Shah et al. (2019), and Desai et al. (2020) (114, 143, 144).
[e]Based on data from Vertex Internal Forecasts in 2021/22 (145).
[f]Based on data from Gragert *et al*., (2014) (142).
Notes: In the current economic model, patients with severe SCD were defined as having recurrent VOCs (≥2 VOCs 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 who do not have a matched HLA donor.

Exa-cel is positioned for the treatment of SCD in patients 12 years of age and older with recurrent VOCs who have β^S/β^S, β^S/β^0 or β^S/β^+, for whom a HLA-matched related HSC donor is not available. The proposed positioning of exa-cel is displayed schematically below in Figure 11.

Figure 11: Proposed positioning of exa-cel in the treatment pathway



Key: HLA: human leukocyte antigen; HSC: haematopoietic stem cell; MRD: matched-related donor; NSAIDs: Non-steroidal anti-inflammatory drugs; SCD: sickle cell disease, SCT: stem cell transplant; VOC: vaso-occlusive crisis.
Notes: *Regular blood transfusions and iron chelation therapy can be used alongside treatment with hydroxycarbamide.
**Indicated for SCD in patients 12 years of age and older with recurrent VOCs who have βS/βS, βS/β0 or βS/β+, for whom a HLA-matched related HSC donor is not available. Recurrent VOCs are defined as ≥2 VOCs experienced per year.

B.1.3.5. Summary of unmet medical need

SCD continues to represent a substantial unmet medical need, with life expectancy reduced by over 30 years compared to that of the general population as highlighted in Section B.1.3.2.1.c (25, 146). In a retrospective analysis of CPRD & HES data, the mean age at death in SCD patients with recurrent acute pain events in the UK was 40.2 years, based on 41 events. A similar age was reported in a broader group of SCD patients in an analysis of the UK HES database between 2009 and 2018, where the mean age at death was 46.7 years (73).

Acute pain events are the hallmark symptom of SCD, resulting in a multi-organ, systemic, and progressive disease. Importantly, higher rates of acute pain events & associated hospitalisations are linked with higher rates of mortality (31). In contrast to this, long-term data has demonstrated the benefit in reduced mortality of treatments that reduce the frequency of acute pain events (101).

Based on the available therapies, there remains a clear unmet need for a potentially curative therapy with a favourable benefit-risk profile to transform the treatment landscape in SCD. Established therapies, such as hydroxycarbamide and transfusions address some of the disease symptoms but do not offer a cure for SCD. Further, they are chronic therapies requiring prolonged, regular dosing and are associated with substantial safety and tolerability issues. The recent crizanlizumab Phase 3 trial results not meeting the primary endpoint and subsequent recommended revocation of the conditional marketing authorisation may reduce the available treatment options for addressing acute pain events even further.

To summarise, a significant unmet need remains due to the very limited number of patients for whom a matched-related donor is available, and the limited effectiveness of current chronic treatments. As a potentially curative treatment derived from a patient's own HSPCs – thereby removing the need for a suitable donor, associated risk of GvHD and rejection – exa-cel represents a paradigm shift in the management of SCD and provides a transformational opportunity to address the health inequalities that persist in SCD.

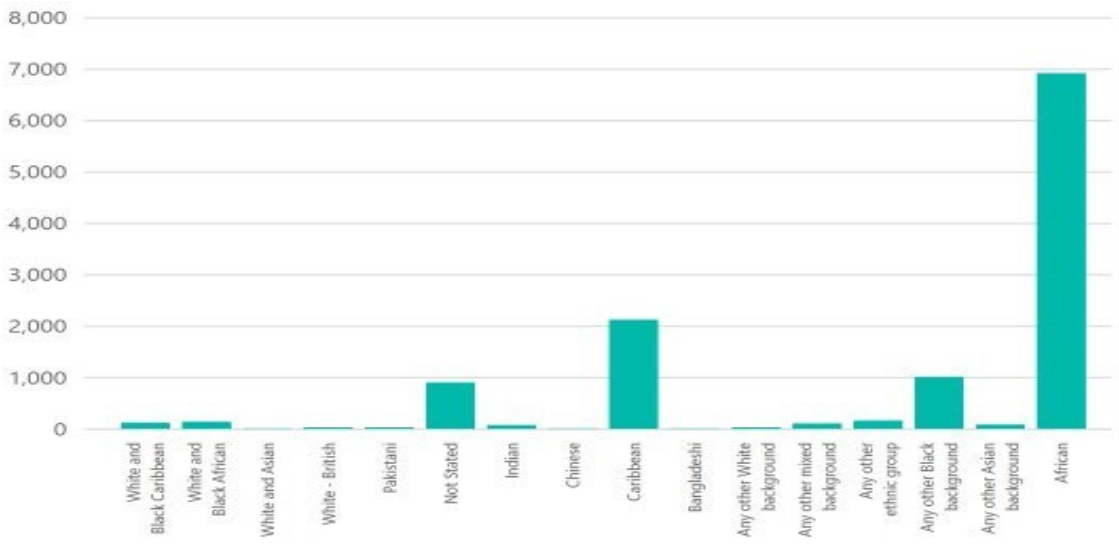
B.1.4 Equality considerations

SCD prevalence is high in regions where malaria is endemic, including sub-Saharan Africa, the Mediterranean, the Middle East and India (25, 147, 148). In part this is due historically to the protection against severe malaria associated with sickle cell trait, Historical and current migration has broadened the global distribution of SCD. Globally, the number of people living with SCD increased by 41.4% from 5.46 million to 7.74 million in 2021 (149).

Data published by the NHR in 2021 indicates that in England SCD predominantly affects individuals of African or Caribbean ethnicity (Figure 12) (137). Further support for this comes from the aforementioned UK BoI study, where the majority of enrolled patients were Black (91.6%) (4, 150).

Moreover, the COVID-19 pandemic has highlighted that these individuals tend to have poorer health outcomes, including higher rates of chronic disease and lower life expectancy, when compared to other ethnicities such as White British (151, 152).

Figure 12: Number of SCD patients by ethnicity in England



Key: NHR: National Haemoglobinopathy Registry.
Source: NHR Annual Report 2020/21 (33).

In the BoI study, 1,117 patients with SCD with recurrent VOCs were matched to 5,585 controls. SCD patients are more likely to live in a more deprived area of the UK, and the majority of SCD patients aged 12-35 years with recurrent VOCs (72.4%) were identified as being in two of the most deprived quintiles according to the Index of

Multiple Deprivation (IMD) (Table 10) (4). In addition, data showing patients admitted to hospital with a primary or secondary SCD diagnosis highlighted that 46% were in the most deprived quintile of the population (153).

Table 10: Socio-economic status of SCD patients identified in Vertex's BoI study

Socio-economic status (IMD), N (%)*	SCD with recurrent VOCs (N=1,117)
Q1 (least deprived)	38 (3.4%)
Q2	81 (7.25%)
Q3	190 (17%)
Q4	395 (35.4%)
Q5 (Most deprived)	413 (37%)

Key: BoI: burden of illness; 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: Table 6, Vertex BoI study (4).

Another important concept emerging from patient voices is the neglect of SCD as a condition by the wider medical community. During the NICE appraisal for crizanlizumab, the Sickle Cell Society (SCS) drew attention to the fact that SCD has been largely overlooked as a disease due to the poor availability of effective therapies, noting this to be one of the direct consequences of equality issues (150). They stated that "*One of the direct consequences of the equality issues [..] such as the lack of investment and innovation in developing disease modifying treatments for SCD over the past 30 years, is the fact that there is only one licensed treatment for SCD; Hydroxycarbamide. This is not for everyone with SCD"* (150).

The All-Party Parliamentary Group (APPG) on Sickle Cell and Thalassaemia advocates for increased awareness and improved care for individuals living with SCD. Following the publication of the Coroner's report into the death of Evan Nathan Smith in 2021, the APPG conducted three evidence submission sessions from patients, clinicians and politicians, receiving over one hundred submissions as a result. Findings from this evidence provides the basis for the APPG's 'No One's Listening' Report, which reveals an unfortunate pattern of many years of suboptimal care, stigmatisation as well as lack of understanding and prioritisation towards SCD patients. Ultimately, SCD patients expect poor treatment, are apprehensive to access hospitals and fear it

is only a matter of time until they encounter serious care failing, as emphasised by the early and avoidable death of Evan Nathan Smith. The APPG report therefore shines light on the lack of understanding of SCD, and the awful inequalities patients endure to access treatment, often with potentially devastating consequences (13).

The 'No One's Listening' report includes recommendations that NICE revise their clinical guideline on pain relief for SCD patients to encompass standards relating to pain management for the entirety of a sickle cell crisis (13). Of note, preliminary results from a global longitudinal survey in adult patients with SCD (n=142) reported that 67% of participants felt they had been treated unfairly due to their race whilst seeking care or requesting additional pain medication (65%) (5).

As previously mentioned, a series of recommendations were suggested during the APPG report and ultimately these recommendations are underpinned by two fundamental insights.

The first is a profound sense of anger and frustration from patients contacted since many of the failings have been highlighted in the past yet have not been properly acted upon. In 2021, the APPG on Sickle Cell and Thalassaemia launched an inquiry following numerous high-profile examples of failings in care for SCD patients, including the tragic death of Evan Nathan Smith. This inquiry has contributed to increasing awareness of the challenges frequently faced by SCD patients when receiving appropriate care. For instance, no evidence was present in Evan's medical records showing the sickle cell team received advice prior to a procedure involving stent removal, despite the increased risk of sepsis present (13).

The second insight to arise from the APPG report concerned race, with an emphasis on the deep inequality shown towards SCD patients in terms of lack of disease understanding and awareness from HCPs, and again failings in accessing treatment. Patients reported often having to educate HCPs on the basics of the condition and regularly being treated with disrespect, not believed or listened to, and being dismissed as a priority case. Patients and clinicians consulted by the APPG attributed HCPs low awareness of SCD to the inadequate training of nurses and medics. Evidence received from patients also highlighted the contribution racism has on the negative attitudes expressed towards SCD patients, which overwhelmingly impacts

individuals with African or Caribbean heritage (13). Of particular note, preliminary results from a global longitudinal survey in adult patients with SCD (n=142) reported that 67% of participants felt they had been treated unfairly due to their race whilst seeking care or requesting additional pain medication (65%) (5).

NICE have provided a written evidence submission to the APPG on Sickle Cell and Thalassaemia for the APPG report, highlighting that their current clinical guideline (CG143) in SCD for the management of acute painful sickle cell episodes in hospital specifically states that "*patients (and their carers) should be regarded as experts in their condition*". SCD patients explained to the APPG on Sickle Cell and Thalassaemia that there are many diligent, dedicated, kind healthcare professionals, however patients frequently encounter secondary care staff who do not believe in them or fail to have regard for their expertise in their condition. One SCD patient stated: '*Going into hospital as a sickle cell patient requires you to put on an armour because from the moment you reach A&E it becomes your job to convince everyone you are really in that much pain and are not simply there for medication*.' It is evident that SCD patients are often not regarded as experts in their condition as highlighted by the APPG report, which emphasises the significant lack of adherence to the NICE standards (13, 121).

This stigma relating to the management of their condition may be linked to racism relating to patient ethnicity or socioeconomic status and can deter SCD patients from seeking medical support (154, 155). The use of opioids to manage acute sickle pain may lead to a health care perception of drug seeking behaviour and this can lead to further stigma.

As previously mentioned, 42% of self-reported severe pain crises were managed at home in the UK survey for SWAY (56). Poor experience in accident and emergency (A&E) or hospital has been reported as the most common reason for refraining from seeking medical care during a VOC and managing it at home (54, 156). For those who do seek medical support, nearly half (48%) of patients hospitalised for SCD in England are from the most socioeconomically deprived 20% of the population and a significant degree of distrust between patients and healthcare providers also exists (54, 153, 156, 157).

Making exa-cel available through the NHS would provide a new potentially curative treatment option for SCD patients in England and Wales, specifically for those do not have a HLA-matched sibling donor. Decisions around the availability of SCD treatments primarily affect individuals from ethnic minorities who have a chronic lifelong health condition, many of whom are economically disadvantaged and subject to health inequalities. These issues were acknowledged by NICE in its evaluation of crizanlizumab (123). As a result of the prevalence in ethnic minorities, deprivation scores, and stigma, patients with SCD are subject to health inequalities that could be addressed by exa-cel.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D: Identification, selection and synthesis of clinical evidence 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: Identification, selection and synthesis of clinical evidence. 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 for the treatment of severe SCD. CLIMB SCD-121 (also known as CTX001-121; NCT03745287) 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 severe SCD (Table 11) (158). Eight records were retrieved relating to CLIMB SCD-121, including a publication in the *New England Journal of Medicine* detailing early results, and seven conference proceedings, where results from subsequent data cuts were presented (14, 159-165).

Severe SCD was defined by the occurrence of at least two of the following events each year during the 2-year period prior to screening, whilst receiving appropriate supportive care (i.e. pain management plan or hydroxycarbamide if indicated) (166):

- Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or IV NSAIDs or RBC transfusions).
- ACS
- Priapism lasting > 2 hours and requiring a visit to a medical facility.
- Splenic sequestration.

In response to a regulatory authority request, 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 16 April 2023, providing up to 46.2 months of follow-up (7). D120 provides the longest duration of follow-up for patients treated with exa-cel, and as such efficacy outcomes reported here from CLIMB SCD-121 and CLIMB-131 focus on the D120 data cut-off (7). As D120 was not pre-specified, the level of detail reported is less than for interim analysis 2 (IA2), the data cut for which was 16 September 2022. For completeness, the IA2 clinical study reports (CSRs) for CLIMB SCD-121 and CLIMB-131 are provided as data on file (166, 167). Furthermore, due to the recency of the D120 data cut, there are no publicly available references to this data. As such, results are taken from the associated report (7).

A total of 63 patients were enrolled at the time of D120. Of these, 43 patients had received exa-cel (7). The final analysis of CLIMB SCD-121 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 (166).

All patients who complete CLIMB SCD-121 (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). Patients participating in CLIMB-131 will be monitored for up to 15 years following exa-cel infusion. The results of this study have not been published as only a small subset of severe SCD patients had completed CLIMB SCD-121 and voluntarily enrolled into CLIMB-131 at the time of submission (7, 166). Details of the ongoing CLIMB-131 study can be found in Section B.2.11.

Table 11: Clinical effectiveness evidence

Study	CLIMB SCD-121 (NCT03745287)
Study design	A Phase 1/2/3 study to evaluate the safety and efficacy of a single dose of autologous CRISPR-Cas9 modified $CD34^+$ Human Hematopoietic Stem and Progenitor Cells (hHSPCs) in patients with severe Sickle Cell Disease (SCD)
Population	Patients with severe SCD aged 12 to 35 years
Intervention(s)	Exa-cel (formerly known as CTX001)
Comparator(s)	None - CLIMB SCD-121 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 severe VOCs** • **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	Not applicable.

Key: hHSPC: human haematopoietic stem cell; SCD: sickle cell disease
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 12: Summary of study methodology for CLIMB SCD-121

Study	CLIMB SCD-121 (NCT03745287)
Location	CLIMB SCD-121 is being conducted at a total of 16 study centres across the US (9 sites), Canada (1 site), UK (1 site), France (1 site), Belgium (1 site), Germany (2 sites) and Italy (1 site).
Study design	A Phase 1/2/3 study to evaluate the safety and efficacy of a single dose of autologous CRISPR-Cas9 modified $CD34^+$ human haematopoietic stem and progenitor cells in patients with severe sickle cell disease (SCD).

Key eligibility criteria for participants	**Inclusion criteria:**
	• β^S/β^S, β^S/β^0, or β^S/β^+ genotype
	• Aged 12 to 35 years
	• Severe SCD defined as experiencing at least 2 of the following events per year during the 2-year period before screening whilst receiving appropriate supportive care:
	  ○ An acute pain event that required a visit to a medical facility and administration of pain medications or red blood cell (RBC) transfusions
	  ○ Acute chest syndrome
	  ○ Priapism lasting >2 hours and requiring a visit to a medical facility
	  ○ Splenic sequestration
	• Eligible for autologous stem cell transplantation
	Exclusion criteria:
	• Willing and healthy 10/10 human leukocyte antigen-matched related donor
	• Prior allogeneic stem cell transplantation (allo-SCT)
	• Clinically significant and active bacterial, viral, fungal, or parasitic infection
	• White blood cell count <3 x 10^9/L or platelet count <50 x 10^9/L
	• Regular blood transfusion that cannot be interrupted after engraftment
	• Alloimmunisation to RBC antigens associated with anticipated insufficiency of suitable RBC units for the duration of the study

	• ≥10 unplanned hospitalisations or accident and emergency visits related to SCD in the past year that reflect significant chronic pain rather than VOCs • Elevated risk of stroke (defined as a history of abnormal Transcranial Doppler (TCD) [time-averaged mean of the maximum velocity ≥200 cm/sec for non-imaging TCD and ≥185 cm/sec for imaging TCD] for patients 12 to 18 years of age • Females who are pregnant or breastfeeding
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 SCD-121.
Study periods and trial drugs	• CLIMB SCD-121 is a single-arm study in which all enrolled participants are dosed with exa-cel. • For each patient, the study is conducted in four stages: • **Screening and pre-mobilisation period (Figure 13; Stage 1):** o Informed consent and determination of patient eligibility. o Fertility preservation via cryopreservation of oocyte or sperm, or gonadal tissue for pre-pubescent patients. o RBC transfusions for ≥8 weeks prior to planned mobilisation to achieve a goal of HbS% <30% and maintaining total haemoglobin ≤11 g/dL • **Mobilisation, autologous CD34+ stem cell collection, exa-cel manufacture and disposition (Figure 13; Stage 2):** o Stem cell mobilisation with plerixafor 2-3 hours prior to apheresis (0.24 mg/kg) followed by apheresis for three consecutive days to collect peripheral blood mononuclear cells. o Target collection of $CD34^+$ cells for manufacturing of exa-cel is ≥15 x 10^6 $CD34^+$ cells/kg (minimum target dose of 3 × 10^6 $CD34^+$ cells/kg). Up to 3 cycles of mobilisation and apheresis, separated by ≥14 days, are allowed to achieve target collection. An additional 2 x 10^6 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. ○ 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 13; Stage 3A) and infusion of exa-cel (Figure 13; Stage 3B):** ○ RBC transfusions for ≥8 weeks prior to planned conditioning to achieve a goal of HbS% <30% and maintaining total haemoglobin ≤11 g/dL ○ Conditioning (Stage 3A): Daily intravenous 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 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 post-exa-cel infusion. • **Post-infusion in-hospital follow-up during engraftment (Figure 13; Stage 4A):** ○ Monitoring in the transplant unit and supportive care according to standard practices for patients undergoing allo-SCT, 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 13; Stage 4B): Follow-up for approximately 2 years from exa-cel infusion, with physical examinations, laboratory and imaging assessments, and evaluations for adverse events. Restarting iron chelation therapy if clinically indicated 3 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 63 patients were enrolled at the time of the D120 data cut-off date (16 April 2023).

	○ All patients who received exa-cel infusion who completed or discontinued CLIMB SCD-121 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 SCD-121 and up to 13 years of follow-up in CLIMB-131.
Prior and concomitant medication	• RBC transfusions for ≥8 weeks prior to planned mobilisation to achieve a goal of Hb ≤11 g/dL before the start of apheresis. • Exchange or simple transfusions required for at least 8 weeks prior to planned conditioning. • SCD-specific symptomatic therapies (i.e. hydroxycarbamide) should be discontinued 8 weeks prior to starting mobilisation. • Patients are administered plerixafor at a dose of 0.24 mg/kg via subcutaneous injection approximately 2 to 3 hours prior to planned apheresis and apheresis was performed for up to three consecutive days. • Myeloablative conditioning with busulfan administered for 4 consecutive days via a central venous catheter at a planned starting dose of 3.2 mg/kg/day once daily or 0.8 mg/kg every 6 hours. • 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 allo-SCT. • During the follow-up period, patients should receive packed RBCs for Hb ≤7 g/dL or for clinical symptoms. • Filgrastim is listed as a prohibited medication (only allowed if engraftment did not occur by Day 21 after exa-cel infusion).
Primary efficacy endpoint	• Proportion of patients achieving an absence of any severe vaso-occlusive crisis (VOC) for at least 12 months after exa-cel infusion (VF12)*
Secondary outcomes used in the model/specified in the scope	• Proportion of patients free from inpatient hospitalisation for severe VOCs (HF12)** sustained for at least 12 months after exa-cel infusion • Severe VOC free duration for patients who achieved VF12 • Relative reduction in annualised rate of severe VOCs: patients who did not achieve VF12 • Proportion of patients with sustained fetal haemoglobin (HbF) • Total Hb and HbF concentration • Proportion of alleles with intended genetic modification • Relative reduction in number of RBC units transfused for SCD-related indications

	• Patient-reported outcomes
Pre-planned subgroups	• Age at screening (12-<18 and 18-35) • Genotype (β^S/β^{S-}like and non-β^S/β^S-like) • Gender (male and female) • ≥3 VOCs/ year for the prior 2 years at baseline

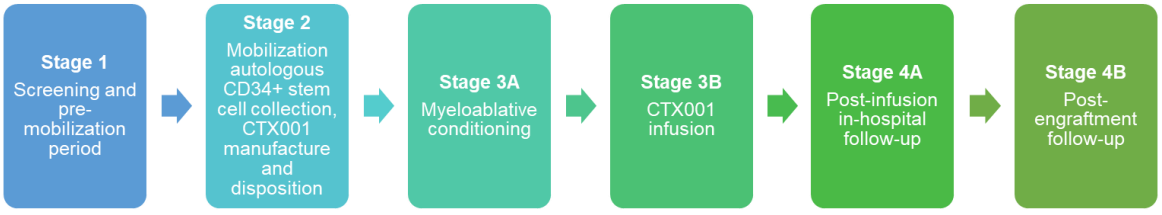
Key: allo-SCT: allogeneic stem cell transplantation; Hb: haemoglobin; HbF: fetal haemoglobin; RBC: red blood cell; SCD: sickle cell disease; TCD: transcranial Doppler: vaso-occlusive crisis.
Notes: *VF12 is defined as the absence of any severe VOC for at least 12 consecutive months after exa-cel infusion. **HF12 is defined as free from inpatient hospitalisation for severe VOCs and sustained for at least 12 months after exa-cel infusion.
Source: Section 9.3, CLIMB SCD-121 CSR and Vertex D120 Report Data on File (7, 166).

B.2.3.2. Study design

CLIMB SCD-121 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 severe SCD. Severe SCD was defined by the occurrence of at least 2 of the following events each year during the 2-year period before screening, while receiving appropriate supportive care (i.e. pain management plan, hydroxycarbamide if indicated) (166):

- Acute pain event that required a visit to a medical facility and administration of pain medications (opioids or IV non-steroidal anti-inflammatory drugs) or RBC transfusions.
- ACS, as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever.
- Priapism lasting >2 hours and requiring a visit to a medical facility.
- Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in Hb concentration of ≥2 g/dL.

Figure 13: CLIMB SCD-121 study design



Source: CLIMB SCD-121 Study Protocol (168).

Approximately 45 patients were planned to be dosed in the CLIMB SCD-121 pivotal study to assess the efficacy and safety of a single dose of exa-cel, with the proportion of patients who achieved an absence of any severe VOC for at least 12 consecutive months (VF12) following exa-cel infusion as the primary endpoint. The evaluation of VF12 starts 60 days after the last RBC transfusion for post-transplant support or SCD management (166).

As described in Table 12 and shown in Figure 13, CLIMB SCD-121 was conducted in four stages (166):

- 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 D120, 63 patients were enrolled in the pivotal CLIMB SCD-121 clinical study. Of these, 43 patients had received exa-cel infusion (7).

B.2.3.3. Eligibility criteria

As previously mentioned, the key inclusion and exclusion criteria for CLIMB SCD-121 are shown in Table 13. For a full list of eligibility criteria, please refer to Section 9.3 of the CLIMB SCD-121 CSR and Table 3 in the D120 Report (7, 166).

Table 13: Key eligibility criteria for CLIMB SCD-121

Key inclusion criteria	Key exclusion criteria

• β^S/β^S, β^S/β^0, or β^S/β^+ genotype
• Aged 12 to 35 years
• Severe sickle cell disease (SCD) defined as experiencing at least 2 of the following events per year during the 2-year period before screening whilst receiving appropriate supportive care:
  ○ An acute pain event that required a visit to a medical facility and administration of pain medications or red blood cell (RBC) transfusions
  ○ Acute chest syndrome
  ○ Priapism lasting >2 hours and requiring a visit to a medical facility
  ○ Splenic sequestration
• Eligible for autologous stem cell transplant
	• Willing and healthy 10/10 human leukocyte antigen-matched related donor
	• Prior allogeneic stem cell transplant
	• Clinically significant and active bacterial, viral, fungal, or parasitic infection
	• White blood cell count <3 x 10^9/L or platelet count <50 x 10^9/L
	• Regular blood transfusions that cannot be interrupted after engraftment
	• Alloimmunisation to RBC antigens associated with anticipated insufficiency of suitable RBC units for the duration of the study
	• ≥10 unplanned hospitalisations or accident and emergency visits related to SCD in the past year that reflect significant chronic pain rather than acute pain crises
	• Elevated risk of stroke (defined as a history of abnormal Transcranial Doppler (TCD) [time-averaged mean of the maximum velocity ≥200 cm/sec for non-imaging TCD and ≥185 cm/sec for imaging TCD] for patients 12 to 18 years of age
	• Females who are pregnant or breastfeeding

Key: RBC: red blood cell; SCD: sickle cell disease; TCD: Transcranial Doppler.
Source: Section 9.3, CLIMB SCD-121 CSR and Vertex D120 Report (7, 168).

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

CLIMB SCD-121 is being conducted at a total of 16 study centres across the US, Canada, UK, France, Belgium, Germany and Italy (166).

Patients are hospitalised to undergo myeloablative conditioning and exa-cel infusion (Stages 3A/3B) and remain 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 occur on an outpatient basis (166).

B.2.3.5. Trial drugs and concomitant medications

B.2.3.5.1. Trial drugs

In CLIMB SCD-121 (Stage 3B), patients received a single infusion of exa-cel at least 48 hours, and within seven days, after the last dose of busulfan. 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 (168).

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 (166).

Details of all other trial drugs used in CLIMB SCD-121 can be found in Table 12.

B.2.3.5.2. Concomitant medication

Filgrastim was listed as a prohibited medication if engraftment occurred before Day 21 after exa-cel infusion (166). Further details on the use of RBC transfusions are outlined below.

RBC 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 and HbS <30% of total Hb (166).

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 (166).

Post-exa-cel infusion, it was recommended that patients received packed RBCs for Hb ≤7 g/dL or for clinical symptoms (166).

B.2.3.5.3. Restricted medications

There were no restricted medications in CLIMB SCD-121 (166).

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

The primary efficacy endpoint of CLIMB SCD-121 is the proportion of patients who achieve VF12, defined as the absence of any severe VOC for at least 12 consecutive months after exa-cel infusion. A minimum of 12 months duration of absence of severe VOCs was robust and considered to be highly unlikely to be due to chance, in patients who had 2 or more severe VOCs per year in the 2 years before screening.

The evaluation of VF12 for each patient starts 60 days after the last RBC transfusion for post-transplant support or SCD management (7).

Other secondary efficacy endpoints used to evaluate the clinical benefit of exa-cel are summarised in Table 14 below (7).

Table 14: CLIMB SCD-121 secondary endpoints

Endpoint	Definition
Severe VOCs	• Proportion of patients achieving HF12* for at least 12 consecutive months after exa-cel infusion. Evaluation of HF12 starts 60 days after last RBC transfusion for post-transplant support or SCD management. • Duration of severe VOC-free period in participants who have achieved VF12** up to 24 months, starting 60 days after exa-cel infusion. • Relative change from baseline in annualised rate of severe VOCs up to 24 months starting 60 days after exa-cel infusion. • Proportion of patients with a reduction in annualised rate of severe VOCs from baseline by at least 90%, 80%, 75%, and 50% up to 24 months, starting 60 days after exa-cel infusion.
HbF and Hb	• Change in HbF and Hb concentration over time. • Proportion of patients with sustained HbF ≥20% for at least 3 months, 6 months or 12 months, starting 60 days after last RBC transfusion for post-transplant support or SCD management. • Change in proportion of F-cells over time.
Allelic editing	• Proportion of alleles with intended genetic modification present in peripheral blood leukocytes and $CD34^+$ bone marrow cells over time.
Haemolysis markers	• Change from baseline in reticulocyte count, indirect bilirubin, haptoglobin and lactose dehydrogenase over time.
RBC transfusions	• Relative reduction from baseline in number of units of RBCs transfused for SCD-related indications up to 24 months starting after Month 12 post exa-cel infusion.

PROs	• Changes in PROs over time from screening: ○ EQ-5D-5L ○ 11-point Numerical Rating Scale (NRS) ○ FACT-BMT ○ ASCQ-Me

Key: ASCQ-ME: Adult Sickle Cell Quality of Life Measurement Information System; 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; NRS: Numerical Rating Scale; PRO: patient-reported outcome; RBC: red blood cell.
Notes: *HF12 is defined as free from inpatient hospitalisation for severe VOCs and sustained for at least 12 months after exa-cel infusion. **VF12 is defined as the absence of any severe VOC for at least 12 consecutive months after exa-cel infusion.
Source: Vertex D120 Report Data on File (7).

The safety of exa-cel was evaluated using the following safety endpoints (166):

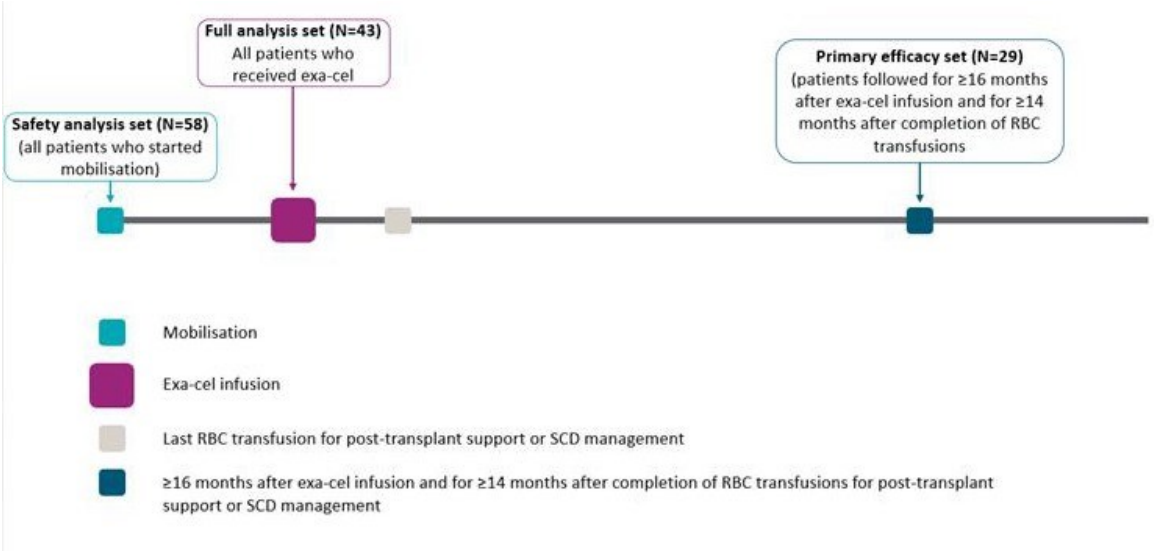
- Safety and tolerability assessments based on AEs, clinical laboratory values, and vital signs
- Successful neutrophil engraftment
- Time from exa-cel infusion to neutrophil engraftment
- Successful platelet engraftment
- Time from exa-cel infusion to platelet engraftment
- Incidence of transplant-related mortality (TRM) within 100 days and within one year after exa-cel infusion
- All-cause mortality

B.2.3.7. Patient datasets

All study analysis sets are summarised in Table 15. Efficacy analyses were performed on the Primary Efficacy Set (169), unless otherwise stated (7, 166).

The PES is a subset of the Full Analysis Set (170), 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 SCD (7, 166). 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, 166).

Figure 14: D120 data collection points and analysis sets for CLIMB SCD-121



Key: FAS: full analysis set; PES: primary efficacy set; RBC: red blood cell; SAS: safety analysis set; SCD: sickle cell disease.
Notes: The number of patients in each analysis set was recorded at the time of the most recent data-cut (16 September 2022). A RBC transfusion washout period of 60 days after the last RBC transfusion for post-transplant support or SCD management was also required post exa-cel infusion.
Source: CLIMB SCD-121 CSR (166) and Vertex D120 Report Data on File (7).

At the time of D120, 58 of the 63 patients enrolled started mobilisation and were included in the SAS, and 43 patients received exa-cel infusion and were included in the FAS (Table 15). As described in Table 15, 2 of the 43 patients in the FAS had less than 60 days of follow-up after the last RBC transfusion for post-transplant support or SCD management. Twenty-nine patients were evaluable for the PES at the time of analysis (Table 15) (7). The D120 analysis sets for CLIMB SCD-121 and CLIMB-131 are presented below.

Table 15: D120 analysis sets for CLIMB SCD-121 and CLIMB SCD-131

Analysis Set	Definition	D120 (N)
Enrolled Set	Includes all enrolled patients who signed informed consent and met eligibility criteria.	63
SAS	Includes patients who started the mobilisation regimen.	58
Started the conditioning regimen	Includes all patients who received exa-cel infusion.	43
FAS	Includes all patients who received exa-cel infusion.	43

FAS beyond initial 60 days after last RBC transfusion for post-transplant support or SCD management	Includes all patients who received exa-cel infusion that were beyond initial 60 days after last post-transplant RBC transfusion.	41
PES	Includes all patients who were 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 SCD management.	29

Key: AE: adverse event; exa-cel: exagamglogene autotemcel; D120: day 120; FAS: Full Analysis Set; n: size of subsample; PES: Primary Efficacy Set; SAS, Safety Analysis Set; SCD: sickle cell disease.
Source: Vertex D120 Report Data on File (7).

The analysis of the study's primary efficacy endpoint, the proportion of patients who achieved VF12, and key secondary endpoint, the proportion of patients who were free from inpatient hospitalisation for severe VOCs and sustained for at least 12 months (HF12) after exa-cel infusion, was limited to the PES (n=29) (Table 16) as not all patients in the FAS had sufficient follow-up to be included in the analysis.

For the remaining efficacy endpoints, the reporting of clinical effectiveness results will focus on the FAS, unless otherwise specified (Table 16), considering that this analysis set includes a larger sample size (n=43) and is more representative of the eligible patient population given the higher proportion of patients aged ≥12 and <18 years (see Table 17 and Section B.2.3.8). The results of the secondary endpoints for the PES are available in Section 3.3.3 of the D120 report (7).

Table 16: D120 analysis of efficacy endpoints (CLIMB SCD-121 and CLIMB-131)

Efficacy endpoint	Analysis set(s)	Relevant trial(s)
Primary endpoint		
VF12	PES	CLIMB SCD-121
Key secondary endpoint		
HF12	PES	CLIMB SCD-121
Additional secondary endpoints		
Duration of VOC free from transfusion	FAS	CLIMB SCD-121, CLIMB-131
Duration free from inpatient hospitalisation	FAS	CLIMB SCD-121, CLIMB-131
Total Hb and HbF concentration	FAS	CLIMB SCD-121, CLIMB-131
Proportion of patients with sustained HbF ≥20%	PES	CLIMB SCD-121, CLIMB-131
Proportion of alleles with intended genetic modification	FAS	CLIMB SCD-121, CLIMB-131

Changes in haemolysis biomarkers	PES	CLIMB SCD-121, CLIMB-131
Reductions in transfusions	PES	CLIMB SCD-121, CLIMB-131
F-cells over time	FAS	CLIMB SCD-121, CLIMB-131
PROs	PES	CLIMB SCD-121

Key: FAS: Full Analysis Set; Hb: haemoglobin; HbF: fetal haemoglobin; PES: Primary Efficacy Set; PRO: patient-reported outcome; RBC: red blood cell.
Notes: HF12 is defined as free from inpatient hospitalisation for severe VOCs and sustained for at least 12 months after exa-cel infusion. VF12 is defined as the absence of any severe VOC for at least 12 consecutive months after exa-cel infusion.
Source: Vertex D120 Report Data on File (7).

B.2.3.8. Baseline characteristics

Table 17 presents the key demographic and baseline characteristics for the CLIMB SCD-121 FAS and PES in the D120 data cut (7).

For the 43 patients in the FAS, the mean age of patients was 21.2 years (range 12 to 34 years), with 12 patients (27.9%) ≥12 and <18 years of age (Table 17) (7). This is slightly younger than the mean age of UK patients enrolled in the BoI study described in Section B1 (24.96 years [range: 1- 86 years]). However, feedback from clinical experts was that younger, fitter patients would be prioritised for treatment with exa-cel, which may result in a lower mean age relative to the BoI study (12). The majority of patients were Black or African American (86.0%) (Table 17) (7).

The CLIMB SCD-121 cohort represent a population with a high VOC burden. The mean (range) annualised rate of severe VOCs per year for the prior two years before screening was 4.2 (2.0-18.5) and the mean (range) annualised rate of inpatient hospitalisations for severe VOCs was 2.7 (0.5-9.5) per year (7). The mean (SD) annualised units of RBC transfusions was 11.6 (SD, 18.5) per year for all patients in the FAS (7).

In addition, the majority of patients (90.7%) in the FAS had a β^S/β^S genotype and 7.0% had a β^S/β^0 genotype (Table 17). Clinical experts consulted as part of this submission felt that the genotype distribution in CLIMB SCD-121 was similar to what would be expected in UK clinical practice (12).

Table 17: Patient demographics in D120 (FAS and PES, CLIMB SCD-121)

Demographics	FAS (N=43)	PES (N=29)
Sex, n (%)		
Male	24 (55.8)	16 (55.2)
Female	19 (44.2)	13 (44.8)
Childbearing potential, n (%)		
Yes	19 (100.0)	13 (100.0)
No	0	0
Age at screening (years), n (%)		
n	43	29
Mean (SD)	21.2 (6.1)	22.2 (6.1)
Median	20.0	21.0
Min, Max	12, 34	12, 34
Age category at screening (years), n (%)		
≥12 and <18 years	12 (27.9)	6 (20.7)
≥18 and ≤35 years	31 (72.1)	23 (79.3)
Race, n (%)		
White	3 (7.0)	1 (3.4)
Black or African American	37 (86.0)	26 (89.7)
Asian	0	0
Not collected per local regulation	0	0
Other	3 (7.0)	2 (6.9)
Multiracial	0	0
Genotype, n (%)		
β^S/β^S	39 (90.7)	28 (96.6)
β^S/β^0	3 (7.0)	1 (3.4)
β^S/β^+	1 (2.3)	0
Total Hb (g/dL), n		
n	42	28
Mean (SD)	9.1 (1.6)	9.1 (1.6)
Median	9.4	9.5
Min, Max	5.7, 12.6	5.7, 12.6
HbF (%), n		
n	43	29
Mean (SD)	5.3 (3.8)	5.1 (3.8)
Median	5.0	5.2
Min, Max	0.0, 14.7	0.0, 14.7
HbF (g/dL), n		
n	42	28
Mean (SD)	0.5 (0.4)	0.5 (0.4)
Median	0.4	0.4
Min, Max	0.0, 1.5	0.0, 1.5
Annualised rate of severe VOCs, n		
n	43	29
Mean (SD)	4.2 (3.0)	3.9 (2.2)
Median	3.5	3.0
Min, Max	2.0, 18.5	2.0, 9.5
Annualised rate of inpatient hospitalisations for severe VOCs, n		
n	43	29
Mean (SD)	2.7 (2.1)	2.7 (2.1)

Median	2.5	2.0
Min, Max	0.5, 9.5	0.5, 8.5
Annualised duration of inpatient hospitalisations for severe VOCs (days), n		
n	43	29
Mean (SD)	19.6 (22.2)	17.4 (14.4)
Median	13.5	12.5
Min, Max	2.0, 136.5	2.0, 64.6

Key: EAC: Endpoint Adjudication Committee; FAS: Full Analysis Set; Hb: haemoglobin; HbF: fetal haemoglobin; max: maximum; min: minimum; N: total sample size; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease; VOCs: vaso-occlusive crises.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation. Baseline severe VOCs, inpatient hospitalisations for severe VOCs, and RBC transfusions were based on the 2 years before the most recent screening. Only severe VOCs adjudicated by an Endpoint Adjudication Committee (171) as meeting the protocol definition of severe VOCs were included. Hb measurements were from central laboratories. Annualised rate = total number of events/number of years. Annualised duration = total duration of events/number of years. Annualised units = total units/number of years. One year = 365.25 days.
Sources: Tables 15 and 16, Vertex D120 Report (7).

Eligibility for treatment with exa-cel is primarily driven by the individual patients' fitness to safely undergo myeloablative conditioning with busulfan. As busulfan would be the conditioning regimen used in UK clinical practice, the eligibility criteria applied to patients enrolled onto CLIMB SCD-121 is likely to be generalisable to those who would be eligible to receive exa-cel in clinical practice (12).

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

B.2.4.1. Analysis population

At D120, efficacy analyses were performed using the PES and the FAS, where applicable (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% (166).

B.2.4.3. Statistical analysis

A summary of statistical analyses for CLIMB SCD-121 is presented below in Table 18.

Table 18: Summary of key statistical analyses used in CLIMB SCD-121

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT03745287 (CLIMB SCD-121)	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% exact CIs were calculated using the	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 1-sided alpha of 2.5%.	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.

		Clopper-Pearson method.		

Key: CI: confidence interval.
Source: CLIMB SCD-121 CSR (166).

B.2.4.3.1. Primary efficacy analysis

As described previously, the primary efficacy endpoint is the proportion of patients who achieved VF12, defined as the absence of any severe VOC for at least 12 consecutive months after exa-cel infusion. The evaluation of VF12 for each patient starts 60 days after the last RBC transfusion for post-transplant support or SCD management (7).

At D120, the analysis of the primary efficacy endpoint was based on the PES. The proportion of patients achieving VF12 will be provided, with a one-sided p-value (against a null hypothesis of 50% response rate) and two-sided 95% exact Clopper-Pearson confidence interval (CI) (7).

Of note, if the prespecified efficacy boundary is crossed at any interim analysis overwhelming efficacy is considered established for exa-cel (166).

B.2.4.3.2. Key secondary efficacy analysis

As described previously the key secondary efficacy endpoint is the proportion of patients who achieved HF12 after exa-cel infusion. The duration of HF12 starts 60 days after last RBC transfusion for post-transplant support or SCD management. As for the primary efficacy endpoint, analysis of the key secondary efficacy endpoint at D120 was based on the PES (7).

B.2.4.3.3. Other secondary efficacy analysis

At D120, the analysis of secondary endpoints was based on the PES and FAS. 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-cause mortality and transplant-related mortality
- Engraftment (neutrophil and platelet)

Safety analyses were based on the SAS, unless otherwise specified. Only descriptive analysis of safety was performed; no statistical testing was performed (166).

B.2.4.4. Participant flow

Details of participant flow in the D120 data cut (16 April 2023) for the CLIMB SCD-121 and CLIMB-131 studies 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 SCD-121, a Phase 1/2/3 single-arm, open-label, multi-site, single-dose study. The quality assessment of CLIMB SCD-121 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 severe SCD has been demonstrated in CLIMB SCD-121 and CLIMB-131.
- Severe SCD was defined by the occurrence of at least 2 VOCs (any of: acute pain crisis, acute chest syndrome, priapism, splenic sequestration) per year in the two years prior to enrolment.
- At the most recent data cut (D120), 28 of 29 patients achieved the primary endpoint of VF12 after exa-cel infusion.
- In addition, all patients (100%) in the PES achieved the secondary endpoint of HF12 after exa-cel infusion.
- In the FAS, 41 of the 43 patients had at least 60 days of follow-up after the last RBC transfusion and have been VOC free for 1.3 to 43.6 months.
- 37 of 41 patients (90.2%) in the FAS did not experience any VOCs and remained VOC-free throughout the duration of follow-up (from 60 days after the last RBC transfusion).
- Despite experiencing events adjudicated as VOCs, the remaining four patients have all demonstrated treatment benefit from exa-cel, and were VOC-free for a duration of 0.7 – 10.4 months at D120.
- Two of the four patients were in the PES. Both of these patients achieved HF12.
- After achieving VF12 and HF12, one of the four patients ([redacted]) experienced an inpatient hospitalisation for a severe VOC approximately 22.7 months following exa-cel infusion. The patient has since been VOC-free for a duration of 10.4 months.
- In the FAS, total Hb concentration increased from 9.1 g/dL at baseline to 12.0 g/dL at Month 3 and between 12.0 – 13.5 g/dL throughout CLIMB SCD-121.
- 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.

B.2.6.1. Primary and key secondary endpoints

As described in B2.1, summary results from the D120 data cut (16 April 2023) have recently been made available, and are presented below to provide evidence on the long-term efficacy of exa-cel (7). Exa-cel cohorts and analysis sets are summarised in Section B.2.3.7, and presented for clarity in Table 15 and Table 16.

Following infusion with exa-cel, 28 of 29 (96.6%) patients in the PES achieved VF12 (95% CI: 82.2%, 99.9%; p<0.0001). In the context of data at baseline, where patients in the PES had a mean of 3.9 severe VOCs per year in the previous two years, this demonstrates the substantial impact of exa-cel treatment in addressing recurrent VOCs in these patients (Table 17) (7).

In addition, 29 of 29 (100%) patients in the PES achieved HF12 (95% CI: 88.1%, 100.0%; p<0.0001) (7).

B.2.6.2. Secondary efficacy endpoints

B.2.6.2.1. Duration of severe VOC free

At the D120 data cut, 41 of 43 patients in the FAS had at least 60 days of follow-up after the last RBC transfusion for post-transplant support or SCD management. Of these patients, 37 of 41 were VOC-free for a duration of 1.3 to 43.6 months (Figure 15), starting 60 days after the last RBC transfusion (7). The remaining four patients experienced events adjudicated as VOCs after exa-cel infusion with at least 60 days of follow-up after the last RBC transfusion for post-transplant support or SCD management (7).

Information on these four patients at the time of the most recent data-cut is presented below and additional detail is provided in Section 3.3.3.1 of the D120 report and Section 11.4 of the CLIMB SCD-121 CSR (7, 166). At D120, 2 patients ([redacted]), who are not yet included in the PES, had pain events adjudicated as VOCs following exa-cel infusion. However, these patients have since experienced either clinical benefit or maintain the potential to achieve VF12 (7).

- [redacted] was VOC-free for approximately 22.7 months after exa-cel infusion, before experiencing an

isolated event adjudicated as a VOC. Approximately 22.8 months after exa-cel infusion, the patient was hospitalised for [redacted] fever and worsening pain, considered to be related to a viral infection. [redacted]

- [redacted] experienced eight acute pain events adjudicated individually as VOCs following exa-cel infusion. [redacted]

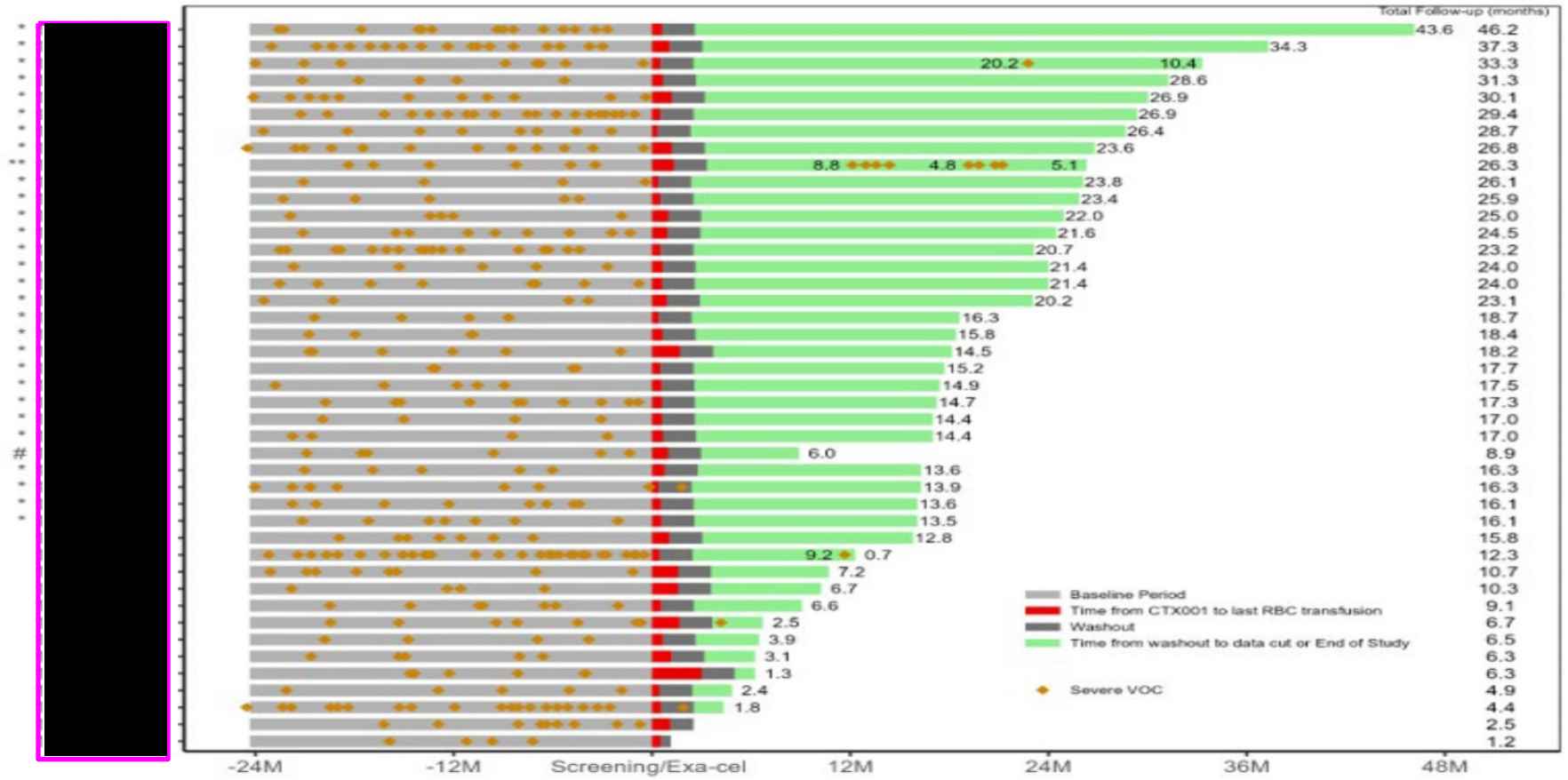
[redacted] Since the last VOC, the patient has been VOC free for approximately 5.1 months (Figure 15).

- [redacted] was VOC free for approximately 11.7 months after exa-cel infusion. [redacted]

- [redacted] had an acute pain event adjudicated as a VOC [redacted] after exa-cel infusion, approximately 2 weeks since having at least 60 days follow-up since the last RBC transfusion for post-transplant support or SCD management. [redacted]

[redacted]

Figure 15: Severe VOC-free duration at D120 (CLIMB SCD-121 and CLIMB-131, FAS)



Key: EAC: Endpoint Adjudication Committee; FAS: Full Analysis Set; RBC: red blood cell; VF12: absence of any severe VOCs for at least 12 consecutive months after exa-cel infusion.
Notes: Only severe VOCs that were adjudicated by the EAC as meeting the protocol criteria were displayed for both the baseline period and the post exa-cel infusion period. Baseline period is the 2 years prior to most recent screening. The number on the right end is the duration of total follow-up in month. Last RBC transfusion refers to the last RBC transfusion for post-transplant support or SCD management during the initial RBC transfusion period.
*Patients in the [SCD]PES who achieved VF12.
**Patients in the [SCD]PES who did not achieve VF12.
#Patient who died during the study.
Source: Figure 16, Vertex D120 Report (7).

Patients [redacted] have achieved a VOC-free duration period of approximately 10.4 months, 5.1 months, 0.7 months and 2.5 months since the last VOC, respectively. [redacted]

Despite experiencing events adjudicated as VOCs post exa-cel infusion, Patients [redacted] have demonstrated treatment benefit from exa-cel. [redacted]. At D120, Patient [redacted] remained free from hospitalisation for 23.0 months (7).

[redacted] was VOC free for ~11.7 months after exa-cel infusion, then had an acute pain event adjudicated as a VOC; the patient has subsequently been VOC free for ~0.7 months. [redacted]

A further two patients had less than 60 days of follow-up after the last RBC transfusion for post-transplant support or SCD management (7).

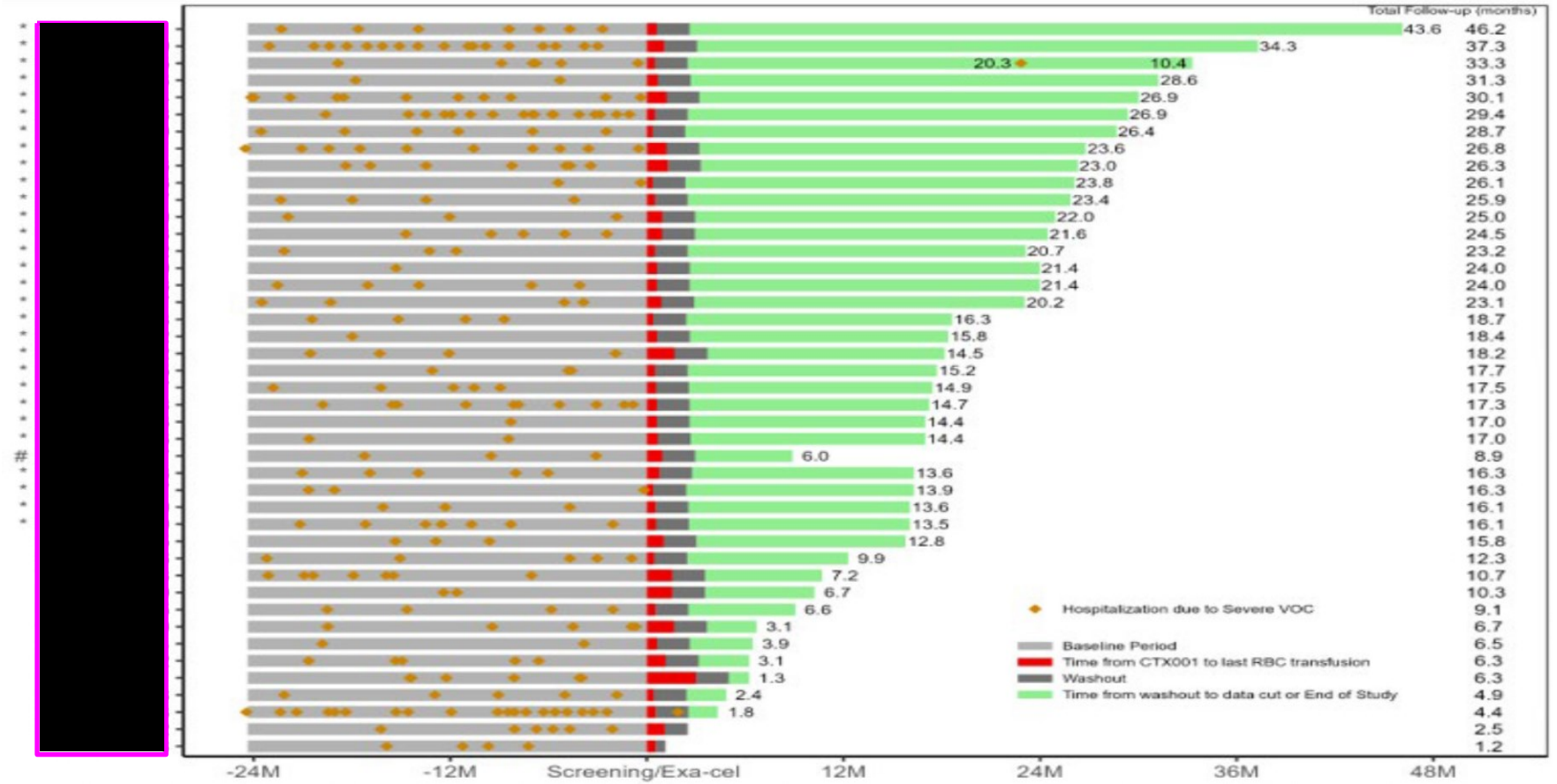
As noted in Section B.1.3.2.1, severe acute pain events are a marker of SCD severity and an increased frequency and associated hospitalisations increases the risk of mortality (31). By achieving VF12 in 96.6% of patients in the PES, exa-cel helps patients eliminate severe VOCs and the associated hospitalisation and potential complications (7).

B.2.6.2.2. Duration free from inpatient hospitalisation

In the FAS, 40 of 41 patients with ≥60 days of follow-up after the last RBC transfusion for post-transplant support or SCD management remained free from inpatient hospitalisation for VOCs after exa-cel infusion throughout CLIMB SCD-121 and CLIMB-131, with a duration of 1.3 to 43.6 months (Figure 16) (7).

As previously described, one patient had an inpatient hospitalisation for a severe VOC in the setting of parvovirus infection after approximately 22.7 months following exa-cel infusion. A further two patients had less than 60 days of follow-up after the last RBC transfusion for post-transplant support or SCD management (7).

Figure 16: Duration free from inpatient hospitalisation for severe VOCs at D120 (CLIMB SCD-121 and CLIMB-131 FAS)



Key: EAC: Endpoint Adjudication Committee; FAS: Full Analysis Set; HF12: free from inpatient hospitalisation for severe VOCs for at least 12 consecutive months after exa-cel infusion; RBC: red blood cell.
Notes: Only severe VOCs that were adjudicated by the EAC as meeting the protocol criteria were displayed for both the baseline period and the post exa-cel infusion period. Baseline period is the 2 years prior to most recent screening. The number on the right end is the duration of total follow-up in month. Last RBC transfusion refers to the last RBC transfusion for post-transplant support or SCD management during the initial RBC transfusion period.
*Patients in the [SCD]PES who achieved HF12.
**Patients in the [SCD]PES who did not achieve HF12.
#Patient who died during the study.
Source: Figure 17, Vertex D120 Report (7).

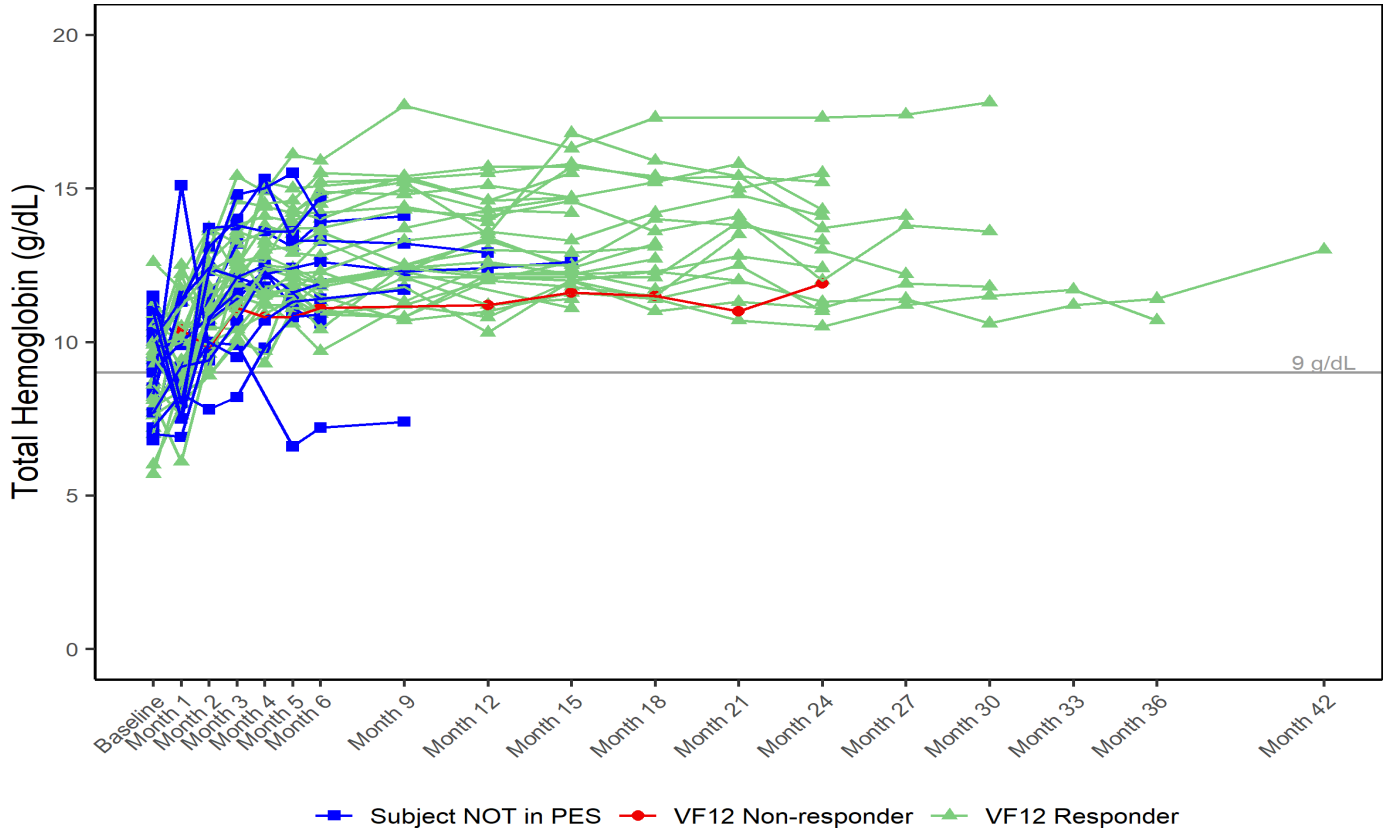
B.2.6.2.3. Total Hb and HbF and concentration over time

In the CLIMB SCD-121 FAS, increases in mean Hb levels and HbF (%) were achieved within three months of exa-cel infusion and were generally maintained over the duration of follow-up (Figure 20) (7).

In the FAS, mean (SD) total Hb concentration increased from 9.1 (1.6) g/dL at baseline to 11.1 (0.5) g/dL at Month 36. Total Hb levels of 12.0 (1.5) g/dL were achieved at Month 3 after exa-cel infusion, and remained between 12.0 g/dL and 13.5 g/dL up to Month 24, remaining above 13.0 /dL up to Month 30, although interpretation of results beyond Month 24 is limited by sample size (Figure 17) (7).

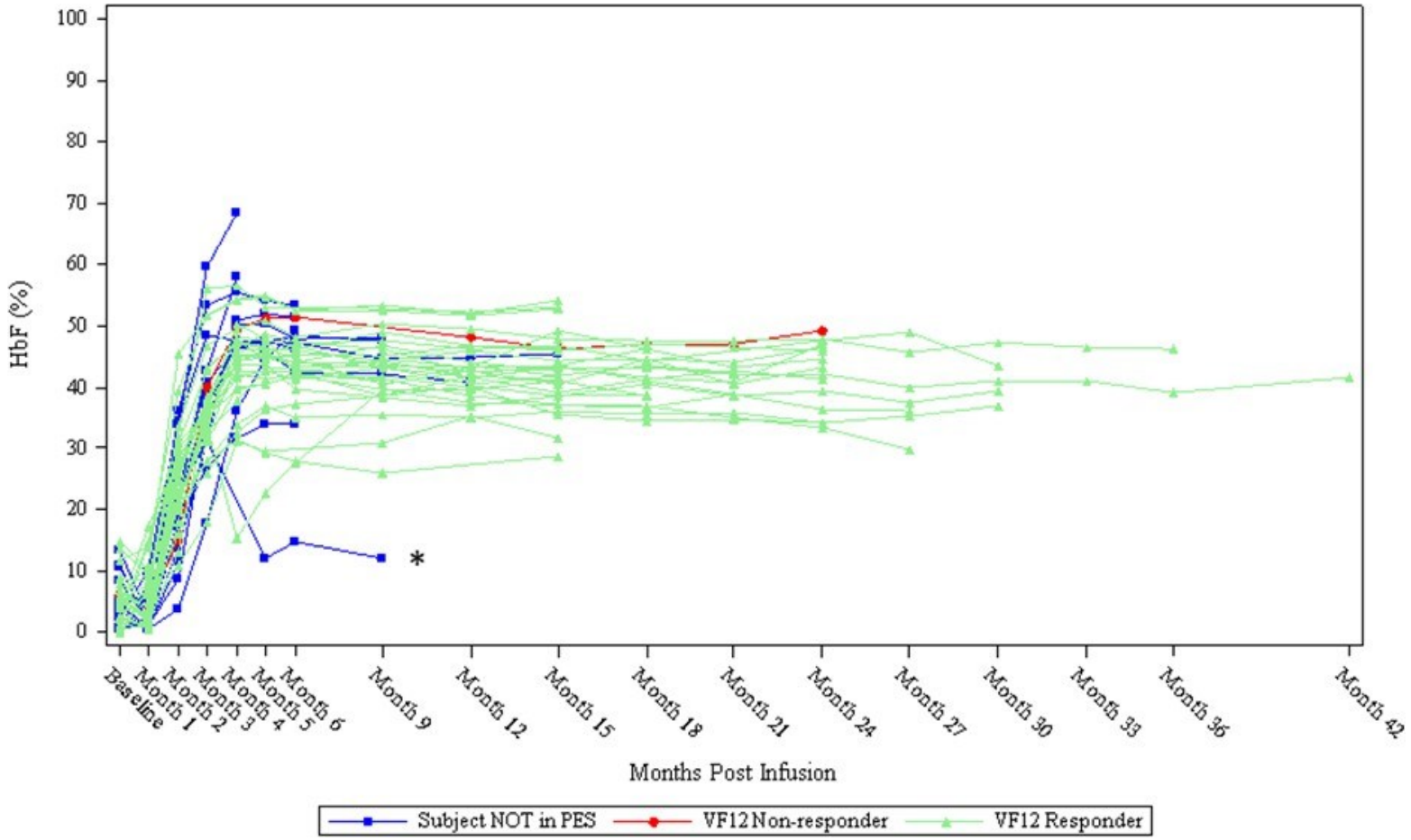
At Month 3 after infusion with exa-cel, the mean (SD) proportion of total Hb comprised by HbF was 37.3% (9.0%), increasing to 43.2% by Month 6 and remaining ≥39.0% throughout the remainder of CLIMB SCD-121 (Figure 18 and Figure 19) (7). The observed increase in HbF levels is consistent with the mechanism of action of exa-cel.

Figure 17: Individual Hb concentration over time in D120 (CLIMB SCD-121 and CLIMB-131, FAS)



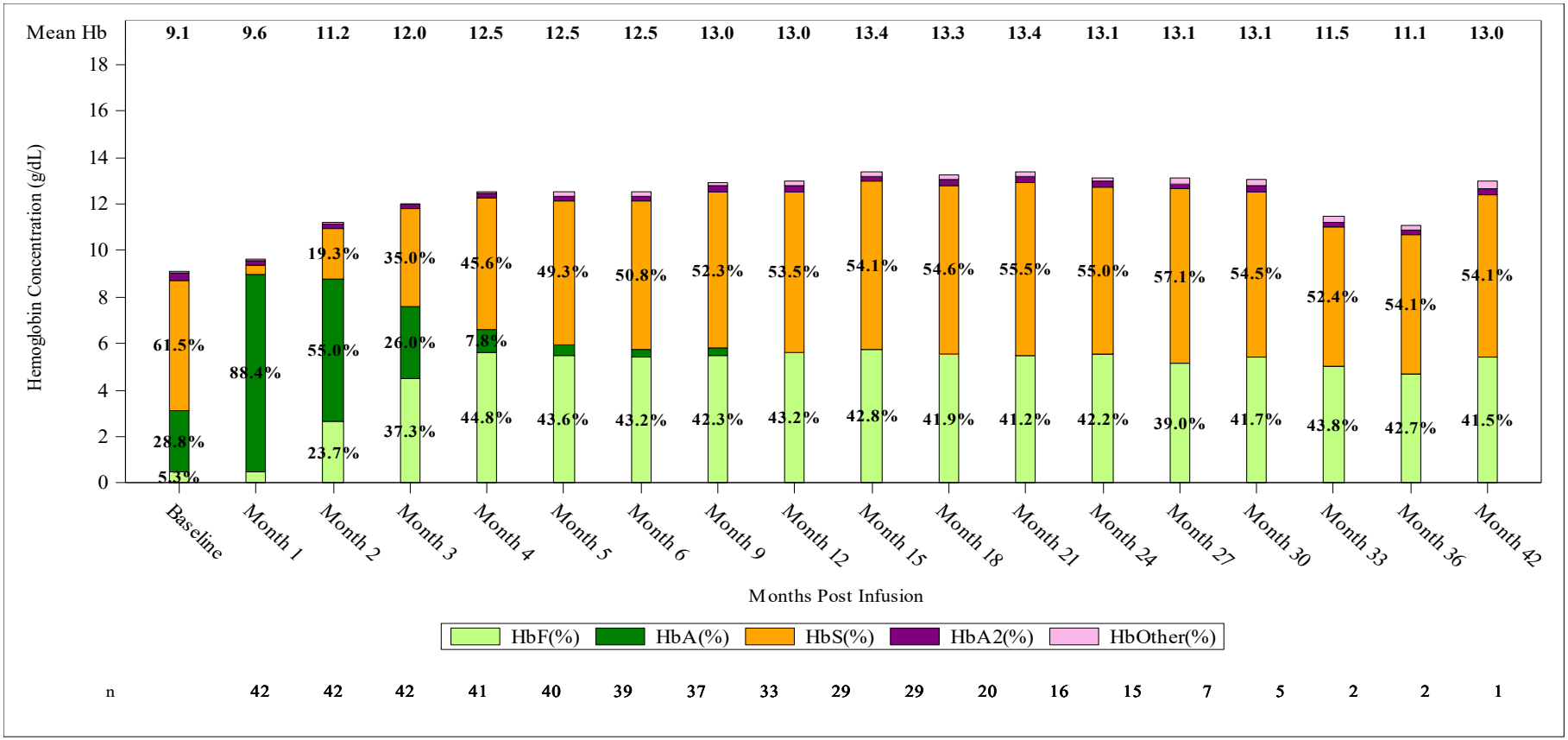
Key: FAS: Full Analysis Set; Hb: haemoglobin; SCD: sickle cell disease; VF12: not experienced any (i.e., absence of) severe VOC for at least 12 consecutive months after exa-cel infusion; VOC: vaso-occlusive crisis.
Notes: Patient-047 died from respiratory failure due to COVID-19 infection. Patient-005 had a VOC after achieving VF12.
Source: Exa-cel KRM Day 120 Update (CLIMB SCD-121 and CLIMB-131) (173).

Figure 18: Individual HbF (%) over time in D120 (CLIMB SCD-121 and CLIMB-131, FAS)



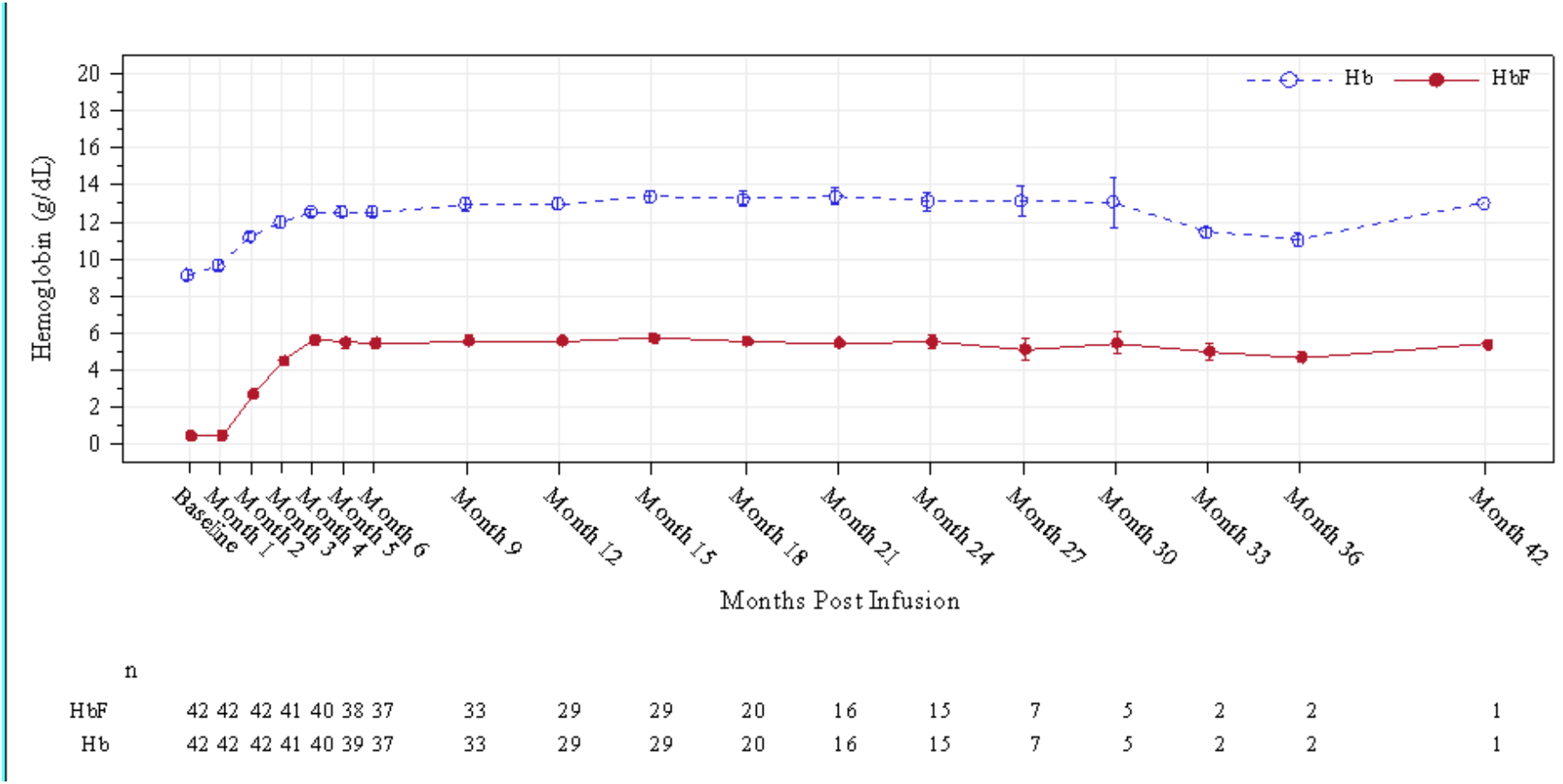
Key: FAS: Full Analysis Set; HbF: fetal haemoglobin; PES: Primary Efficacy Set; SCD: sickle cell disease; VF12: not experienced any (i.e., absence of) severe VOC for at least 12 consecutive months after exa-cel infusion; VOC: vaso-occlusive crisis.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation in Study 121. Analysis visit was used in the figure. Patients in the [SCD]PES who achieved VF12 (termed as VF12 responders) are presented in green and patients who did not achieve VF12 (termed as VF12 non-responders) are presented in red. Patients who were not yet eligible to be part of the [SCD]PES are presented in blue. * Indicates Patient 047 who died due to COVID-19 infection that resulted in respiratory failure and was not related to exa-cel.
Source: Figure 20, Vertex D120 Report (7)

Figure 19: Hb fraction summary over time in D120 (CLIMB SCD-121 and CLIMB-131, FAS)



Key: FAS = full analysis set; Hb: haemoglobin; HbA: haemoglobin A; HbA2: haemoglobin A2; HbF: fetal haemoglobin; Hb Other: Total Hb - HbA - HbA2 - HbF - HbS; HbS: haemoglobin S; n: size of subsample; SCD: sickle cell disease.
Notes: Mean Hb fractions are plotted at each visit. The number 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 in CLIMB SCD-121. Analysis visit was used in the figure.
Source: Figure 21, Vertex D120 Report (7).

Figure 20: Summary of total Hb (g/dL) and HbF (g/dL) over time in D120 (CLIMB SCD-121 and CLIMB-131, FAS)



Key: FAS: full analysis set; Hb: haemoglobin; HbF: fetal haemoglobin; n: size of subsample; SCD: sickle cell disease.
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 in CLIMB SCD-121. Analysis visit was used in the figure.
Source: Figure 22, Vertex D120 Report (7).

B.2.6.2.4. Proportion of patients with sustained HbF ≥20%

Increases in HbF level ameliorate the clinical manifestations of SCD, even in the presence of HbS (174). Patients who co-inherit SCD and HPFH who have HbF levels >20% have few, if any, disease complications (7, 9, 175, 176).

In the PES, all 29 (100%) patients had sustained HbF ≥20% for at least 12 consecutive months (7).

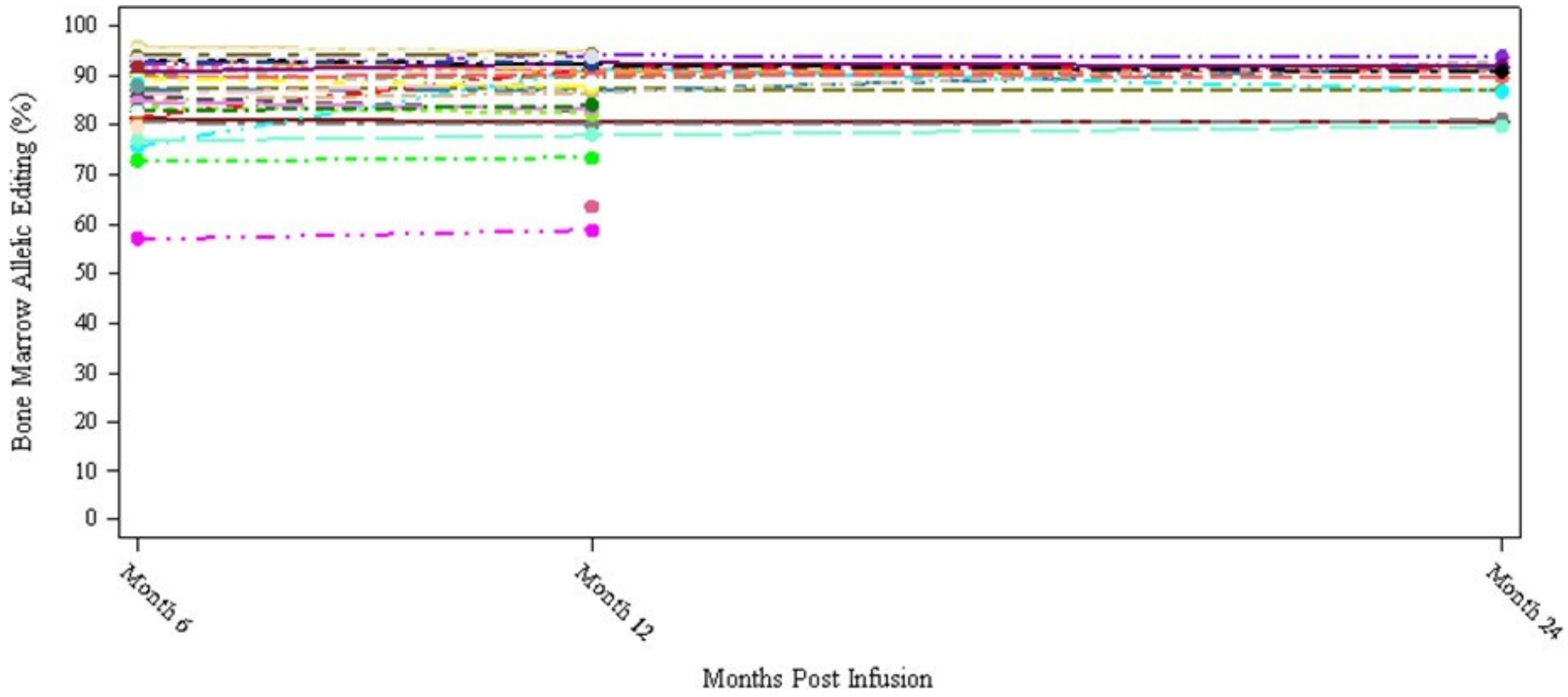
B.2.6.2.5. Proportion of alleles with intended genetic modification

At the D120 data cut, 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).

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 86.1% (7.5%) in the FAS, 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 6 onwards (Figure 21) (7).

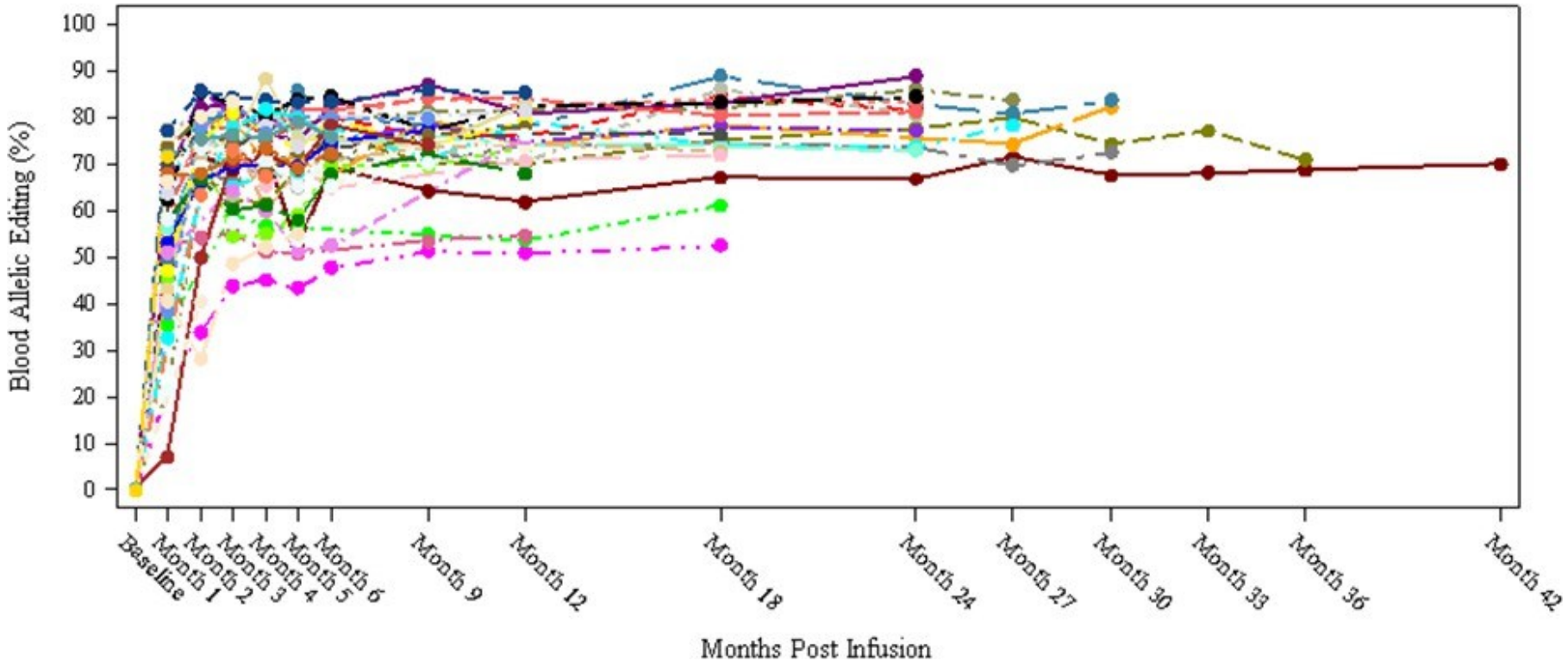
Similarly, allelic editing in the peripheral blood was detectable within one month after exa-cel infusion. The mean (SD) proportion of alleles with the intended genetic modification in peripheral blood was 71.4% (10.1) at Month 3. Moreover, this remained ≥69.9% from Month 3 onwards (Figure 22). In CLIMB-131, allelic editing in the peripheral blood remained stable (7).

Figure 21: Proportion of edited alleles in CD34+ bone marrow over time at D120 (%) (CLIMB SCD-121 and CLIMB-131, FAS)



Key: FAS: full analysis set; SCD: sickle cell disease.
Notes: Analysis visit was used in the figure. One patient (represented by dark green dot) had bone marrow allelic editing data at Month 12 but not at Month 6.
Source: Figure 25, Vertex D120 Report (7).

Figure 22: Proportion of edited alleles in peripheral blood cells over time at D120 (%) (CLIMB SCD-121 and CLIMB-131, FAS)



Key: FAS: full analysis set; SCD: sickle cell disease.
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: Vertex D120 Report (7).

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, 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 (177).

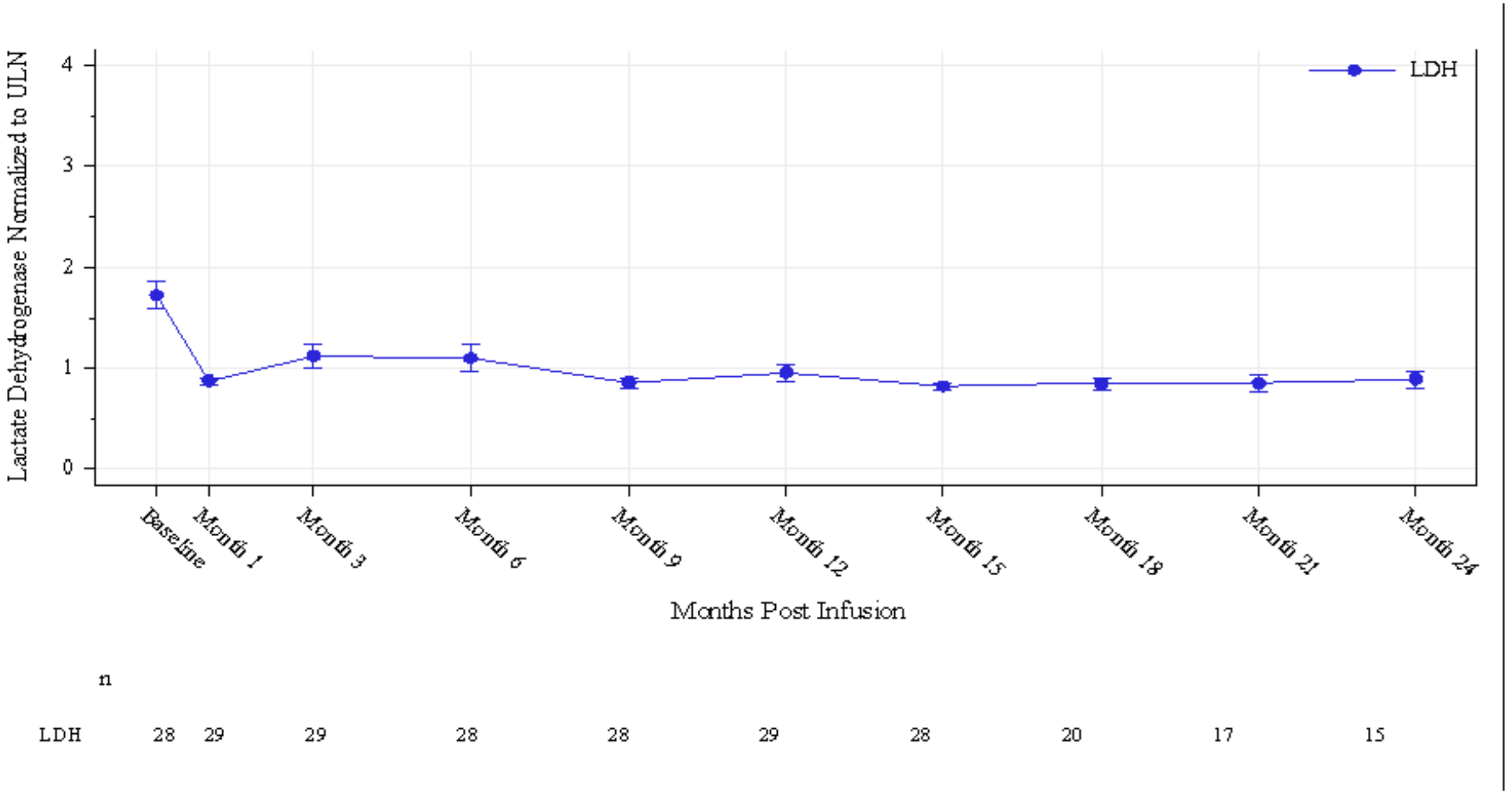
B.2.6.2.6. Changes in haemolysis biomarkers

A summary of haemolysis assessments including the change from baseline in reticulocyte count, indirect bilirubin, lactose dehydrogenase (LDH), and haptoglobin over time for the 29 patients in the PES are presented in Table 19, Figure 23 and Figure 24, respectively (7).

Following exa-cel infusion, reductions from baseline in mean values of absolute reticulocyte count and indirect bilirubin level were maintained over time. There was a substantial reduction from baseline in mean LDH level in patients in the PES, which were maintained or decreased further over time (7).

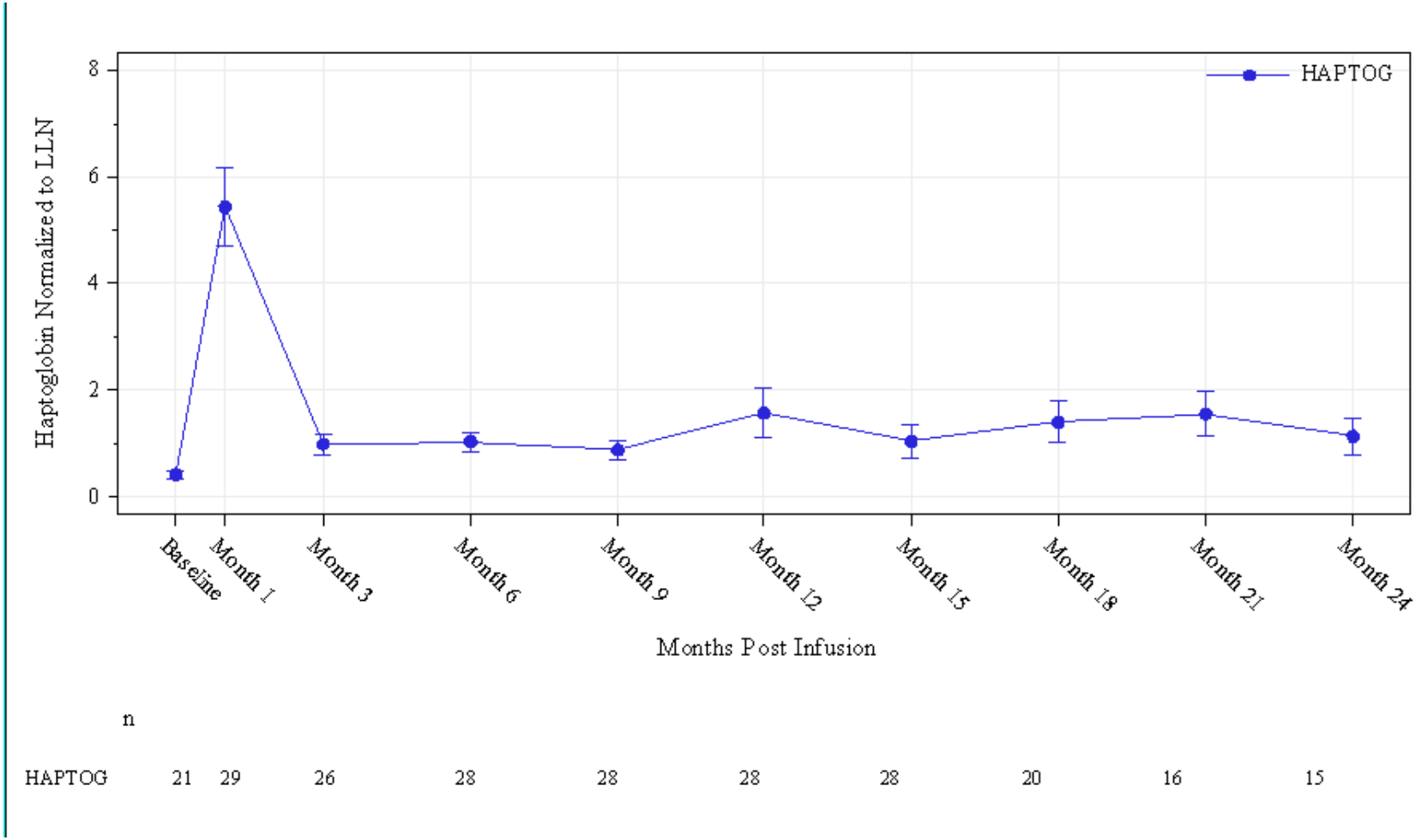
This data shows that exa-cel increases in HbF, distributed pancellularly, lead to improvement and normalisation in haemolysis assessments as observed in patients with HbS/HPFH who have insignificant haemolysis. Improvements in haemolysis are expected to be associated with reduced end-organ damage and reduction in other disease complications, which will be measured for 15 years after exa-cel infusion in the long-term follow-up CLIMB-131 study (7).

Figure 23: Lactose dehydrogenase level normalised to upper limit of normal summary over time at D120 (CLIMB SCD-121, PES)



Key: n: size of subsample**;** PES: primary efficacy set; SCD: sickle cell disease; 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 values available at the corresponding visits are shown at the bottom. Analysis visit is used in the figure.
Source: Figure 29 Vertex D120 Report (7).

Figure 24: Haptoglobin level normalised to lower limit of normal summary over time at D120 (CLIMB SCD-121, PES)



Key: HAPTOG: haptoglobin; n: size of subsample**;** PES: primary efficacy set; SCD: sickle cell disease.
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 values available at the corresponding visits are shown at the bottom. Analysis visit is used in the figure.
Source: Figure 30 Vertex D120 Report (7).

Table 19: Summary of haemolysis markers at D120 (CLIMB SCD-121 and CLIMB-131, PES)

Visit	Statistics	Reticulocytes (109/L) N = 29	Indirect Bilirubin (µmol/L) N = 29
Baseline	n Mean (SD) Median Min, max	29 265.46 (113.85) 251.49 116.34, 679.60	29 55.4 (48.4) 32.5 12.0, 210.3
Month 12	n Mean (SD) Median Min, max	28 142.00 (67.64) 130.45 66.20, 413.28	28 21.5 (21.1) 13.7 4.3, 100.9
Month 24	n Mean (SD) Median Min, max	14 152.20 (47.93) 149.63 79.92, 273.10	14 24.9 (21.0) 19.7 3.4, 78.7
Month 30	n Mean (SD) Median Min, max	5 132.05 (81.17) 106.11 64.00, 269.00	5 24.3 (13.8) 20.5 5.1, 39.3
Month 36	n Mean (SD) Median Min, max	2 131.61 (20.24) 131.61 117.30, 145.92	2 15.4 (14.5) 15.4 5.1, 25.7
Month 42	n Mean (SD) Median Min, max	1 106.75 (--) 106.75 106.75, 106.75	1 6.8 (--) 6.8 6.8, 6.8

Key: N: total sample size; n: size of subsample; PES: Primary Efficacy Set; SCD: sickle cell disease.
Notes: If there was at least 1 measurement before mobilisation, baseline was defined as the most recent one prior to start of exchange transfusions. Otherwise, the baseline was defined as the measurement that was most distant from the last exchange transfusion prior to this measurement and still before start of mobilisation. Lab values with "below detectable limit" were considered as 0. The follow-up periods in both CLIMB SCD-121 and -131 (if any), after exa-cel infusion in CLIMB SCD-121, were included in this analysis.
[a]Patients with a medical history of Gilbert's syndrome were excluded from the summary of indirect bilirubin.
Source: Table 53 Vertex D120 Report (7).

B.2.6.2.7. Reduction in transfusions

Following exa-cel infusion, no patients in the PES received RBC transfusions for SCD-related indications at the D120 data cut (7). Prior to exa-cel infusion, patients in the PES had a mean (SD) of 8.7 (15.1) annualised units of RBCs for SCD-related indications per year at baseline, with 26 of 29 patients receiving RBC transfusions in the two years prior to screening. The relative reduction in RBC transfusions starting 12 months after exa-cel infusion was therefore 100% (7). D120 data for the FAS was not available at the time of submission.

B.2.6.2.8. F-cells over time

Consistent with the observed HbF increases, the mean (SD) proportion of F-cells was 70.4% (14.0%) at Month 3 and was maintained ≥90% from Month 6 over the duration of follow-up at the Day 120 data cut (Table 20 and Figure 25). The high percentage of F-cells observed after exa-cel (≥90%) is consistent with a pancellular distribution of HbF, indicating almost all RBCs in circulation are derived from exa-cel. High levels of pancellular HbF, as seen in HPFH, are associated with the absence of VOCs and haemolytic anaemia (7).

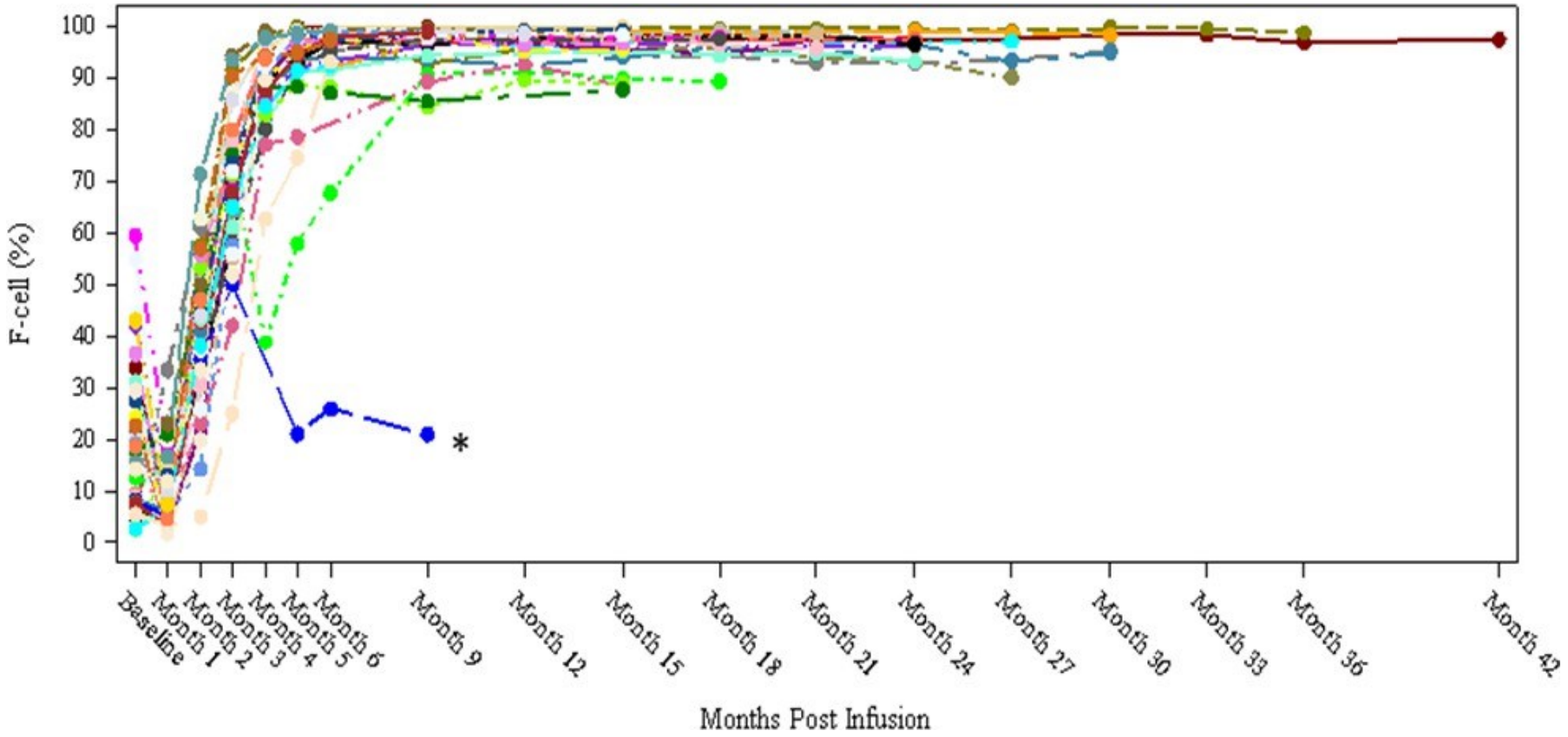
Table 20: Summary of F-cells (%) over time in D120 (CLIMB SCD-121 and CLIMB-131, FAS)

Visit	Statistics	Day 120 Data Cut
		F-Cell (%)
		FAS (n = 43)
Baseline	n	43
	Mean (SD)	20.7 (13.6)
Month 3	n	41
	Mean (SD)	70.4 (14.0)
Month 6	n	38
	Mean (SD)	93.9 (12.6)
Month 12	n	30
	Mean (SD)	96.8 (2.5)
Month 18	n	20
	Mean (SD)	96.7 (2.3)

Month 24	n	15
	Mean (SD)	96.4 (2.0)
Month 36	n	2
	Mean (SD)	97.9 (1.3)

Key: exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; F-cells: erythrocytes expressing γ-globin (fetal haemoglobin); N: total sample size; n: size of subsample; SCD: sickle cell disease
Source: Table 49 Vertex D120 Report (7).

Figure 25: Individual F-cells (%) Over Time at D120 (CLIMB SCD-121 and CLIMB-131, FAS)



Key: FAS: Full Analysis Set; F-cells: erythrocytes expressing fetal haemoglobin; n: size of subsample; SCD: sickle cell disease.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation in CLIMB SCD-121. Analysis visit was used in the figure. * Indicates Patient-047 who died due to COVID-19 infection that resulted in respiratory failure and was not related to exa-cel.
Source: Figure 23, Vertex D120 Report (7).

B.2.6.2.9. Patient-reported outcomes:

As determined by a panel convened by FDA in partnership with the American Society of Hematology (ASH), the three key PRO domains of particular saliency in SCD are: pain (acute and chronic), affect (emotional impact, sleep quality and fatigue) and functioning (social, physical and cognitive functioning as well as self-efficacy for disease management and occupational function) (7).

Of the PRO tools mentioned earlier in Table 14, the ASCQ-Me tool is validated in SCD, and the other instruments are well-established tools used frequently across numerous conditions, including SCD and HSCT in haematologic malignancies (7). PRO scores in CLIMB SCD-121 indicate substantial improvement in general well-being, HRQoL, and overall health status, including improvements in pain episode frequency and severity after exa-cel infusion as summarised in Table 21. Consistent improvements were observed in the EQ-5D-5L (mapped to the EQ-5D-3L) and EuroQol Visual Analogue Scale (EQ-VAS) scores. Refer to Appendix N for further detail relating to PRO scores (7).

Table 21: Summary of change in PRO scores from baseline to Month 24 at D120 (CLIMB SCD-121, PES)

	EQ VAS and EQ-5D-5L		FACT-BMT		NRS	ASCQ-Me						
Endpoint	VAS	UK Index	FACT-G	BMT	NRS	Emotional	Pain	Social	Stiffness	Sleep	Pain episode frequency	Pain episode severity
Change from baseline at M24*	**29.3**	**0.11**	**22.5**	**3.5**	**-1.7**	**11.7**	**9.6**	**17.5**	**6.6**	4.2	**-20.2**	-4.8
MCID	7-10[a]	0.08[b]	3-7[c]	2-3[d]	-1[e]	5[f]					-5[f]	

Key: BMTS: bone marrow transplantation subscale; EQ-5D-5L: EuroQol Quality of Life 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; FAS: full analysis set, MCID: minimal clinically important difference.
[a] Sourced from Henry *et al*., (2020) (178).
[b] Sourced from Pickard *et al*., (2007) (179).
[c] Sourced from Shah *et al.* (2021), Maziarz *et al.* (2020) and Clinical Review Report (180-182).
[d] Sourced from McQuellon *et al*., (1997) (183).
[e] Sourced from Correll et al., (2011) (109).
[f] Sourced from Norman *et al.* (2003), Keller *et al.* (2014), HealthMeasures.net, Correll (2007) (184-186).
Notes: Baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation.
*Bold numbers represent changes exceeding MCID.
Source: Vertex Data on File PRO Review for D120 Update and Section 3.3.3.6 Vertex D120 Report (7, 187).

In addition, the minimal clinically important difference (MCID) thresholds provided to contextualise the data in Table 21 are SCD-specific for ASCQ-Me and not SCD-specific for the other tools; however, they are largely consistent across numerous haematologic conditions (7).

a. EQ-5D-5L

At baseline, mean (SD) EQ-5D-5L utility index scores in CLIMB SCD-121 were reported to be lower (0.81 points [SD: 0.19]) than the average UK population score (0.86 points), indicating HRQoL impairment prior to exa-cel infusion (Table 22) (7).

EQ-5D-5L utility scores showed clinically meaningful improvements in overall health status from Month 6 onwards, with a mean (SD) change from baseline at Month 24 of 0.11 (SD: 0.18) points for the UK index score. This score exceeds the MCID for the UK EQ-5D-5L of 0.08 points, highlighting an improvement in overall health status following exa-cel infusion (7).

For patients ≥18 and ≤35 years of age, EQ VAS scores demonstrated substantial improvement at Month 6 which was sustained at Month 24, with mean (SD) change from baseline at Month 24 of 29.3 (SD: 22.9) points. This score greatly exceeds the MCID for EQ VAS of 7 to 10 points, indicating early and meaningful improvement in patients' self-rated health status (7).

Table 22: Summary of EQ-5D-5L scores for patients ≥18 and ≤35 years of age at D120 (CLIMB SCD-121, PES)

Visit	PES	
	EQ VAS	UK Health Utility Index Score
Baseline		
n	23	22
Mean (SD)	69.0 (23.2)	0.81 (0.19)
Median	75.0	0.84
Min, Max	5.0, 100.0	0.46, 1.00
Month 3		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Change at Month 3		

n	23	22
Mean (SD)	14.3 (30.1)	0.06 (0.18)
Median	8.0	0.01
Min, Max	-40.0, 85.0	-0.34, 0.44
Month 6		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Change at Month 6		
n	20	20
Mean (SD)	23.1 (25.8)	0.08 (0.18)
Median	20.0	0.06
Min, Max	-15.0, 90.0	-0.24, 0.44
Month 12		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Change at Month 12		
n	23	22
Mean (SD)	20.8 (21.8)	0.08 (0.16)
Median	15.0	0.01
Min, Max	-1.0, 90.0	-0.12, 0.40
Month 18		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Change at Month 18		
n	16	16
Mean (SD)	30.3 (25.5)	0.14 (0.17)
Median	25.0	0.13
Min, Max	-6.0, 95.0	-0.10, 0.46
Month 24		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Change at Month 24		
n	15	15
Mean (SD)	29.3 (22.9)	0.11 (0.18)
Median	20.0	0.11

Min, Max	5.0, 95.0	-0.14, 0.40

Key: EQ-5D-5L: EuroQol Quality of Life Scale-5-dimensions-5 levels of severity; FAS: full analysis set; n: size of subsample; PES: primary efficacy set; SD: standard deviation.
Notes: The PES included 23 patients ≥18 and ≤35 years of age at screening. Baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilisation.
Source: Table 54 Vertex D120 Report (7).

b. Numeric Pain Rating Scale

For patients ≥18 and ≤35 years of age, the mean (SD) pain Numeric Pain Rating (NRS) score at baseline was 2.5 (SD: 2.5) points. Pain NRS scores were consistently below baseline from Month 6 to Month 24 and showed a clinically meaningful improvement with a ≥1-point reduction from baseline by Month 24 (7). Further information can be found in Appendix N.

c. FACT-BMT

The mean Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) total scores showed substantial improvement from Month 6 onward, with a mean (SD) change from baseline at Month 18 of 27.2 (SD: 26.0) points, indicating improvement in general well-being and HRQoL after exa-cel infusion that was sustained through the duration of follow-up (7).

Similarly, the Functional Assessment of Cancer Therapy-General (FACT-G) and Bone Marrow Transplantation Subscale (BMTS) scores progressively increased from Month 6 onwards, with a mean (SD) change from baseline of 22.5 (SD: 17.9) points for FACT-G and 3.5 (SD: 5.0) points for BMTS at Month 24 (7). Further information can be found in Appendix N.

d. ASCQ-Me

All ASCQ-Me subscales including emotional, social, stiffness, and sleep impact standardised scores demonstrated meaningful changes from Month 6 to Month 24, indicating substantial improvements in these subscales following exa-cel infusion. Mean (SD) change from baseline in standardised ASCQ-Me scores at Month 24 showed an improvement for the domains of emotional impact (11.7 ([SD: 10.9] points), social impact (17.5 [SD: 11.4] points), stiffness (6.6 [SD: 11.0] points) and sleep impact (4.2 [SD: 8.4] points) (Table 23) (7).

Table 23: Summary of ASCQ-Me scores for patients ≥18 and ≤35 years of age at D120 (CLIMB SCD-121, PES)

Visit	Statistics	Emotional Impact Standardised Score	Pain Impact Standardised Score	Social Functioning Impact Standardised Score	Stiffness Impact Standardised Score	Sleep Impact Standardised Score	Pain Episode Frequency Standardised Score	Pain Episod Severity Standardise Score
Baseline	N Mean (SD) Median Min, max	22 51.8 (7.7) 53.3 26.8, 60.5	22 53.7 (9.0) 54.0 36.7, 63.8	22 50.1 (11.4) 47.2 32.5, 69.8	22 52.7 (8.1) 53.7 38.4, 65.4	22 47.2 (8.2) 46.7 27.9, 61.9	23 52.9 (6.3) 51.8 40.2, 63.5	23 52.4 (9.2) 52.3 31.2, 66.3
Month 6	N Mean (SD) Median Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change at Month 6	N Mean (SD) Median Min, max	19 8.7 (9.9) 5.9 -5.3, 33.7	19 5.2 (8.9) 5.5 -9.8, 27.1	19 10.8 (12.7) 6.6 -9.2, 37.3	19 0.5 (11.6) 2.7 -25.5, 17.3	19 4.3 (12.5) 1.5 -15.0, 28.8	20 -16.5 (9.1) -15.5 -31.1, -3.9	20 -0.2 (12.4) -1.2 -21.1, 25.7
Month 12	N Mean (SD) Median Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change at Month 12	N Mean (SD) Median Min, max	22 9.3 (9.2) 8.3 -5.3, 38.8	22 5.1 (8.8) 4.8 -8.0, 27.1	21 14.0 (11.9) 15.8 -4.9, 35.1	22 4.6 (9.7) 6.8 -15.7, 17.3	22 4.2 (7.1) 1.8 -5.3, 18.0	23 -19.4 (8.2) -19.4 -31.1, 0.0	23 -3.4 (12.4) -2.3 -28.1, 16.4
Month 18	N Mean (SD) Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change at Month 18	N	15	15	15	15	15	16	16
	Mean (SD)	10.1 (10.5)	10.1 (9.8)	15.6 (13.3)	4.7 (8.7)	2.9 (9.4)	-19.7 (9.2)	-2.6 (12.1)
	Median	9.0	9.8	19.0	4.6	0.0	-19.4	-3.5
	Min, max	-8.9, 28.4	-5.8, 27.1	-12.6, 35.1	-17.1, 17.2	-13.5, 16.9	-35.0, 0.0	-28.1, 23.4
Month 24	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)							
	Median							
	Min, max							
Change at Month 24	N	14	14	14	14	14	15	15
	Mean (SD)	11.7 (10.9)	9.6 (11.0)	17.5 (11.4)	6.6 (11.0)	4.2 (8.4)	-20.2 (7.2)	-4.8 (11.7)
	Median	11.1	9.8	20.2	8.4	2.9	-19.4	-2.3
	Min, max	-3.2, 38.8	-13.9, 27.1	-1.9, 35.1	-18.6, 22.7	-12.7, 18.7	-31.1, -7.8	-37.4, 9.4

Key: ASCQ-Me: Adult Sickle Cell Quality of Life Measurement System; PES: primary efficacy set.
Source: Table 56, Vertex D120 Report (7).

B.2.6.3. Summary of exa-cel clinical effectiveness

The efficacy of exa-cel for the treatment of patients with severe SCD aged 12-35 years has been demonstrated at the D120 data cut (16 April 2023), for the ongoing Phase 1/2/3 single arm CLIMB SCD-121 study.

In the FAS, baseline mean (range) annualised rate of severe VOCs per year for the prior two years before screening was 4.2 (2.0-18.5). The vast majority of the patients enrolled onto CLIMB SCD-121 had a β^S/β^S-like genotype (90.7%). A further 7.0% had a β^S/β^0 genotype, and the remaining 2.3% of patients had a β^S/β^+ genotype (Section B.2.3.8) (7). Clinical experts consulted as part of this submission felt that the genotype distribution in CLIMB SCD-121 was representative of what would be seen in UK clinical practice (12).

Treatment with exa-cel resulted in high clinical efficacy. In the PES, 28 of 29 patients (96.6%) had been free of severe VOCs for at least 12 consecutive months after exa-cel infusion (VF12), with a mean (SD) VOC-free duration of 20.7 (7.1) months. Furthermore, all 29 patients (100%) in the PES were free from inpatient hospitalisation for severe VOCs for at least 12 months after exa-cel infusion (HF12) (7).

In the FAS, 41 of 43 patients had at least 60 days of follow-up after the last RBC transfusion for post-transplant support or SCD management. Of these patients, 37 of 41 were did not experience any VOCs, starting 60 days after the last RBC transfusion, for a duration of 1.3 to 43.6 months (7). In contrast, in the crizanlizumab SUSTAIN trial, only 11 of 65 SCD patients (17%) remained VOC-free during the 52-week treatment phase (188).

Following exa-cel infusion, 4 of 41 patients in the FAS (2 of whom were in the PES) experienced events adjudicated as VOCs, starting 60 days after the last RBC transfusion. [redacted]

[redacted] (7).

Despite experiencing events adjudicated as VOCs, the remaining four patients have all demonstrated treatment benefit from exa-cel. The two patients in the PES achieved HF12, and all four patients have remained free from inpatient hospitalisation, with a range of 0.7 – 10.4 months since their last VOC. After achieving VF12 and HF12, one of the four patients ([redacted]) experienced an inpatient hospitalisation for a severe VOC approximately 22.7 months following exa-cel infusion. The patient has since been VOC-free for a duration of 10.4 months (7).

Clinically meaningful increases in mean total Hb and HbF levels were demonstrated early and were maintained over time from Month 3 onwards in the FAS, indicating durability of response (7). Mean (SD) total Hb concentration increased from 9.1 (1.6) g/dL at baseline to 13.1 (1.9) g/dL at Month 24. Total Hb levels of 12.0 (1.5) g/dL were achieved at Month 3 after exa-cel infusion, and remained between 12.0 g/dL and 13.5 g/dL up to Month 24, remaining above 13.0 /dL up to Month 30, although interpretation of results beyond Month 24 is somewhat limited by sample size (Figure 17) (7). There was expectation amongst clinical advisors that this Hb concentration sustained at 12-13 g/dL would be associated with substantial improvement in condition. In addition, these levels are comparable to what is seen with rare natural phenotypes of sickle and HPFH in SCD patients who do not show any symptoms (12).

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).

The currently available data indicates that exa-cel results in robust, consistent, and durable benefits, offering the potential to deliver a disease-free state for patients with severe SCD.

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. For the subgroup analyses, the FAS and PES were stratified by age, genotype, and sex (see Appendix D for more information).

As expected, in the context of 28 of 29 patients achieving the primary endpoint, results across subgroups were consistent and confirm a substantial treatment benefit of exa-cel in all patients with severe SCD, regardless of age, genotype, and sex (7). It must also be noted that subgroup analyses should be interpreted with caution given the small sample sizes involved (166).

B.2.8 Meta- analysis

Meta-analysis is not required for exa-cel as a single study (CLIMB SCD-121) 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 the CLIMB SCD-121 trial, an indirect treatment comparison (ITC) was performed to generate estimates of comparative effectiveness, including versus standard-of-care (SoC) (189). It's important to note, the ITC outcomes versus SoC do not inform the economic model. Instead, data from CLIMB SCD-121 was used in the economic analysis to inform the relative efficacy and safety of exa-cel in patients with severe SCD (189).

A total of 51 studies were identified from the SLR results, however only 5 studies (from 6 data sources) were considered. To be considered in the ITC, identified studies had to fulfil the following criteria (189):

- Patients with ages overlapping with CLIMB SCD-121 efficacy data
- Report of a VOC-related outcome
- Administered an FDA-approved dose, and
- Include five or more treated patients

As mentioned, 6 data sources across 5 studies were considered in the ITC feasibility assessment. These studies were the HOPE trial (assessing voxelotor versus SoC) (190, 191); the SUSTAIN trial (evaluating crizanlizumab versus SoC) (188) and the NCT01179217 trial (evaluating L-glutamine versus SoC) (55). An ITC was not considered feasible against two of the five studies identified due to a lack of baseline characteristics for the subgroup of patients with the outcome of interest and/or due to insufficient information on VOC definition (189).

A summary of the comparator arms for the ITCs considered feasible in SCD is summarised in Table 24**.** Full details of the trial methodologies are presented in the ITC report (189).

Table 24: Summary of the trials used to carry out the indirect treatment comparison

References of trial	Intervention				
	Exa-cel	Voxelotor	Crizanlizumab	L-glutamine	SoC
CLIMB SCD-121	Yes				
HOPE		Yes			Yes
SUSTAIN			Yes		Yes
NCT01179217				Yes	Yes

Key: MAIC: matching-adjusted indirect comparison; SoC: standard of care; VOC: vaso-occlusive crisis
Source: Table 1, Exa-cel SCD ITC Report (189).

Although we present the results of the ITCs between exa-cel and SoC, these do not inform the economic model. Instead, data from CLIMB SCD-121 was used in the economic analysis to inform the relative efficacy and safety of exa-cel in patients with severe SCD (189). For further detail on the rationale for this, refer to Section B3.3.

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

The ITC employed unanchored matching-adjusted indirect comparison (MAIC) methodology, due to the single-arm design of the exa-cel CLIMB SCD-121 trial, and the lack of access to individual-patient data (IPD) for non-Vertex trials of comparator therapies (189). In the context of this evidence submission, comparison with crizanlizumab, voxelotor and L-glutamine was not considered relevant, since these therapies are not available in the UK for the treatment of SCD. However, the BSC arms for crizanlizumab, voxelotor and L-glutamine were considered potentially informative and as such are presented here. Comparison versus crizanlizumab, voxelotor and L-glutamine is included in the ITC report (189).

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, individual patient data from CLIMB SCD-121 was re-weighted to make key baseline characteristics comparable with the comparators' aggregated data. The MAIC methodology proposed by Signorovitch *et al*., (2010) was used to re-weight individual patient data from CLIMB SCD-121 to align with the matching variables' aggregate summary statistics as reported for each selected comparator. 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 (189).

These steps above resulted in a CLIMB SCD-121 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 SCD-121. 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 (189).

Due to the small sample size in the CLIMB SCD-121 PES at the time of ITC design (n=17), no more than three variables were used for matching based on health technology assessment (HTA) expert input, starting with the variables ranked as the most important and moving onto lower-ranking variables if a match was not possible (189).

The list of matching variables ranked by importance was:

- Genotype (proportions of patients with β^S/β^S vs non- β^S/β^S genotype)
- Baseline annualised number of VOCs
- Age (mean and SD were preferred; however, where not reported, median was used)
- Sex
- Race/ethnicity (proportions of Black vs non-Black)

The MAIC with HOPE matched on median age, sex and race. The MAIC with SUSTAIN matched on the proportion of patients with annualised number of VOCs ≤4 vs >4 at baseline, median age and sex. Finally, the MAIC with NCT01179217 matched with the proportion of patients with annualised number of VOCs ≤5 vs >5 at baseline, mean age and sex. Of note, matching on genotype was not feasible, as all patients in the CLIMB SCD-121 PES had the β^S/β^S genotype. Matching characteristics used for each analysis are further described in the ITC report (189).

VOC-related efficacy outcomes were assessed in the MAIC. The definition of VOC reported in all studies was generally similar to that of the CLIMB SCD-121 trial (refer to Table 2 in the ITC report), however some caveats included (189):

- The HOPE trial does not include priapism or splenic sequestration in VOC definition, therefore, there could be slightly fewer VOCs captured in the HOPE trial (impact differs by outcome considered).

- The SUSTAIN trial includes hepatic sequestration, which could make it more inclusive. Hepatic sequestration is considered a rare event in SCD, so the potential impact of including these events is likely minimal. Of note, VOC was referred to as sickle cell-related pain crises in the SUSTAIN trial.

For comparisons versus HOPE, the percentage of patients who were VOC-free for at least 6 months (VF6) was compared to the percentage of patients who were severe VOC-free for at least 6 months after exa-cel infusion in CLIMB SCD-121. It should be noted that in CLIMB SCD-121, the follow-up period for both endpoints started 60 days after last RBC transfusion for post-transplant support or SCD management. In both HOPE and SUSTAIN, the evaluation started on Day 1 of treatment (189).

B.2.9.2. Results of the MAIC

Using data from the four included studies (CLIMB SCD-121, HOPE, SUSTAIN and NCT01179217), the following sets of MAICs were conducted:

- Exa-cel versus SoC (as defined in HOPE trial)

- Exa-cel versus SoC (as defined in SUSTAIN trial)

- Exa-cel versus SoC (as defined in NCT01179217 trial)

In this submission, we only present the results on the MAIC versus SoC (as defined in the HOPE and SUSTAIN trials) as SoC is the relevant comparator as described in the final scope and decision problem considered in this submission. No data was reported in the NCT01179217 trial on the proportion of patients who remained VOC-free (189). The results of the MAICs versus crizanlizumab and voxelotor can be found in the accompanying ITC report (189). However, crizanlizumab's conditional marketing

authorisation is expected to be imminently revoked by EMA, while voxelotor was recently the subject of negative final draft guidance issued by NICE (122, 124).

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

The re-weighted proportion of patients who did not experience a VOC for at least 6 consecutive months for exa-cel was 100% compared with 30.8% of patients who were VOC-free at 24-week follow-up reported in the HOPE trial (Table 25). Due to a small effective sample size (ESS) (less than 5), the rate ratio, 95% CI and p-value are not reported (189).

Table 25: Proportion of patients who remained VOC-free for 12 months, exa-cel vs SoC as defined in the HOPE trial of voxelotor

	SOC (N = 91)	Exa-cel unweighted (before matching) (N = 17)	Exa-cel re-weighted (after matching) (ESS = 4)
Proportion (95% CI)	30.8% (-, -)	100% (80.5%, 100%)	100%
Rate Ratio (95% CI)			NC
***P* value**			Not applicable[a]

Key: CI: confidence interval; ESS: effective sample size; NC: not calculated; SoC: standard of care; VOC: vaso-occlusive crisis.
Notes: [a]No statistical testing was conducted due to ESS less than 5.
Source: Table 10, Exa-cel SCD ITC Report (189).

B.2.9.2.2. Exa-cel versus SoC (defined in SUSTAIN trial)

The re-weighted proportion of patients who did not experience a VOC for at least 12 consecutive months for exa-cel was 92.7% (95% CI: 62.2 to 99.0) compared with 16.9% of patients in the SoC group who were VOC-free at 52-week follow-up as reported in the SUSTAIN trial (Table 26). The resulting rate ratio was 5.5 (95% CI: 3.1 to 9.6; p<0.0001) indicating that exa-cel resulted in a statistically significant, 5.5-times higher proportion of patients remaining VOC-free for 12 consecutive months compared with SoC as defined in the SUSTAIN trial (189).

Table 26: Proportion of patients who remained VOC-free for 12 months, exa-cel vs SoC as defined in the SUSTAIN trial of crizanlizumab

	SOC (N = 65)	Exa-cel unweighted (before matching)	Exa-cel re-weighted (after matching) (ESS = 12)

		(N = 17)	
Proportion (95% CI)	16.9% (-, -)	94.1% (71.3%, 99.9%)	92.7% (62.2%, 99.0%)
Rate Ratio (95% CI)			5.5 (3.1, 9.6)
***P* value**			<0.0001

Key: CI: confidence interval; ESS: effective sample size; SoC: standard of care; VOC: vaso-occlusive crisis.
Source: Table 4, Exa-cel SCD ITC Report (189).

B.2.9.3. Conclusions

Overall, the MAIC findings support the high clinical benefit of exa-cel compared to SoC in SCD, resulting in higher proportions of patients being VOC-free at 12 months after exa-cel infusion. For instance, there was over a five-fold increase in the proportion of patients who were VOC-free at 12 months following exa-cel infusion compared to SoC as defined in the SUSTAIN trial (189).

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

Due to the small sample size in the CLIMB SCD-121 PES at the time the ITC was originally conducted (N=17), no more than three variables were used for matching variables for each MAIC.

Exa-cel demonstrated superior efficacy relative to all comparators and across all outcomes included in the MAICs, despite the fact that the analyses may have underestimated the efficacy of exa-cel as matching on genotype was not feasible. Overall, the MAIC results support the overwhelming efficacy of exa-cel compared to currently available therapies in SCD, resulting in higher proportions of patients who are VOC-free and a reduction in the rate of VOCs.

Limitations of the analysis include the small exa-cel ESS, resulting from the relatively small sample size of the CLIMB SCD-121 PES (N=17). HTA expert input recommended a maximum of three matching variables for each MAIC. Notably, for the comparison versus SOC as defined in the HOPE trial, the resulting ESS was less than 5 following weighting, and between-treatment statistical comparisons were not recommended. Not all outcomes of interest were available for all comparators: the proportion of patients who were VOC-free was not reported in the NCT01179217 trial. While the definition of VOC reported in all included studies were generally similar to

that of the CLIMB SCD-121 trial, some differences were noted. For the SUSTAIN trial, while the definition of VOC included hepatic sequestration, this is considered a rare event in SCD; the potential impact of including these events is likely minimal. For the HOPE trial, these included the lack of priapism or splenic sequestration, therefore, there could be slightly fewer VOCs captured in the HOPE trial. Finally, the annualised rate of VOC as reported in the HOPE trial was adjusted for baseline hydroxycarbamide use, age, and geographic region.

B.2.10 Adverse reactions

The safety and tolerability of exa-cel for the treatment of patients aged 12-35 years with severe SCD was evaluated in the SAS of CLIMB SCD-121.The SAS was defined as all patients who have started mobilisation (Stage 1) (n=58) (see Figure 14). The discussion of AEs focuses on the period from exa-cel infusion to Month 24, except where noted (7). Safety results are presented for the D120 data cut, which has a larger sample size and longer duration of follow-up.

AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. Only AEs related or possibly related to exa-cel, SAEs, new malignancies, and new or worsening haematologic disorders were collected in CLIMB-131, starting after the Month 24 following exa-cel infusion (166).

B.2.10.1. Exposure to exa-cel

At D120, the median dose of exa-cel was 4.0 x 10^6 CD34+ cells/kg (range: 2.9 to 14.4 x 10^6 $CD34^+$ cells/kg) in the FAS. The median follow-up duration after exa-cel infusion was 17.5 months (range: 1.2 to 46.2) months) (Table 27) (7).

Exa-cel exposure for CLIMB SCD-121 and CLIMB-131 for the D120 data cut is presented below in Table 27.

Table 27: Summary of exa-cel exposure (CLIMB SCD-121 and CLIMB-131, FAS)

	D120 (N = 43)
Exa-cel dose (10^6 CD34+ cells/kg)	
n	43
Mean (SD)	4.7 (2.47)
Median	4.0
Min, Max	2.9, 14.4

Follow-up duration after exa-cel infusion (months)	
n	43
Mean (SD)	18.6 (9.99)
Median	17.5
Min, Max	1.2, 46.2
Follow-up duration after exa-cel infusion by interval[a], n (%)	
≤3 months	2 (4.7)
>3 months to ≤6 months	2 (4.7)
>6 months to ≤12 months	8 (18.6)
>12 months to ≤24 months	16 (37.2)
>24 months[a]	15 (34.9)

Key: FAS: Full analysis set; N: total sample size; n: size of subsample; SCD: sickle cell disease SD: standard deviation.
Note: Follow-up duration (months) after exa-cel infusion = (Data cutoff date or end date of Study 131 whichever is earlier – exa-cel infusion date + 1)/30. Exposure (patient-months/patient-years) after exa-cel infusion = Sum of the after exa-cel infusion follow-up duration (months/years) from patients who have received exa-cel infusion in the FAS.
[a]Follow-up duration is not equivalent to study visit (see calculation above). Due to protocol-specified visit windows, a patient in this category may not have completed the Month 24 visit in CLIMB TDT-111 or CLIMB SCD-121, as applicable, thus had not enrolled in CLIMB-131.
Source: Table 22 Vertex D120 Report (7).

B.2.10.2. Summary of safety

The safety profile of exa-cel in CLIMB SCD-121 was generally consistent with myeloablative busulfan conditioning, which has a well-established safety profile. The therapy used for mobilisation and apheresis (plerixafor) also has a well-characterised safety profile (7).

From exa-cel infusion onwards, 58 patients (100.0%) had at least one AE and 16 patients (37.2%) had at least one SAE. Thirteen patients (30.2%) had AEs considered related or possibly related to exa-cel (i.e., related to exa-cel only or exa-cel and busulfan). No patients had an SAE that was considered possibly related or related to exa-cel. Moreover, a total of 40 of 58 patients (69.0%) experienced Grade 3 or 4 AEs (7).

One patient had a fatal AE, however it was not related to exa-cel. The patient died at Day 130 following exa-cel infusion due to respiratory failure after COVID-19 infection, with a potential contribution of busulfan lung injury and pre-existing lung disease. The patient's medical history included thrombocytopenia, chest pain, seizure, splenectomy, nephropathy, cellulitis, herpes simplex, rhinitis, sinusitis, hepatic enzymes increased, haemochromatosis, chronic pain, arthralgia, osteoarthritis, anxiety, and depression (7, 166, 173).

In CLIMB-131, one patient [redacted] had an SAE of gastroenteritis norovirus o[redacted]; the event was considered not related to any study drug. No patients had AEs

or SAEs related or possibly related to exa-cel in CLIMB-131. No patients had AEs of new malignancies, new or worsening haematologic disorders, or SCD-related complications (7). As such, reporting of AEs is presented for CLIMB SCD-121 only.

An overview of the AEs experienced by patients in the SAS are presented in Table 28 (7).

Table 28: Overview of AEs before and after exa-cel infusion and overall (CLIMB-121, SAS)

Visit	Enrolment to <exa-cel[a] (n=58)	D120 exa-cel to M24[a] (n = 43)
Patients with exa-cel infusion, n	--	43
Patients with busulfan dosing, n	35	43
Patients with any AEs, n (%)	56 (96.6)	43 (100.00)
Patients with AEs related or possibly related to exa-cel, n (%)	--	13 (30.2)
Patients with AEs related or possibly related to busulfan, n (%)	27 (77.1)	43 (100.0)
Patients with Grade 3 or 4 AEs	43 (74.1)	41 (95.3)
Patients with SAEs	38 (65.5)	16 (37.2)
Patients with SAEs related or possibly related to exa-cel	--	0
Patients with SAEs related or possibly related to busulfan	0	4 (9.3)
Patients with AEs leading to study discontinuation	0	0
Patients with AEs leading to death	0	1 (2.3)[a]

Key: AE: adverse event; exa-cel: exagamglogene autotemcel; M: month, SAE: serious adverse event; SAS: safety analysis set.
Notes: MedDRA version 26.0. Evaluable patients, N1: The number of patients in the SAS who were on or after the start date of each study interval. N2/N3: The number of patients in the SAS who were on or after the start date of each study interval and had received exa-cel infusion (i.e., FAS)/busulfan dosing. 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.
[a]As reported in the initial MAA, 1 patient died due to COVID-19 infection that resulted in respiratory failure, not related to exa-cel; this resulted in study discontinuation.
Source: Table 24 Vertex D120 Report (7) and CLIMB SCD-121 CSR (166).

B.2.10.3. Common adverse events

AEs that occurred in ≥25% of patients who completed myeloablative busulfan conditioning and received exa-cel (n=43) are summarised below in Table 29 (7). From exa-cel infusion to Month 24, the most common AEs were nausea (69.8%), stomatitis (62.8%) and vomiting (58.1%) (7). All common AEs were consistent with myeloablative busulfan conditioning, allo-SCT and underlying disease (166).

Table 29: AEs occurring in ≥25% of patients after exa-cel infusion by preferred term (CLIMB SCD-121, FAS)

MedDRA Preferred Term[a], n (%)	D120 exa-cel to M24[a] (n = 43)
Patients with any AEs	43 (100.00)
Nausea	30 (69.8)
Stomatitis	27 (62.8)
Vomiting	25 (58.1)
Febrile neutropenia	23 (53.5)
Abdominal pain	22 (51.2)
Headache	22 (51.2)
Pruritus	21 (48.8)
Decreased appetite	20 (46.5)
Pain in extremity	20 (46.5)
Platelet count decreased	20 (46.5)
Arthralgia	19 (44.2)
Constipation	18 (41.9)
Diarrhoea	17 (39.5)
Neutrophil count decreased	17 (39.5)
Pyrexia	17 (39.5)
Anaemia	16 (37.2)
Mucosal inflammation	16 (37.2)
Back pain	15 (34.9)
Fatigue	15 (34.9)
Hypokalaemia	15 (34.9)
Skin hyperpigmentation	14 (32.6)
Neutropenia	13 (30.2)
Oedema peripheral	12 (27.9)
Thrombocytopenia	12 (27.9)
Abdominal pain upper	11 (25.6)
Alanine aminotransferase increased	11 (25.6)
COVID-19	11 (25.6)
Gastritis	11 (25.6)
Pain	11 (25.6)

Key: AE: adverse event; exa-cel: exagamglogene autotemcel; M: month; n: size of subsample; PT: preferred term; SAS: safety analysis set..
Notes: AEs were coded using MedDRA Version 25.0. The Safety Analysis Set included 58 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 by PT.
[a] All PTs are described in busulfan product information by matching PT or similar medical concept.
Source: Table 26 Vertex D120 Report (7).

The majority of Grade 3 or above AEs (70%) occurred in the first six months after exa-cel infusion and are summarised below in Table 30. All of these events were resolved (7, 166). In the long-term follow-up study CLIMB-131, no patients experienced AEs related to exa-cel (7).

Table 30: Grade 3 or above AEs occurring in >5% of patients after exa-cel infusion (CLIMB SCD-121, SAS)

MedDRA preferred term, n (%)	D120 exa-cel to M24[a] (n=58)
Evaluable patients (N1)	43
Patients with any Grade 3 or above AEs	41 (95.3)
Febrile neutropenia	23 (53.5)
Platelet count decreased	20 (46.5)
Decreased appetite	20 (46.5)
Neutrophil count decreased	17 (39.5)
Mucosal inflammation	17 (39.5)
Anaemia	14 (32.6)
Thrombocytopenia	11 (25.6)
Neutropenia	11 (25.6)
White blood cell count decreased	10 (23.3)
Abdominal pain	6 (14.0)
CD4 lymphocytes decreased	5 (11.6)
Cholelithiasis	5 (11.6)
Pruritus	5 (11.6)
Constipation	5 (11.6)
Headache	4 (9.3)
Non-cardiac chest pain	4 (9.3)
Pneumonia	4 (9.3)
Abdominal pain upper	4 (9.3)
Arthralgia	3 (7.0)
Back pain	3 (7.0)
Deep vein thrombosis	3 (7.0)
Nausea	3 (7.0)
Oropharyngeal pain	3 (7.0)
Pain	3 (7.0)
Weight decreased	3 (7.0)

Key: AE: adverse event; exa-cel: Exagamglogene autotemcel; M: month; N1: evaluable patients (number of patients in the SAS who are on or after the start date of each study interval); WBC: white blood cell; n: size of subsample; PT: preferred term.
Notes: AEs were coded using MedDRA Version 26.0. The Safety Analysis Set included 58 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 PT.
Source: Table 14.3.2.4.1 Vertex Data on File and Table 14.3.2.4.1, Vertex D120 Report (7, 192).

B.2.10.4. Engraftment

All patients with at least 43 days of follow-up after exa-cel infusion achieved neutrophil (n=43) and platelet (n=43) engraftment. The median (range) time to neutrophil engraftment was 27.0 (15.0 to 40.0) days, while the median (range) time to platelet engraftment was 35.0 (23.0 to 126.0) days (Table 31) (7).

There was no use of backup $CD34^+$ stem cells in any patient enrolled onto CLIMB SCD-121 (166).

Table 31: Summary of neutrophil and platelet engraftment (CLIMB SCD-121, SAS)

Summary of Neutrophil and Platelet Engraftment	D120 (n=43)
Patients whose neutrophil engraftment was evaluable*, N	43
Time to NE (days) for patients who achieved NE at any time	
Mean (SD)	26.7 (6.0)
Median	27.0
Min, max	15, 40
Patients who achieved NE by Study Day 43	
n	43
%, 95% CI	100 (91.8, 100.0)
Patients who achieved NE at any time	
n	43
%, 95% CI	100.0 (91.8, 100.0)
Patients who achieved platelet engraftment, N	43
Time to PE (days) for patients who achieved PE at any time	
Mean (SD)	43.2 (22.2)
Median	35.0
Min, max	23, 126

Key: NE: neutrophil engraftment, PE: platelet engraftment; SD: standard deviation.
Notes: *A patient is evaluable for neutrophil engraftment if the patient has achieved NE or has at least 43 days follow-up post exa-cel infusion and 19 (44.2%) patients received G-CSF prior to NE.
Source: Vertex D120 Report (7).

B.2.10.5. Safety overview

The longer duration of the D120 data cut (16 April 2023) supports the safety profile of exa-cel, which was generally consistent with myeloablative conditioning and allo-SCT,

both having well established safety profiles. While all patients experienced AEs, these were mostly related to myeloablative conditioning with busulfan rather than exa-cel (7).

The majority (>70% in CLIMB SCD-121) of AEs, SAEs, and Grade 3 or above AEs, occurred in the first 6 months after exa-cel infusion. None of the SAEs that occurred ≥6 months after exa-cel infusion were considered related or possibly related to busulfan or exa-cel (7). One patient had a fatal AE, however this was not related to exa-cel. The patient died [redacted] following exa-cel infusion due to respiratory failure after COVID-19 infection, with a potential contribution of busulfan lung injury [redacted] (7, 166, 173).

The number and time-adjusted rate of AEs, Grade 3 or above AEs, and SAEs was highest within the first 6 months following myeloablative conditioning with busulfan and exa-cel infusion, compared to all the following 6 months intervals (6 to <12, 12 to <18, and 18 to 24 months). After the first 6 months following exa-cel infusion, the time-adjusted AE rates decreased markedly in successive 6-month intervals through Month 24, including an approximately 6 to 29-fold reduction between the 0 to 6 months and each of the subsequent 6-month intervals (7).

Furthermore, evaluation of the first 6 months by 3-month intervals showed that the time adjusted rates for AEs, Grade 3 or higher AEs, and SAEs during the first 3 months were overall the highest of any subsequent time interval (7).

In CLIMB-131, there was one new SAE observed on [redacted] , however this was gastroenteritis norovirus therefore was not related to exa-cel (7). No patients had AEs or SAEs related or possibly related to exa-cel in CLIMB-131. In addition, no patients had AEs of new malignancies, new or worsening haematologic disorders, or SCD-related complications over the duration of follow-up (7).

Exa-cel uses the patient's own HSPCs thereby removing the need for a suitable donor, associated risk of GvHD and graft rejection, in comparison to the increased mortality linked with allo-SCT as highlighted in Section B.1.3.1 (21, 22). As anticipated, given the autologous nature of exa-cel, no patients experienced GvHD or graft rejection (7).

Moreover, D120 provides a longer follow-up duration for patients in the FAS of 46.2 months, further supporting the safety profile of exa-cel (7).

Notably, EQ-5D-5L and FACT-BMT data presented in Section B.2.6.2.5 suggests minimal long-term impact of AEs on patient HRQoL, with results improving from Month 6 onwards (7).

B.2.11 Ongoing studies

CLIMB SCD-121 is ongoing and will provide additional evidence for the efficacy and safety of exa-cel in patients aged 12-35 years of age with severe SCD. Results presented herein are taken from the D120 data cut-off (16 April 2023). Further data cut-offs are expected to be made available during the evaluation process, with the next data cut-off planned for [redacted]. 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 SCD-121 (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. As described in Section B.2.3, 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 SCD-121 or CLIMB THAL-111) for a total follow-up of 15 years after infusion (193). On this basis, the final study completion date is estimated to be September 2039.

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 patients aged 12-35 years with severe SCD is currently being investigated in a Phase 1/2/3 single-arm, open-label, multi-site, single-dose study. Findings below are presented for the D120 data cut (16 April 2023).

The CLIMB SCD-121 cohort represents a population with a high VOC burden, with patients in the FAS averaging (SD) 4.2 (3.0) severe VOCs per year. The majority of patients (90.7%) had a β^S/β^S genotype (7).

In the PES, 28 of 29 patients (96.6%) had achieved VF12 at D120, with a mean (SD) VOC-free duration of 20.7 (7.1) months. Moreover, in the FAS, 41 of 43 patients had at least 60 days of follow-up after the last RBC transfusion for post-transplant support or SCD management. Of these patients, 37 of 41 did not experience any VOC, starting 60 days after the last RBC transfusion, for a duration of 1.3 to 43.6 months (7).

Following exa-cel infusion, 4 of 41 patients in the FAS experienced events adjudicated as VOCs, starting 60 days after the last RBC transfusion. [redacted] (7).

Despite experiencing events adjudicated as VOCs, the remaining four patients have all demonstrated treatment benefit from exa-cel. Both patients in the PES achieved HF12, and all four patients remained free from inpatient hospitalisation (HF12) and VOC-free for a duration of 0.7 – 10.4 months since their last VOC. After achieving

VF12 and HF12, one of the four patients ([redacted]) experienced an inpatient hospitalisation for a severe VOC approximately 22.7 months following exa-cel infusion. The patient has since been VOC-free for a duration of 10.4 months (7).

Clinically meaningful increases in mean total Hb and HbF levels were demonstrated early and were maintained over time from Month 3 onwards in the FAS, indicating durability of response (7). Mean (SD) total Hb concentration increased from 9.1 (1.6) g/dL at baseline to 13.1 (1.9) g/dL at Month 24. Total Hb levels of 12.0 (1.5) g/dL were achieved at Month 3 after exa-cel infusion, remaining between 12.0 g/dL and 13.5 g/dL up to Month 24, and remaining above 13.0 /dL up to Month 30, although interpretation of results beyond Month 24 is limited by sample size (Figure 17) (7). There was expectation amongst clinical advisors that Hb concentrations sustained at 12-13 g/dL would be associated with substantial improvement in condition. In addition, these haemoglobin levels are comparable to what is seen with rare natural phenotypes of sickle and HPFH in SCD patients who do not show any symptoms (12).

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 (7). In CLIMB SCD-121 and CLIMB SCD-131, the durability of response has been confirmed for up to 43.6 months (7). 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 (12).

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 be explored further in CLIMB-131, the ongoing long-term follow-up study of patients enrolled in CLIMB SCD-121 (7, 167).

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 avoids 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 severe SCD.

As demonstrated by the currently available data, exa-cel results in robust, consistent, and durable benefits, offering the potential to deliver a one-time functional cure for patients with severe SCD while maintaining a favourable benefit to risk profile. Exa-cel represents a paradigm shift in the treatment of SCD and helps to address the substantial unmet medical need faced by patients with severe SCD.

B.2.12.2. Strengths and limitations of the evidence base

To date, following a single dose of exa-cel, almost all evaluable patients (90.2%) with SCD in the CLIMB SCD-121 study have remained VOC-free, starting from 60 days after the last RBC transfusion for post-transplant support or SCD management. Summary results from the D120 data cut (16 April 2023) provide support for the transformational and durable benefit of exa-cel treatment in adults and adolescents with SCD, with duration of VOC-free of up to 43.6 months (CLIMB SCD-121, FAS n=43) (7).

Both primary and key secondary endpoints in CLIMB SCD-121 were VOC-related, given that recurrent VOCs lead to significant morbidity and mortality in SCD. Additional secondary endpoints selection was based on the ability to further demonstrate the additional clinical benefit of exa-cel, in particular the rapid, robust, sustained and durable effect observed following treatment.

CLIMB SCD-121 is a single-arm, open-label, trial; this design was used due to lack of equipoise with existing SoC and the need for a transplant procedure to deliver exa-cel. The treatment procedure for exa-cel means it would be impossible to blind against existing SoC; and it would neither be feasible nor ethical to perform apheresis, myeloablation and transplantation in a placebo group.

This presents challenges both with contextualisation of clinical efficacy versus BSC, correct attribution of AEs to aspects of treatment, and methodological consideration of observer and potential bias. However, in the natural history of SCD, patients do not spontaneously stop experiencing VOCs and as such, in this context they can reasonably serve as their own controls.

Due to the single-arm nature of CLIMB SCD-121, an ITC was used to generate estimates of comparative effectiveness versus BSC (See Section B2.9).

B.2.12.3. Applicability of clinical evidence to practice

B.2.12.3.1. Patient characteristics

The population enrolled in CLIMB SCD-121 is considered highly generalisable to those expected to receive exa-cel in UK clinical practice. For the 43 patients in the FAS, the mean (SD) age of patients was 21.2 years (SD 6.1) (7), slightly younger than the mean age of UK patients enrolled in a retrospective CPRD-HES study of UK Burden of Illness (24.96 years [range: 1- 86 years]). However, feedback from clinical experts was that younger, fitter patients would be prioritised for treatment with exa-cel, which may result in a lower mean age relative to the BoI study (12).

The majority of patients were Black or African American (86.0%), a similar figure to that reported in the NHR 2020/2021 annual report (4, 7, 33). In addition, almost all patients (90.7%) in the FAS had a β^S/β^S genotype; 7.0% had a β^S/β^0 genotype and 2.3% had a β^S/β^+ genotype (Section B.2.3.8) (7). Clinical experts consulted as part of this submission felt that the genotype distribution in CLIMB SCD-121 was similar to what would be seen in UK clinical practice (132).

The eligibility criteria for CLIMB SCD-121 are primarily driven by the individual patients' fitness to safely 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 SCD-121 (12).

Although the majority of patients in the FAS were recruited from study sites in Canada, France, Germany, Belgium, Italy and the US, local guidelines in each of the study locations are closely aligned with those issued by the British Society for Haematology (61, 117-119). Thus, the management and treatment of patients with SCD in CLIMB SCD-121 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 SCD-121 (n=43) is presented and this data is used in the subsequent cost-effectiveness analysis. This analysis set includes all patients dosed with exa-cel in

CLIMB SCD-121, irrespective of follow-up, and as such provides the largest sample size (7). Details on analysis sets are presented in Table 15.

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 identify published cost-effectiveness studies of potentially curative stem-cell therapies (i.e. exa-cel) for the treatment of SCD. The SLR methods are detailed in Appendix G. None of the cost-effectiveness studies identified address the decision problem presented in Section B.1.1 from a UK perspective, although a draft US evaluation of exa-cel has been published by the Institute for Clinical and Economic Review (194).

B.3.2 Economic analysis

The SLR of cost-effectiveness studies identified that none of the studies address the decision problem presented in section B.1.1 from a UK perspective. A *de novo* cost-effectiveness model was therefore developed in Microsoft Excel® to appraise the cost-effectiveness of exa-cel for the treatment of SCD in patients 12 years of age and older with recurrent VOCs who have β^S/β^S, β^S/β^0 or β^S/β^+, for whom a HLA-matched related HSC donor is not available (1).

B.3.2.1. Patient population

In accordance with the anticipated licensed indication of exa-cel, the modelled patient population is patients with SCD who are 12 years of age and older with recurrent VOCs who have the β^S/β^S, β^S/β^+ or β^S/β^0 genotype, for whom an HLA-matched related HSC donor was not available. The model population was derived from the FAS population of the pivotal clinical trial, CLIMB SCD-121 (NCT03745287), in which recurrent VOC status was defined as having two or more VOCs per year in the 2 years preceding trial enrolment (158, 162).

Patient baseline characteristics used in the model are summarised in Table 32. Mean age at baseline is 21.2 years and 44.2% are female, in line with CLIMB SCD-121. Patient weight was required in the model for estimating costs for treatments requiring weight-based dosing. Modelled SCD patients were assumed to be the same weight as the general UK population (ratio vs standard national reference = 1.0) accounting for patient age and gender (195, 196).

At baseline, patients were assumed to experience an average of 4.2 VOCs per year (162). Chronic complications at baseline were informed by CLIMB SCD-121. Five out of 35 patients had retinopathy, and 1 out of 35 patients had neurocognitive impartment. No patient had any of the following complications at baseline: pulmonary hypertension, chronic kidney disease (trial criteria excluded estimated glomerular filtration rate (eGFR) <60ml/min), post-stroke, heart failure, or liver disease since none of the conditions fall within the hepatic complications considered by the model. Twelve patients (34.3%) had osteonecrosis at baseline, but it is unknown whether they had ongoing costs and/or pain from this historical morbidity. Due to the uncertainty of the ongoing impact associated with avascular necrosis, this was excluded as a baseline morbidity. Values are reported in percentages in Table 32.

The utilisation of hydroxycarbamide, RBC transfusions and iron chelation therapy (ICT) at baseline was informed by CLIMB SCD-121 and the literature.

Table 32: Baseline clinical inputs

Variable	Value	Reference
Patient demographics		
Age	21.2	D120 data from CLIMB SCD-121 (7)
Weight ratio of SCD/general population	1.0	Chawla et al, 2013 (197)
Female (%)	44.2	CLIMB SCD-121 (166)
Proportion aged under 18 years of age (%)	27.9	D120 data from CLIMB SCD-121 (7)
Baseline VOC		
Frequency of VOC per year	4.2	CLIMB SCD-121 (166)
Utilisation (%)		
Hydroxycarbamide	63.8	CLIMB SCD-121 (166)
RBC transfusion	16	Bradt, 2020 (198)
Iron chelation therapy (among those receiving RBC transfusion)	34.6	Shah et al., 2019 (143)
DFO	6.1	Alkindi et al., 2021 (47)
DFX	89.8	Alkindi et al., 2021 (47)
DFP	4.1	Alkindi et al., 2021 (47)
DFO+DFX	0	Assumption
DFO+DFP	0	Assumption

DFX+DFP	0	Assumption
Proportion of patients with chronic complications (%)		
Pulmonary hypertension	0	IA2 data from CLIMB SCD-121 (166)
Chronic kidney disease	0	Exclusion criterion
Post-stroke	0	IA2 data from CLIMB SCD-121 (166)
Avascular necrosis	0	Assumption - unknown whether ongoing symptoms
Retinopathy	14.3	IA2 data from CLIMB SCD-121 (166)
Heart failure	0	IA2 data from CLIMB SCD-121 (166)
Neurocognitive impairment	2.9	IA2 data from CLIMB SCD-121 (166)
Liver disease	0	IA2 data from CLIMB SCD-121 (166)

Key: DFO, desferrioxamine, DFP, deferiprone; DFX, deferasirox; EHA, European Haematology Association; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

B.3.2.2. Model structure

A Markov cohort state-transition model was developed in Microsoft Excel®. The Markov model is driven by VOC frequency and includes SCD-related complications as health states in order to simulate the natural history and clinical pathways of SCD for the modelled patient population. SCD complications are associated with increased mortality, decreased quality of life, and increase healthcare resource utilisation and costs. The risk of developing SCD-related complications has been shown to be correlated with the frequency of VOCs, a primary clinical outcome among SCD patients (100). VOC frequency was included as a relevant health state in the economic model to capture the treatment efficacy of exa-cel based on the absence or reduction of VOC frequency and predict the impact on the development of SCD-related complications. The Markov structure is presented in Figure 26. The model utilises a monthly cycle length and costs and outcomes are measured over a lifetime horizon.

There is a precedent for using a Markov model structure in the evaluation of therapeutic options for SCD. Both the NICE submission for crizanlizumab for preventing sickle cell crises in SCD (ID1406) and the economic assessment of SCD treatments by the Institute for Clinical and Economic Review utilised Markov models with SCD-related complications as health states (150, 198). The cost-effectiveness model of crizanlizumab in the NICE submission consisted of three health states based on the annual frequency of VOCs (<1 VOC, ≥1–<3 VOCs, and ≥3 VOCs) and death

(150). The SCD-related acute complications were accounted for within each VOC health state. Alternatively, the cost-effectiveness model constructed by the Institute for Clinical and Economic Review considered the following health states – uncomplicated SCD, acute conditions including VOCs and complications, chronic conditions/complications, acute conditions on top of chronic conditions/complications and death (198). This modelling approach also captures the long-term chronic nature of the disease and its multiple re-occurring events (198). Hence, given the aforementioned considerations, a Markov model structure was selected for this analysis. A summary of the features of the cost-effectiveness model for exa-cel is provided in Table 33.

Neither the NICE nor Institute for Clinical and Economic Review models evaluated the cost-effectiveness of a treatment that eliminates VOCs. Therefore, there are features of the *de novo* model that were developed to consider the gene therapy curative nature of exa-cel such as having a VOC-free health state. In addition to that, the Markov model considers SCD-related complications as health states. The complications considered in the model are informed by previous models of SCD, published literature and clinical expert opinion and were selected to represent major clinical events over the course of a SCD-patient's lifetime. Acute complications included in the model are stroke, ACS, acute infection, acute kidney injury or infarction, gallstones, pulmonary embolism, and leg ulcers (143, 150, 198-200). Chronic complications included in the model are CKD, pulmonary hypertension, avascular necrosis, heart failure, neurocognitive impairment, post-stroke, sickle retinopathy, and liver complications (143, 150, 171, 198). These complications were selected based on cost impact and validated by clinical experts (12).

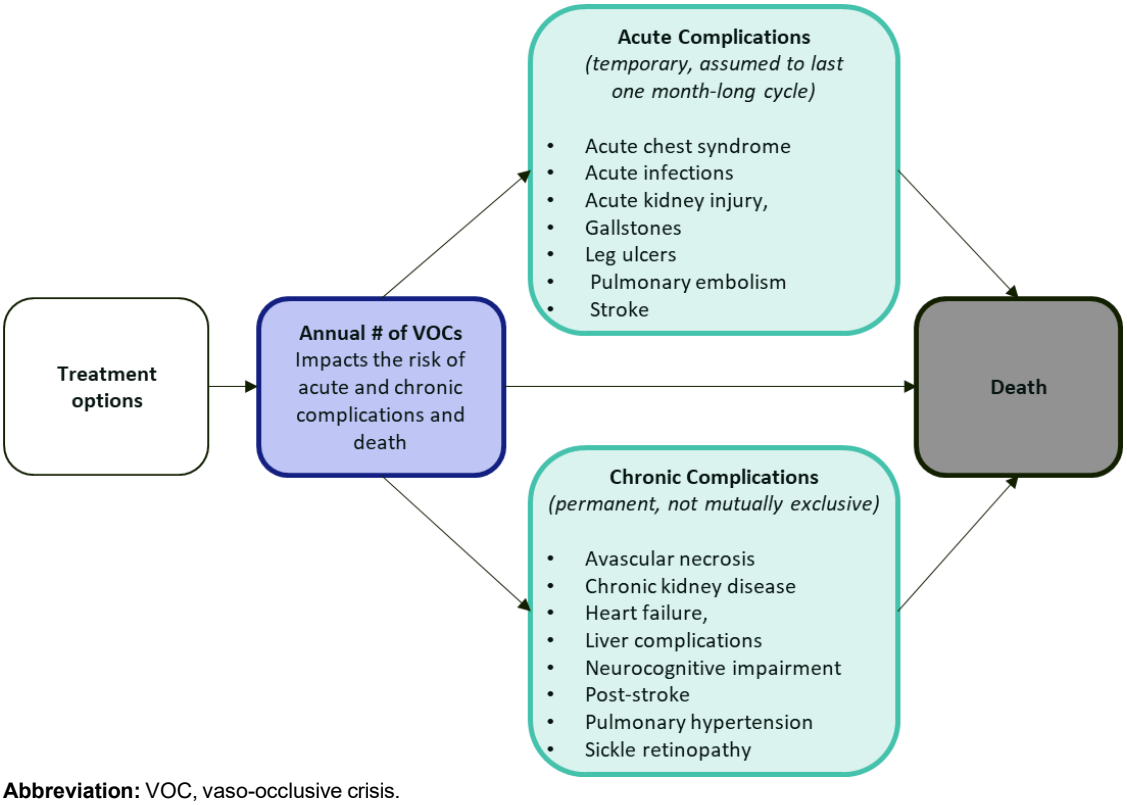
The incidence of acute complications and the risk of chronic complications is dependent on whether the patient is considered to be functionally cured and on the frequency of VOCs (if uncured). Thus a "functionally cured" patient who does not experience VOCs carries no risk of complications compared to an "uncured" patient who does not experience VOCs within a model cycle. This is an important differentiator from models of non-curative treatments that may reduce or prevent VOC but do not treat the underlying disease pathology. Due to the lifetime horizon of the model and the application of age and gender-matched general population utility and mortality

rates, the model assumes that the impact of complications in functionally cured patients is already captured.

Since each complication has an impact on patients' mortality, HRQoL, and HCRU over time, each of these complications are modelled independently. Acute complications are assumed to last for only one model cycle and not accumulate. Chronic complications are considered permanent conditions that are assumed to last until death once developed, that is, they are permanent health states.

For exa-cel, only patients who are infused are included in the modelled cohort. Patients who withdraw from treatment prior to infusion or transplant in the clinical trial are assumed to withdraw prior to myeloablation, and these patients are not included in the modelled cohort. However, the costs of pre-mobilisation, mobilisation and apheresis for these patients are included as additional costs in the pre-transplantation costs.

Figure 26*:* Markov model structure



Abbreviation: VOC, vaso-occlusive crisis.

Table 33: Features of the base-case economic analysis

Factor	Previous evaluations		Current evaluation	
	TA743 Crizanlizumab	**STA ID1403 Voxelotor**	**Chosen values**	**Justification**
Time horizon	55 years (lifetime horizon)	55 years (lifetime horizon)	Lifetime	As per the NICE reference case. Sufficient to capture meaningful differences in technologies.
Cycle length	12 months (with half-cycle correction)	No cycle length - model structure is discrete-event simulation	1 month (with half-cycle correction)	Sufficient to capture meaningful changes in patient disease history and treatment effects
Discount rate	3.5%	3.5%	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. • SCD is a chronic disease, characterised by unpredictable episodes of severe pain, chronic haemolytic anaemia, widespread organ damage, and shortened life expectancy, with a mean age at death of 40.2 year in a UK severe SCD cohort (3, 4). The disease affects multiple organs leading to acute and chronic complications such as ACS, stroke, priapism, splenic sequestration, osteonecrosis, renal failure, pulmonary hypertension, liver disease, bone damage, limited growth, increased susceptibility to infections, fatigue,

				and progressive cognitive decline. • Acute pain events, the hallmark clinical feature of SCD, reflect vaso-occlusion, impaired oxygen supply, and tissue injury from infarction and reperfusion (15, 30-32). These events are characterised by the unpredictable acute onset of severe pain which commonly manifests in the extremities, chest, back or as dactylitis (severe pain of the hands and feet), or as priapism (15, 33). In the pivotal clinical trial of exa-cel, 94.8% of patients had received opioids at baseline, most commonly morphine, fentanyl, and oxycodone. • In summary, SCD 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 burden of frequent pain episodes and the associated substantial impact on HRQoL (5). <u>Exa-cel is likely to restore these patients to full or near-full health:</u> • Patient treated with exa-cel will experience improved survival, reduced risk of co-morbidities and they will no longer need to receive treatment, and experience the associated side-effects of hydroxycarbamide and transfusions,

				which are highly burdensome. Notably, 63.8% of patients in the pivotal trial had received hydroxycarbamide at baseline. In addition, by resulting in a functional cure, exa-cel will reduce the need for opioids and other strong analgesics to manage severe pain episodes. SCD patients treated with potentially curative therapies such as stem-cell transplant (SCT) or gene therapy experienced large positive effects in all HRQoL domains (6). At Month 24 in CLIMB SCD-121, EQ-5D had increased by 0.11, exceeding the minimal clinically important difference, and even exceeding general population norms for EQ-VAS and FACT-G in the clinical study. (7). • Long-term survival following stem cell transplant in SCD 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) (8). • 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 (8). Patients with HPFH will

				experience few or no SCD symptoms, particularly with HbF level of approximately 30% or more (9-11); (9-11) by mimicking this exa-cel will restore patients to near normal health. <u>The benefits are likely to be sustained over a very long period:</u> • The expected benefits of exa-cel as a one-time gene editing therapy include long-term amelioration 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. Mean proportion of Hb comprised by HbF increased to 36.8% at Month 3 and was maintained above 40% thereafter (See B.2.6). • Allele editing data in CD34+ cells of the bone marrow and peripheral blood were 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 (B 2.6). The stable, durable allelic editing observed is consistent with the stability of HbF production over time and indicative that the clinically meaningful effect of absence of VOCs will persist long-term. • 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 (12).
Efficacy inputs	Mean change in vaso-occlusive crisis (VOC) frequency	Impact of haemoglobin levels	Mean change in VOC frequency	VOCs are the landmark complication of SCD and are associated with the occurrence of other complications based on literature (100). Mean change in VOC is available for exa-cel and comparators.
Treatment waning effect?	No	No	No	See section B.3.3.1. Graft failure has not been observed during the trial period and late relapses following allo-SCT are extremely rare. There is no evidence of treatment waning effect with well-maintained allelic editing (8).
Source of utilities	36-Item Short Form Survey assessments from the LEGACY registry study were grouped based on annualised VOC incidence (<1 VOC, ≥1–<3 VOC, or ≥3	Overall population: UK population norms (adjusted to match HOPE trial population) Decrement due to SCD: calculated from HOPE trial Utility decrements for SCD complications were taken from	Baseline health state utilities for complicated and uncomplicated SCD were sourced from the CLIMB SCD-121	EQ-5D responder status were not available from CLIMB SCD-121 at the time of submission development. The baseline health state utilities were sourced from the CLIMB SCD-121 FAS population where HRQoL was prospectively measured in a UK sample of patients with SCD and are

	VOC) and mapped to EQ-5D-3L using the algorithm published by Rowen et al. (2009). EuroQoL 3-Dimensions 5-Level (EQ-5D-3L) utilities were applied to VOC health states in the base case analysis.	suitable sources in the literature		thus deemed representative of the patient population (166).
Source of costs	Costs were sourced from NHS reference costs and auxiliary price lists, eMIT, BNF, PSSRU, NICE guidelines, and supplemented by the literature.	Costs were drawn from a range of sources, including NHS costs, costs from previous technology appraisals and, where necessary, costs from the literature.	As per the reference case	See section B.3.5
Health inequalities	Individuals with SCD represent a group of patients who may experience health inequalities due to their ethnicity and socioeconomic status: individuals of African or African-Caribbean ethnicity have poorer health outcomes compared to other ethnic groups in the UK, as has been seen in the COVID-19 pandemic,	The great majority of people with SCD are from ethnic minorities (people of African, Caribbean, Middle Eastern or South Asian descent), and race is a protected characteristic under the Equality Act 2010. Therefore, there are equality considerations associated with issuing guidance on the use of voxelotor, as these groups will be disproportionately affected.	Yes	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 (201). Furthermore, the National Healthcare Inequalities Improvement Programme (HiQiP) established in January 2021, is also keen to increase the scale and pace of NHS action to tackle healthcare inequalities to protect those at greatest risk. Furthermore, the majority of SCD patients are from African or Caribbean ethnicity and these groups have reduced health outcomes (202).

	and patients with SCD are more likely to live in more impoverished areas of the UK.			*Udeze et al.,* (2023) conducted a burden of illness study in a severe SCD UK cohort. This study analysed patients' characteristics, and looked at many variables including the socio-economic status (4). This analysis used the Index of Multiple Deprivation instrument which is a composite measure derived from several indicators covering different aspects ('domains') of material socio-economic deprivation: income, employment, education and skills, health, housing, crime, access to services, and living environment. Each domain index can itself be a composite score derived from two or more sub-domain indicators. The overall composite index is calculated as a weighted sum of the domain indices for small areas of England and represented as five quintiles (Q1 being the least deprived and Q5 the most deprived). Result shows that 72.3% of patients with SCD fit in the two most deprived quadrants. Improving the health outcomes of SCD patients with the use of exa-cel would potentially reduce health inequalities in this population and therefore contribute to NICE's and HiQiP aims and objectives. 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. One output of DCEA is to explicitly incorporate a decision-maker's aversion to inequality, based on a Social Welfare Function, into the calculation of the incremental cost-effectiveness ratio (ICER). Using this function, quality-adjusted life years 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 could potentially reduce health inequalities. The DCEA methods are described in more detail in Section B.3.9.

Key: Allo-SCT: allogeneic stem cell transplantation; DCEA: distributional cost-effectiveness analysis; EQ-5D-3L: EuroQoL 5-Dimensions 3-Level; HiQiP: National Healthcare Inequalities Improvement Programme; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; SCD: sickle cell disease; VOC: vaso-occlusive crisis.

In the economic analysis we have incorporated one deviation from the NICE reference case (use of a 1.5% discount rate) as well as two modifiers: the severity modifier, which is part of the NICE reference case, and a DCEA modifier, which is not part of the NICE reference case. Justification for incorporation of the 3 factors is provided below:

Severity

Severity is represented in the NICE methods guide 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. It is worth noting that the modifier is applied based on the discounted QALY shortfall, which can penalise diseases such as SCD where the QALY loss occurs over a long time period.

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.

There is precedent for applying 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*.

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 limitation could lead to failure in adequately addressing health inequalities in the SCD population. The current submission endeavours to quantity the impact of exa-cel on health inequalities of SCD patients by applying published methods and 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.

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.

B.3.2.3. Intervention technology and comparators

The intervention considered in the cost-effectiveness model is exa-cel and the comparator is SoC.

Exa-cel is an autologous, *ex vivo* CRISPR/Cas9 gene-edited therapy, in which a patient's own haematopoietic stem cells are edited to produce high levels of fetal HbF in RBCs. The elevation of HbF by exa-cel has the potential to reduce painful and debilitating sickle cell crises for patients with SCD. Exa-cel is provided as a one-time potentially curative treatment.

SOC is assumed to comprise of symptomatic care. A proportion of patients treated with SoC are assumed to receive hydroxycarbamide and/or RBC transfusions.

B.3.3 Clinical parameters and variables

Key clinical parameters for the exa-cel arm were informed by the pivotal clinical trial, CLIMB SCD-121. Data from the most recent data cut (16 April 2023) was used to inform the model. CLIMB SCD-121 is a single-arm trial and thus could not provide comparator data for SoC. Some individuals will have more VOCs and some will have less, however, on a population level this is likely to balance out (61). Therefore, the model assumes that SoC does not reduce the baseline frequency of VOC and that patients maintain the same frequency of VOC for the modelled time horizon.

B.3.3.1. VOC frequency

Exa-cel arm

The exa-cel, treatment phase includes pre-mobilisation, mobilisation and apheresis, myeloablative conditioning and infusion, and engraftment. The treatment phase is assumed to last for 12 months, based on CLIMB SCD-121. This assumption was considered appropriate by consulted clinicians. Treatment efficacy with exa-cel is only assumed in the post-treatment phase.

Treatment withdrawal is defined as patients who were never dosed with exa-cel; thus these patients were not analysed in the FAS or PES trial data. Eleven out of 58 patients withdrew from the exa-cel arm. Patients with engraftment failure from exa-cel were assumed not to receive any clinical benefits from exa-cel and would continue receiving SoC as per baseline. The initial engraftment success rate was 100% based on the FAS. During the treatment phase, patients' VOC frequency is assumed to remain at the baseline value. This is considered a conservative model assumption, given patients treated with exa-cel are receiving additional supportive care including exchange transfusions to lower the risk of VOCs during the treatment phase.

Among modelled patients treated with exa-cel, all of whom achieved engraftment success, 96.6% were assumed to be functionally cured and experience no subsequent VOCs. This estimate is based on the most recent data-cut of the CLIMB SCD-121 trial, in which 28 of 29 patients in the primary efficacy set achieved the VF12 primary endpoint (proportion of patients who have not experienced any severe VOC for at least 12 consecutive months) after exa-cel infusion (VOC-free duration ranged from 13.6 to

43.6 months, with a mean of 20.7 months) (169). The remaining 3.4% of exa-cel patients were assumed to be non-responders from exa-cel treatment based on the one patient who experienced VOCs, starting at 8.8 months after infusion. [redacted]

Exa-cel patients who are VOC-free for 12 months are assumed to remain functionally cured for a lifetime as exa-cel is a gene edited HSC-based therapy for which there is no known mechanism to convert back to a wild-type sequence following CRISPR/Cas9 editing. In the most recent data cut-off for the pivotal trial of exa-cel, at month 24, the mean proportion of edited *BCL11A* alleles in bone marrow $CD34^+$ HSPCs and peripheral blood mononuclear cells was 88.7% and 79.2% respectively. Patients with SCD also had clinically meaningful increases in HbF and total haemoglobin levels that occurred early and were sustained over time.

[redacted]

[redacted]

Treatment waning for exa-cel is not considered in the base-case analysis. A detailed discussion regarding exa-cel's mechanism of action and the anticipated permanence of gene editing is discussed in the clinical effectiveness sections of this submission. 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 continue over a patient's lifetime. Long-term efficacy following exa-cel is also the most plausible outcome based on the published literature on SCD patients treated with allo-SCT. Exa-cel technology avoids the occurrence of graft failure and GvHD which are the main cause of poor outcomes following SCT, more commonly seen with reduced intensity conditioning or non HLA-matched donors.

Table 34: Treatment procedure and response inputs for exa-cel

Variable	Value	Reference
Treatment phase		
Duration of treatment phase (months)	12.0	Assumption (based on expert opinion)
Treatment withdrawal (%)	19.0	CLIMB SCD-121 (Day 120 cut) (7)
Initial engraftment success (%)	100	Grupp et al., 2021 (161)
Post-treatment period (among patients with engraftment success)		
Functionally cured (%)	96.6	CLIMB SCD-121 trial (166)
VOC reduction (%)	0	CLIMB SCD-121 trial (166)

Standard of Care arm

The CLIMB SCD-121 trial was a single-arm study, thus no data was available for patients who remain on SoC. As discussed in section B.2.9, ITCs were carried out, but these were not used to inform the model. The ITC results are not relevant for the model because the number of baseline VOCs among SCD patients on SoC incorporates any efficacy associated with SoC. Exa-cel inclusion criteria requires patients to have 2+

VOCs/year for 2 consecutive years while receiving best available care. This assumes that the same VOC frequency is applied throughout the model lifetime horizon, which is the same assumption used in previous SCD HTA assessments (198). Patients in the SoC arm are therefore assumed to retain their baseline VOC frequency over the model time horizon.

B.3.3.2. Complication inputs

Literature-based rates and risk equations were used to estimate the rate of developing acute complications of SCD based on VOCs. Literature-based rates and risk equations were selected according to the transferability of the study population to the model population as well as the appropriateness of the results to the model health states. 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 (203).

B.3.3.2.1 Acute complications

As discussed in the model structure section, acute complications included in the model are stroke, ACS, acute infection, acute kidney injury or infarction, gallstones, pulmonary embolism, and leg ulcers (143, 150, 198-200).

The incidence of acute complications were estimated separately for patients with successful engraftment and 100% VOC absence with exa-cel (functionally cured patients) and those not cured from SCD (i.e. patients not experiencing a VOC within a model cycle). For uncured patients, the risk of complications was based on the number of VOCs occurring in the model cycle.

In uncured patients, the incidence of acute complications was derived as a weighted average of incidence among patients experiencing no VOCs and patients experiencing a VOC in any given monthly cycle. The incidence of acute complications in patients without a VOC was derived based on the literature; the incidence of acute complications in patients experiencing a VOC was assumed to increase based on a hazard ratio (HR) or odds ratio (OR) associated with the presence of VOC obtained from the literature as detailed below.

Among patients with SCD receiving SoC, the incidence of acute complications was estimated based on the number of VOCs occurring in the model cycle. In the literature, the incidence was adjusted by VOC occurrence, instead of the number of VOCs. Therefore, the model assumed patients could only experience a maximum of one VOC per monthly model cycle and the mean number of VOCs occurring in the model cycle was equivalent to the proportion of patients with VOC in the model cycle. The incidence of acute complications was then derived as a weighted average of incidence between patients with the VOC number as zero and patients with VOC occurrence. The equation was as below:

$$\begin{aligned} &Incidence\ in\ overall\ patient\ population\ with\ and\ without\ VOC\ occurrence \\ &= Proportion\ of\ patients\ with\ VOC\ number\ as\ 0 \\ &\times Incidence\ when\ VOC\ number\ as\ 0 \\ &+ Proportion\ of\ patients\ with\ VOC\ occurrence \\ &\times Incidence\ when\ VOC\ occurs \end{aligned}$$

The incidence in patients with the VOC number as zero was derived based on the incidence in patients without VOCs, as reported in the literature.

The incidence in patients with VOC occurrence was derived based on the incidence in patients with the VOC number as zero and the HR/OR of incidence when VOC occurred. The HR/OR was directly obtained from the literature. The equation was as below.

$$I_0 = Incidence\ (rate)\ when\ VOC\ number\ as\ 0$$
$$I_V = Incidence\ (rate)\ when\ VOC\ occurs$$
$$I_V = I_0 \times HR$$
$$I_V = -LN(1 - 1/(EXP(-I_0)/(OR \times (1 - EXP(-I_0))) + 1))$$

The incidence of acute complications among functionally cured patients following treatment with exa-cel was assumed to be zero. The model applies age and gender-matched general population utility values and mortality rates over a lifetime horizon and thus it is assumed that the impact of complications in functionally cured patients

is already captured, as this would be reflected in general population utility and mortality.

The model inputs for acute complications are summarised in Table 35.

Table 35: Monthly incidence rate of acute complications

Variable	Value	Reference
Stroke		
Incidence rate when VOC = 0	0.0021	Shah et al., 2019 (143)
HR by VOC occurrence	2.26	Shah et al., 2019 (143)
Incidence rate among functionally cured patients	0	Assumption
Acute chest syndrome		
Incidence rate when VOC = 0	0.0003	Shah et al., 2019 (143)
HR by VOC occurrence	58.67	Shah et al., 2019 (143)
Incidence rate among functionally cured patients	0	Assumption
Acute infections		
Incidence rate when VOC = 0	0.0197	Shah et al., 2019 (143)
HR by VOC occurrence	2.26	Assumption (same as stroke)
Incidence rate among functionally cured patients	0	Assumption
Acute kidney injury/infarction		
Incidence rate when VOC = 0	0.0012	Yeruva et al., 2016 (200)
OR by VOC occurrence	2.20	Yeruva et al., 2016 (200)
Incidence rate among functionally cured patients	0	Assumption
Gallstones		
Incidence rate when VOC = 0	0.0027	Shah et al., 2019 (143)
HR by VOC occurrence	2.26	Assumption (same as stroke)
Incidence rate among functionally cured patients	0	Assumption
Pulmonary embolism		
Incidence rate when VOC = 0	0.0011	Shah et al., 2019 (143)
HR by VOC occurrence	2.82	Shah et al., 2019 (143)
Incidence rate among functionally cured patients	0	Assumption
Leg ulcers		
Incidence rate when VOC = 0	0.0083	Singh et al., 2016 (199)Singh et al., 2016 (199)
HR by VOC occurrence	2.26	Assumption (same as stroke)
Incidence rate among functionally cured patients	0	Assumption

Key: BoI: burden of illness; HR, hazard ratio; OR, odds ratio; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

B.3.3.2.2 Chronic complications

As discussed in the model structure section, chronic complications included in the model are CKD, pulmonary hypertension, avascular necrosis, heart failure,

neurocognitive impairment, post-stroke, sickle retinopathy, and liver complications (143, 150, 171, 198). Chronic complications were modelled using similar methodology as for acute complications, but using risk instead of incidence. This approach is detailed below. The risk of chronic complications in patients without a VOC was derived based on the literature or assumption; the risk in patients experiencing a VOC was assumed to increase based on a HR or OR associated with the presence of VOC obtained from the literature.

Among patients with SCD receiving SoC or chronic medication, the risk of chronic complications was estimated based on the number of VOCs occurring in the model cycle. In the literature, the risk was adjusted by VOC occurrence, instead of the number of VOCs. Therefore, the model assumed patients could only experience one VOC per monthly model cycle and the mean number of VOCs occurring in the model cycle was equivalent to the proportion of patients with VOC in the model cycle. The risk of chronic complications was then derived as a weighted average of the risk between patients with the VOC number as zero and patients with VOC occurrence. The equation was as below.

$$\begin{aligned} &Incidence\ or\ risk\ in\ overall\ patient\ population\ with\ and\ without\ VOC\ occurrence \\ &= Proportion\ of\ patients\ with\ VOC\ number\ as\ 0 \\ &\times Risk\ when\ VOC\ number\ as\ 0 \\ &+ Proportion\ of\ patients\ with\ VOC\ occurrence \\ &\times Risk\ when\ VOC\ occurs \end{aligned}$$

The risk in patients with the VOC number as zero was derived based on the risk in patients without VOCs, as reported in the literature.

The risk in patients with VOC occurrence was derived based on the risk in patients with the VOC number as zero and the HR/OR of risk when VOC occurred. The HR/OR was directly obtained from the literature. The equation was as below.

$$R_0 = Risk\ (probability)\ when\ VOC\ number\ as\ 0$$

$$R_V = Risk\ (probability)\ when\ VOC\ occurs$$

$$R_V = 1 - EXP(LN(1 - R_0) \times HR)$$

$R_V = 1/((1 - R_0)/(OR \times R_0) + 1)$

In the model, 35% of patients who experienced a stroke (an acute complication event) were assumed to have experienced a severe stroke, a chronic complication health state (titled "post-stroke") which is associated with long-term costs and quality-of-life decrements (121). All other chronic complications included in the model were assumed to be independent of other complications and were estimated separately for patients with SCD and for functional cure patients. Among patients with SCD receiving SoC the risk of chronic complications was estimated based on the number of VOCs occurring in the model cycle. The mean number of VOCs occurring in the model cycle was equivalent to the proportion of patients with VOC in the model cycle. The risk of chronic complications was derived as a weighted average of risk among patients experiencing no VOCs and patients experiencing a VOC in the given monthly cycle.

The incidence of chronic complications among functionally cured patients was assumed to be zero. The same assumptions were applied as for the acute complications, whereby it is assumed that the impact of chronic complications in functionally cured patients is captured within the age and gender-matched general population utility and mortality estimates that are applied over the lifetime horizon of the model. The model inputs for chronic complications are summarised in Table 36.

Table 36: Monthly risk of chronic complications

Variable	Value	Reference
Chronic kidney disease		
Risk when VOC = 0 (%)	0.120	Bradt et al., 2020 (198)
OR by VOC occurrence	3.00	Bradt et al., 2020 (198)
Risk among functionally cured patients (%)	0	Assumption
Pulmonary hypertension		
Risk when VOC = 0 (%)	0.067	Shah et al., 2019 (143)
HR by VOC occurrence	4.12	Shah et al., 2019 (143)
Risk among functionally cured patients (%)	0	Assumption
Avascular necrosis		
Risk when VOC = 0 (%)	0.227	Shah et al., 2019 (143)
HR by VOC occurrence	4.12	Assumption (same as pulmonary hypertension)
Risk among functionally cured patients (%)	0	Assumption
Heart failure		
Risk when VOC = 0 (%)	0.063	Bradt et al., 2020 (198)
HR by VOC occurrence	4.12	Assumption (same as pulmonary hypertension)

Risk among functionally cured patients (%)	0	Assumption
Neurocognitive impairment		
Risk when VOC = 0 (%)	0.171	Cahill et al., 2019 (171)
HR by VOC occurrence	4.12	Assumption (same as pulmonary hypertension)
Risk among functionally cured patients (%)	0	Assumption
Post-stroke		
Proportion with severe stroke that incur long-term costs/disutility (%)	35	NICE SCD guideline (121)
Sickle retinopathy		
Risk when VOC = 0 (%)	0.042	American Academy of Ophthalmology (204)
HR by VOC occurrence	4.12	Assumption (same as pulmonary hypertension)
Risk among functionally cured patients (%)	0	Assumption
Liver complications		
Risk when VOC = 0 (%)	0.041	Assumption; 5 times of risk among general population
HR by VOC occurrence	4.12	Assumption (same as pulmonary hypertension)
Risk among functionally cured patients (%)	0	Assumption

Key: BoI: burden of illness; HR, hazard ratio; NICE, National Institute for Health and Care Excellence; OR, odds ratio; SCD, sickle cell disease; VOC, vaso-occlusive crisis

B.3.3.3. Other condition inputs

Among patients treated with SoC, the risk of infertility was taken from an infertility questionnaire which included a study population of 2,108 men and women (205). Seventeen percent of the males and 24% of females reported infertility (205).

Among patients treated with exa-cel, the risk of infertility following myeloablative conditioning was assumed to increase by 24% (prevalence ratio: 1.24) in males and by 57% (prevalence ratio: 1.57) in females, based on the assumption applied in the NICE assessment for betibeglogene autotemcel (beti-cel) in transfusion-dependent β-thalassemia (TDT) (206). 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 median age of menopause in females in the UK. These inputs are summarised in Table 37.

Table 37: Other conditions

Variable	Value	Reference
Age at Fertility and Infertility		
Age at fertility	16	Datta et al., 2016 (207)
Age at infertility	51	British Menopause Society, 2022 (208)
Infertility rate (by sex)		

SoC (annual %)		
Male	17	Stevenson et al., 2023 (205)
Female	24	Stevenson et al., 2023 (205)
Exa-cel (prevalence ratio)		
Male	1.24	NICE ID968 (206)
Female	1.57	NICE ID968 (206)

Abbreviations: GvHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; NICE, National Institute for Health and Care Excellence

B.3.3.4. Mortality inputs

Patients are at risk of death throughout the modelled lifetime horizon. Outside of general population mortality, risk of death is dependent on the patients' VOC status, frequency of VOCs and occurrence of complications and other transplant-related events. A summary of mortality inputs can be found in Table 38. Similarly, to complication inputs, mortality input values were based on a targeted literature review. The results of the literature search are provided in a separate spreadsheet (39). Mortality values were selected according to the suitability of the study population to the model population and decision context.

Among patients with SCD (non-cured) and without SCD-related complications, the model inputs for SCD mortality rates by age were informed by Bradt et al., 2020 (198). The model also includes alternative functionality to estimate mortality rates for SCD patients without complications by applying a hazard ratio to the general (non-SCD) population mortality rates; this is included as a scenario (Section B.3.12.3 for further details). Among functionally cured patients, the mortality rates in the model were estimated by applying a hazard ratio (standardised mortality ratio, SMR) of 1.25 to the age- and gender-specific mortality rates in the general (non-SCD) UK population. The increased risk of death among functionally cured patients accounts for the potential impact of disease that had occurred before the VOC reduction and the potential impacts due to use of myeloablative conditioning for the potentially curative therapies. This is likely a conservative assumption as it is applied for the remainder of a patient's lifetime even though the impact of myeloablative conditioning is not expected to extend beyond the transplant year. The mortality hazard ratio of 1.25 versus the general population was also considered a reasonable assumption by the Evidence Assessment Group (EAG) in the NICE assessment for beti-cel for TDT (206). Data are

available on the long-term survival of SCD patients following SCT, but these will not be relevant to patients treated with exa-cel given transplants were not autologous and a large proportion of deaths following autologous SCT were due to GvHD. Furthermore, many patients were treated with immunosuppressive regimens not relevant to exa-cel patients (8). The all-cause mortality rates for the UK general population were obtained from the England and Wales life tables based on patient age and gender (209). Survival was capped at 100 years of age (209). The all-cause mortality rates for the UK general population were obtained from the England and Wales life tables based on patient age and gender (209). Survival was capped at 100 years of age (209).

Patients treated with exa-cel were assumed to have no risk of 100 day transplant-related mortality based on the CLIMB SCD-121 FAS data (162), where no patients experienced treatment-related death. In the model base-case, death following engraftment failure is set to zero, as the exa-cel engraftment rate was 100%. The risks of transplant-related mortality events were applied at the end of the treatment phase (at 12 months) (210). Patients treated with exa-cel were assumed to have no risk of 100 day transplant-related mortality based on the CLIMB SCD-121 FAS data (162), where no patients experienced treatment-related death. In the model base-case, death following engraftment failure is set to zero, as the exa-cel engraftment rate was 100%.

Patients with VOCs were assumed to have a 1.56x increased risk of death compared to patients with SCD without VOCs (143). This hazard ratio was derived using a Cox model examining the relationship between the frequency of VOCs and death in a retrospective claims-based study of 20,909 people with SCD in the US (143). Development of either acute or chronic complications was associated with a further increased risk of mortality, applied with a HR adjustment, sourced from the literature. Each stroke event was associated with an instant risk of death of 7.7% (198). Infertility was not associated with additional mortality.

Table 38: Mortality inputs

Variable	Value	Reference
Annual SCD-specific mortality rate by age (%)		
0 years old	0.13	Bradt et al., 2020 (198)
1-4 years old	0.04	

5-9 years old	0.03	
10-14 years old	0.03	
15-19 years old	0.07	
20-24 years old	0.16	
25-34 years old	0.23	
35-44 years old	0.47	
45-54 years old	0.70	
55-64 years old	1.12	
65-74 years old	0.68	
75+ years old	8.47	
SCD functionally cured mortality		
HR adjustment applied to general mortality	1.25	Assumption
Transplant-related mortality		
Instant risk (rate) of death due to procedure (%)		
Exa-cel	0.00	Locatelli et al., 2022 (162)
Instant mortality (rate)		
Engraftment failure (exa-cel) (%)	25.00	Assumption
VOC-specific mortality		
HR by VOC occurrence	1.56	Shah 2019 (143)
Complication-dependent mortality		
HR by acute complication		
Acute chest syndrome	1.27	Elmariah et al., 2014 (32)
Acute renal failure	9.50	Yeruva et al., 2016 (200)
Pulmonary embolism	2.75	Brunson et al., 2017 (211)
Leg ulcers	1.66	Elmariah et al., 2014 (32)
Acute infection	1.00	Assumption
Mortality rate post-event (%)		
Stroke	7.7	Bradt et al., 2020 (198)
HR by chronic complication		
Chronic kidney disease	9.57	Bradt et al., 2020 (198)
Pulmonary hypertension	12.57	Bradt et al., 2020 (198)
Heart failure	12.57	Bradt et al., 2020 (198)
Liver complications	2.53	Gardner et al., 2016 (212)
Infertility mortality, SMR		
Male	1.00	Assumption

Female	1.00	Assumption

Key: GvHD, graft-versus-host disease; HR, hazard ratio; SCD, sickle cell disease; SMR, standardised mortality ratio; VOC, vaso-occlusive crisis.

In the base-case analysis, mortality risks were combined multiplicatively, which inherently assumes that the mortality risks related to transplantation, VOC occurrence, and complications are independent of each other. The impact of combining mortality using additive interactions was explored in a scenario analysis.

An overall SMR of 5.21 vs. the age- and gender- matched general population is predicted from the model from the SoC arm. This lies between the SMRs of 4.9 and 7.4 in the overall and 2014-2018 cohorts of the Vertex burden of illness study, respectively (0.78 person-years in the SCD overall cohort vs. 0.16 general population and 0.81 person-years in the SCD 2014-2018 cohort vs. 0.11 general population) (4). The model therefore appears to predict mortality in line with the UK estimates general population (4).

B.3.3.5. Adverse event inputs

Only grade 3+ treatment-related AEs were considered in the model. All adverse event inputs are summarised in Table 39.

For patients receiving exa-cel, all AEs are assumed to occur during the hospital stay that patients undergo as part of the transplant procedure. AEs are thus not explicitly modelled for the exa-cel arm, as it is assumed that these are one-off events and the impact of these is captured within the transplantation or transplant-related hospitalisation disutility and costs. This is in line with the NICE assessment of beti-cel in TDT (206).

For SoC, recurring AE rates are applied in each model cycle while patients remain on treatment. Only overall Grade 3+ AE rates were available for SoC in the literature, and these are used in the base case. That is, there was no data available to inform the incidence of individual AEs.

Table 39: Adverse events inputs

Treatment	Monthly rates of any grade 3+ AEs	Reference
SoC	2.19%	Average across placebo arms of crizanlizumab, voxelotor and L-glutamine trials (188, 213, 214).

Abbreviations: AE, adverse event, 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 were calculated based on life years and various utility/disutility inputs, including utilities for uncomplicated SCD and functionally cured SCD patients, age- and gender-related utility adjustments and decrements in utility for transplantation, VOCs, complications, and infertility.

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

The EQ-5D-5L was used to measure patients' health-related quality of life in the CLIMB SCD-121 trial. In line with the NICE methods guide, 5L utility values were mapped to the 3L UK value set using the Hernandez-Alava algorithm to generate utilities (215). EQ-5D utility scores showed meaningful improvements in overall health status by Month 6 after exa-cel infusion, which was sustained at Month 24.

The results from the latest data cut of the trial show a baseline EQ-5D health utility index score of 0.81 and changes from baseline at months 12, 18 and 24 of 0.08, 0.14 and 0.11, respectively, exceeding the MCID for EQ-5D of 0.08 (Table 40) (7, 178).

Table 40: **CLIMB SCD-121/131 trial EQ-5D-5L results for adults in PES**

Timepoint	N	EQ-5D UK index Mean (SD)
Baseline	22	0.81 (0.19)
Month 12 (148)	23	0.89 (0.11)
Month 18 (148)	16	0.90 (0.13)
Month 24 (148)	15	0.88 (0.13)

Abbreviations: EQ-5D-5L, European Quality of Life-5 Dimensions 5 levels; PES, primary efficacy set; SD, standard deviation; UK, United Kingdom

The baseline EQ-5D score in CLIMB SCD-121 (0.81) was assigned to the uncomplicated SCD (SCD in the absence of acute or chronic complications) health state. The utility input for patients cured from SCD was assumed to be 0.92 based on the change in EQ-5D score from baseline to month 24 in the trial (representing an increase of 0.11). It is to be noted that the utility values from CLIMB SCD-121 do not adjust for the occurrence of VOCs or prevalence of complications. However, a previous economic assessment in SCD used a utility value of 0.80 for uncomplicated SCD, based on a longitudinal hospital-based study of 510 patients with SCD (198). Further, O'Brien *et al.,* (2009) in a decision analysis model used a utility value of 0.95 among SCD patients without graft failure or chronic GvHD after undergoing allo-SCT (216).

B.3.4.2. Mapping

The trial used the EQ-5D data as an appropriate tool for measuring HRQoL since its dimensions allow capturing the QoL of SCD patients given the nature of the disease, such as pain intensity, pain relief, and mobility limitations (217). EQ-5D data are also the preferred HRQoL methods in NICE's hierarchy of methods, therefore, the utility data used in the model are in line with the NICE reference case and thus no mapping of utility data was undertaken.

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

An SLR was conducted in order to identify supplemental utility data for the economic model (see Appendix H).

B.3.4.4. Adverse reactions

For exa-cel, the model assumed that disutilities associated with AEs are captured in the transplantation-related disutility.

Disutilities related to transplantation, complications and infertility are applied to the proportion of the cohort experiencing these events. Transplantation-related disutilities were sourced from a vignette study in the UK (218). The disutility due to engraftment failure (-0.40) was estimated based on the utility difference between patients without graft failure (0.95) and patients experiencing graft failure (0.55) respectively, from a

decision analysis model used to compare allo-SCT with other treatment strategies in SCD (216).

The disutility per VOC event per month was assumed to be -0.18 based on the NICE submission of crizanlizumab, in which the disutility of VOC was reported as -0.46 per event for a duration of 12 days (123). Disutilities due to SCD-related complications were sourced from the literature and are summarised along with all health state utility and disutility inputs in Table 41. Similar to mortality risks, in the base-case analysis, disutilities due to VOCs, acute and chronic complications were aggregated using a multiplicative interaction. Other aggregation interactions, namely additive interactions were explored in the scenario analyses.

For SoC, disutilities associated with AEs were not considered in the model, as they were expected to have minimal impact on the outcomes; this was a conservative assumption when comparing with exa-cel.

B.3.4.5. Caregiver disutility

A large proportion of SCD patients who receive exa-cel will be adolescents or young adults who will require support from family members to attend healthcare appointments as well as support with education due to school absenteeism. In the societal perspective scenario analysis, it was assumed that caregivers of SCD patients who are ≤26 years of age experience 10% of the disutility experienced by the patient due to complications (e.g., VOC, acute or chronic complication, transplant-related) based on Institute for Clinical and Economic Review in the assessment of crizanlizumab, voxelotor, and L-glutamine for SCD (198). For example, for every VOC event experienced by an adolescent patient, the caregiver is assumed to experience a disutility of -0.018 (10% of the -0.18 experienced by the patient). Additionally, the caregiver is assumed to experience a 0.05 decrease in utility following the death of the SCD patient, which is applied until the end of the model horizon. This assumption is consistent with that used by the Institute for Clinical and Economic Review in the assessment of crizanlizumab, voxelotor, and L-glutamine for SCD (198).

B.3.4.6. Health-related quality-of-life data used in the cost-effectiveness analysis

The health state utilities applied in the model are provided in Table 41.

An age- and gender-related utility adjustment based on Ara and Brazier was applied to health state utilities over the modelled time horizon to reflect decreases in health-related quality of life seen in the UK general population (219). The utility adjustment was estimated by a regression model with age and gender as variables, with the equation:

$$0.95086 + 0.02121 * \%male - 0.00026 * age - 0.00003 * age^2.$$

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. Thus, this means that the age- and gender-related utility adjustment impacts exa-cel more than the comparator.

Table 41: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Base utility				
Uncomplicated SCD	0.81	0.72, 0.88	CLIMB SCD-121	See section B.3.4.3
Functionally cured	0.92	0.81, 0.99	CLIMB SCD-121	See section B.3.4.3
Transplantation-related disutilities				
Treatment with Exa-cel in transplant year	-0.11	-0.09, -0.13	Matza et al., 2020	See section B.3.4.3
Engraftment failure in transplant year	-0.40	-0.480, 0.320	O'Brien et al., 2009	See section B.3.4.4
Infertility	-0.06	-0.05, -0.07	Krol et al., 2019 (220)	See section B.3.4.4
Acute complications				
VOC	-0.18	-0.15, -0.22	NICE crizanlizumab	As per the

			STA (150)	literature
Acute chest syndrome	-0.56	-0.45, -0.67	Lloyd et al., 2007 (221)	
Stroke	-0.57	-0.45, -0.68	Jiao et al., 2021 (222)	
Acute kidney injury	-0.14	-0.11, -0.17	Bradt et al., 2020 (198)	
Pulmonary embolism	-0.05	-0.03, -0.08	Ojelabi et al., 2019 (223)	
Acute infections	-0.16	-0.13, -0.19	Drabinski et al., 2001 (224)	
Gallstones	-0.12	-0.10, -0.14	NICE CG188 (225)	
Leg ulcers	-0.11	-0.09, -0.13	Michaels et al., 2009 (222)	
Chronic complications				
Pulmonary hypertension	-0.21	-0.17, -0.25	Keogh et al., 2007 (226)	As per the literature
Chronic kidney disease	-0.14	-0.11, -0.17	Bradt et al., 2020 (198)	
Avascular necrosis	-0.05	-0.03, -0.08	Ojelabi et al., 2019 (223)	
Post-stroke	-0.13	-0.10, -0.16	Cherry et al., 2012 (227)	
Neurocognitive impairment	-0.05	-0.04, -0.06	Stites et al., 2018 (228)	
Retinopathy	-0.05	-0.03, -0.08	Ojelabi et al., 2019 (223)	
Heart failure	-0.12	-0.01, -0.36	Bradt et al., 2020 (198)	
Liver complications	-0.05	-0.03, -0.08	Ojelabi et al., 2019 (223)	
Caregiver assumptions and disutility applied in scenario analysis				
Patient caregiver up to age (years)	26	20.8, 31.2	Beaudoin et al., 2022 (194)	See section B.3.4.5
Annual caregiver utility decrement as percentage of event disutility (%)	10	8, 12	Bradt et al., 2020 (198)	
Utility decrement for patient death (included until end of model time horizon)	-0.05	-0.04, -0.06	Bradt et al., 2020 (198)	

The uncomplicated SCD utility value was adjusted according to age in the model.

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

The cost-effectiveness analysis was conducted from the UK NHS and Personal Social Services perspective. Therefore, only direct costs were considered in the base-case analysis. A scenario analysis was conducted for the societal perspective, including both direct healthcare costs and indirect costs (Section B.3.12.3). Costs were inflated to 2022 UK pound sterling using the UK Health Consumer Price Index (229) where required.

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

For exa-cel, the drug acquisition and transplant costs were applied to all patients assigned to the therapy at the beginning of the model. As exa-cel is a one-time treatment, the acquisition and administration costs are applied on a one-off treatment basis in the model. Exa-cel acquisition and administration costs are summarised in Table 42.

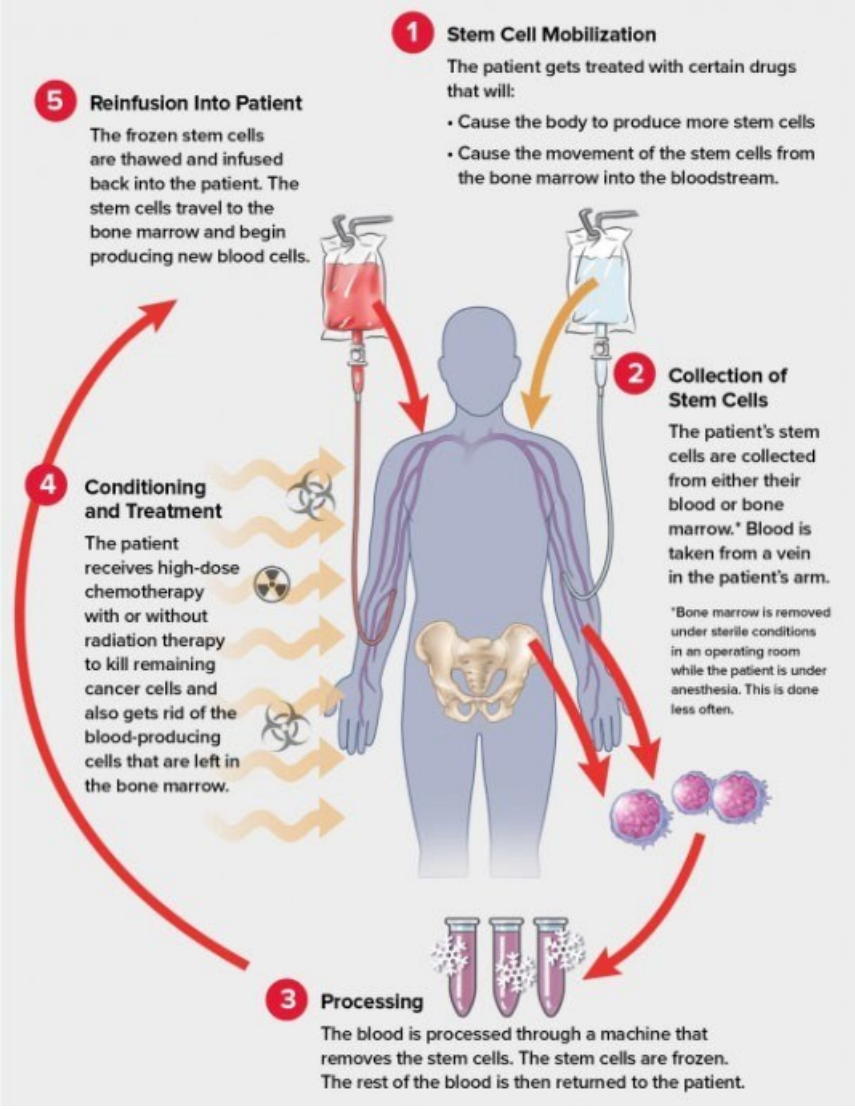
In addition to the treatment acquisition costs for exa-cel, other costs related to transplant were also considered in the model, including pre-transplant costs, hospitalisation/procedure costs, and post-transplant monitoring costs. Pre-transplant costs included both mobilisation/apheresis costs and all other transplant preparation costs (e.g., labs, physician visits, transfusions). 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 SCD-121 trial and clinical expert feedback.

Clinical experts were consulted to determine what procedures would be required as preparation for treatment with exa-cel in the UK NHS. As part of the pre-transplant costs, all exa-cel patients incur the cost of a consultant haematologist outpatient appointment, at which point they also undergo a blood test and screening comprised of a brain MRI, diffusing capacity of the lungs for carbon monoxide test, Echocardiogram, and TCD ultrasound. Brain magnetic resonance imaging should only be done if it has not been done in the last year, however, due to a lack of data to inform this proportion, it was assumed to be done for all patients. TCD ultrasound is only recommended for patients between the ages of 12 and 18, thus the unit cost of this

was weighted by the proportion of paediatric patients (27.9%) in the CLIMB SCD-121 trial FAS population. These pre-treatment costs are summarised in Table 42.

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 almost identical resource to that required for autologous SCT, as can be seen by comparing Figure 27 below with Figure 3 in section B.1. This was confirmed via consultation with UK clinical experts. There are therefore published NHS reference costs available to provide reasonable estimates of the cost of exa-cel delivery.

Figure 27: Autologous stem cell transplantation process



Source: Leukemia & Lymphoma Society (230).

Exa-cel patients also undergo stem cell mobilisation and apheresis collection with a combination of plerixafor based on the CLIMB SCD-121 trial protocol. The apheresis collection cost is £5,375, based on the NHS reference cost for Peripheral Blood Stem Cell Harvest. As the average number of days required for mobilisation was 3, whereas a typical harvesting procedure in the NHS would take 1 to 2 days (231), the unit cost was multiplied by 2. Following this, patients receive myeloablative conditioning with intravenous busulfan administration and RBC transfusions. Relevant costs were estimated based on resource use estimates from CLIMB SCD-121 and unit costs sourced from the NHS reference costs schedule (232). Patients also require hospitalisation for the exa-cel infusion procedure. The cost of hospitalisation for exa-cel infusion is £5,375 and myeloablative conditioning is £25,387. This value is based on a weighted average of the NHS reference cost codes for autologous peripheral blood stem cell transplant tariff for 19 years and over (SA26A), and 18 years and under (SA26B) (233). The appropriateness of this costing approach was validated with two clinical experts. The unit cost of busulfan was obtained from NHS Reference Costs (232).

As part of exa-cel delivery, patients will also receive exchange blood transfusions. The unit cost of exchange transfusions (£261) was sourced from the NHS Blood and Transplant price list (234). It was assumed that patients with SCD who were transfused would receive 2.5 exchange transfusions prior to each mobilisation (average of 2 to 3 times based on clinical expert opinion). As there are two mobilisation cycles (the median), patients with SCD would receive 5 units of Automated Red Cell Exchange each, leading to a total acquisition cost of £1,305.

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 (208, 235). 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.

All patients who are treated with exa-cel incur a hospital stay following transplant. For these post-treatment hospitalisation costs, a weighted average of the adult and

paediatric NHS reference cost codes for Peripheral Blood Stem Cell Transplant, Autologous was applied. These unit costs include 100 nights of inpatient stay and were thus assumed to cover post-treatment hospitalisation and follow-up costs for the first 3 months after exa-cel treatment. This approach was validated with a clinical expert.

As detailed previously, SoC is assumed to comprise of symptomatic care. A proportion of patients treated with SoC are assumed to receive hydroxycarbamide and/or RBC transfusions. Only hydroxycarbamide costs are included within the treatment acquisition costs for SoC as RBCs are included in the disease monitoring costs. For SoC, dosing schedules were based on product information where available. The unit cost of hydroxycarbamide was obtained from the UK drugs and pharmaceutical electronic market information tool (236). Costs of other supportive therapies that are part of SoC were assumed to be negligible and therefore not included in the model. No administration cost was applied to SoC, as these treatments are administered orally. SoC treatment costs are summarised in Table 43.

Table 42: Exa-cel treatment and transplant related costs

Variable	Value	Reference/Source for assumption
Exa-cel acquisition costs		
Acquisition cost	[redacted]	[redacted]
Discount	[redacted]	[redacted]
Pre-transplant costs (exa-cel)		
Assessments during the pre-mobilisation period		
Haematology outpatient appointment, follow-up, unit cost	£209	Non-admitted face-to-face attendance, Follow-up, OP, Consultant Led, Clinical Haematology Service, Currency code: WF01A, Service Code: 303. NHS reference costs 2021-22 (232)
Haematology outpatient appointment, follow-up, frequency	1	KOL
Brain MRI/MRA unit cost	£198	Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over, IMAG, Imaging: Outpatient, Currency code: RD02A. NHS reference costs 2021-22 (232)

Brain MRI/MRA, frequency	1	KOL
DLCO (corrected) test unit cost	£141	Full Pulmonary Function Testing, DZ52Z, DADS. NHS reference costs 2021-22 (232)
DLCO (corrected) test frequency	1	KOL
Echocardiogram unit cost	£134	Simple Echocardiogram, 19 years and over, RD51A, IMAG. NHS reference costs 2021-22 (232)
Echocardiogram frequency	1	KOL
Transcranial Doppler (TCD) ultrasound unit cost	£85	Weighted average of Ultrasound Scan with duration of 20 minutes and over, without and With Contrast, IMAG, Imaging: Outpatient, Currency code: RD42Z, RD43Z. NHS reference costs 2021-22 (232)
TCD ultrasound frequency	1	KOL
Fertility preservation		
One-time retrieval surgery	£1,787	Weighted average of CLIMB SCD-121 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 (232)
Monthly storage costs	£19	Price chart from an NHS fertility centre (237)
Proportion of patients requiring fertility preservation	100%	Assumption
Mobilisation costs		
Mobilisation cost	£5,375	Peripheral Blood Stem Cell Harvest, APC, Elective Inpatients, Currency code: SA34Z. NHS reference costs 2021-22 (232)
Mobilisation cost multiplier	2	Mobilisation in the NHS typically takes 1-2 days (231), whereas 3 were required pre- exa-cel.
Plerixafor cost per unit (vial)	£4,880	Plerixaform, BNF (238)

Plerixafor unit concentration (mg/1ml)	24	Plerixaform, BNF (238)
Busulfan cost per unit (vial), scenario only	£169	Busulfan, eMIT
Busulfan unit concentration (mg/10ml), scenario only	60	Busulfan, eMIT
Mobilisation HCRU		
Mobilisation cycles	2.2	CLIMB SCD-121 (168)
Plerixafor daily dose (mg/kg)	0.24	CLIMB SCD-121 (168)
Plerixafor treatment duration (days)	4	CLIMB SCD-121 (168)
Busulfan daily dose (mg/kg), scenario only	2.98	D120 data from CLIMB SCD-121 (7)
Busulfan treatment duration (days)	4	D120 data from CLIMB SCD-121 (7)
Busulfan administration costs, applied in scenario, scenario only	£314	Busulfan, eMIT
Pre-transplantation RBC transfusion costs		
RBC exchange costs per unit	£261	NHS Blood and Transplant price list (234)
Number of RBC transfusions required prior to exa-cel transfusion	5	Assumption
Total RBC transfusion costs	£13,488	Calculated
Hospitalisation costs for procedure		
Hospitalisation cost for inpatient stay during exa-cel procedure	£25,387	NHS reference cost Elective Inpatient Peripheral Blood Stem Cell Transplant SA26A and SA26B HRG codes, weighted by CLIMB SCD-111 age distribution

Key: eMIT, Drugs and pharmaceutical electronic market information tool; NICE, National Institute for Health and Care Excellence; SoC, standard of care; STA, single technology appraisal; VOC, vaso-occlusive crisis.
Notes: *DFO recommended dose is 20-60 mg/kg/day; the midpoint (40 mg/kg/day) was used as base case model input.

Table 43: SoC treatment costs

Variable	Value	Reference
Cost per pack of hydroxycarbamide	£14.06	NHS drug tariff August 2023
Unit strength (mg)	500.0	
Pack size	100 tablets	
Cost per unit	£0.15	
Dose (mg/kg)	15.0	Product Information for Siklos® (239); assumptions based on NICE crizanlizumab STA [ID1406] (150)
Administrations per month	30.4	
Administration costs per month	£0	No cost for orally administered drugs

B.3.5.2. Blood transfusion and iron chelation therapy costs

The model assumes patients with SCD who are receiving RBC transfusions at baseline continue receiving RBC transfusions throughout the model time horizon unless they are functionally cured. The cost of blood transfusions was estimated based on the cost of packed RBCs per unit and the cost of administration per RBC transfusion. It was assumed that patients with SCD who were being transfused would receive 10 RBC units every 6 weeks, based on the assumption used in the NICE assessment of crizanlizumab (150). Patients who were receiving ICT at baseline are also assumed to continue receiving ICT throughout the model time horizon. These costs are summarised in the table below.

Table 44: Red blood cell transfusion and iron chelation therapy costs

Variable	Value	Reference
RBCT costs		
Number of transfusions per month among SCD patients	0.7	NICE crizanlizumab STA [ID1406] (150)
Number of RBC units per administration	10.0	
Cost per RBC unit	£261	NHS Blood and Transplant price list (234)
Administration cost per transfusion	£90	NICE crizanlizumab STA [ID1406] (150)
Iron chelation costs		
Deferoxamine (DFO)		
Cost per unit	£4.66	NHS drug tariff (June 2023)
Unit strength (mg)	500.0	NHS drug tariff (June 2023)
Dose (mg/kg)	41.2	Cappellini 2021 and clinical expert opinion. (240)
Administration per month	22.4	Cappellini 2021 and clinical expert opinion (240)
Administration costs per dose	£0	UKTS: self-administered using balloon infusers
Deferasirox (DFX)		
Cost per unit	£4.20	NHS drug tariff (June 2023)
Unit strength (mg)	90.0	NHS drug tariff (June 2023)
Dose (mg/kg)	14.0	EPAR of Exjade®
Administration per month	30.4	EPAR of Exjade®
Administration costs per dose	£0	Zero cost for oral drug
Deferiprone (DFP)		
Cost per unit	£1	NHS drug tariff (June 2023)
Unit strength (mg)	500.0	NHS drug tariff (June 2023)
Dose (mg/kg)	75.0	EPAR of Ferriprox®

Administration per month	30.4	EPAR of Ferriprox®
Administration costs per dose	£0	Zero cost for oral drug

B.3.5.3. Disease monitoring costs

The model includes the cost of routine disease monitoring for patients with SCD (i.e., those not cured), which includes lab tests and physician visits (Table 45). The model assumed a haematological test was performed every other month and the other specified lab tests were performed every 3 months. Physician visits were assumed to occur every 3 months based on consulted clinical opinion. The unit cost per lab test and the cost per physician visit were obtained from a previous NICE assessment and the National Schedule of NHS Cost, respectively.

Table 45: Disease monitoring costs applied for all patients

Variable	Value	Reference
Lab/test/physician visit frequency		
Haematological tests/labs	0.50	Beti-cel NICE committee papers (206)
Renal tests/labs	0.33	
Hepatic tests/labs	0.33	
Lactate dehydrogenase test	0.33	
Fetal haemoglobin lab	0.33	
Physician visits	0.33	Assumption
Unit cost		
Haematological tests/labs	£2.79	Beti-cel NICE committee papers (206)
Renal tests/labs	£1.10	
Hepatic tests/labs	£1.10	
Lactate dehydrogenase test	£1.10	
Fetal haemoglobin lab	£1.10	
Physician visit	£168	National Schedule of NHS Costs (241)

Patients treated with exa-cel are also assumed to incur post-transplant monitoring costs. The model assumed 15 years of post-transplant monitoring based on the duration of the open-label extension study following CLIMB SCD-121.

Table 46: post-treatment monitoring costs applied to the exa-cel arm

Variable	Value	Reference
Number of years to apply post-transplant monitoring costs	15	Patients will be followed up for 15 years, CLIMB SCD-121 protocol (168).
Year 1	£100	

Year 2	£100	Based on a micro-costing exercise in NICE ID968 (206)
Year 3	£82	
Year 4	£82	
Year 5	£82	

B.3.5.4. Complication and other condition costs

The event cost per acute complication and the monthly cost of chronic complications were estimated based on the National Schedule of NHS Cost or published UK-based studies Table 47.

The cost of VOCs and acute complications were applied in the cycle in which they occurred. In the base case analysis, the cost of a VOC was assumed to be £1,567, aligned with the input used in the NICE assessment of crizanlizumab (150). A scenario analysis was conducted exploring an alternative input for the cost per VOC (150). This scenario considers the cost per VOC as £1,300 which was based on a weighted average of the NHS reference costs 2018–19 for sickle-cell anaemia with crisis (weighted average of costs for SA36A-C: Sickle-Cell Anaemia with Crisis, with CC Score 0–6+ [non-elective short stay, non-elective long stay, Day Case]).

For chronic complications, the cost per episode of care reported from the National Schedule of NHS Cost were assumed to be incurred once per year (thus assuming one episode per year), except for pulmonary hypertension, which was assumed to occur for 3.2 episodes per year based on published literature (241, 242).

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 an NHS fertility centre (237). All complications and other conditions costs are presented in Table 47 below.

Table 47: Complication and other condition costs

Variable	Value	Reference
Acute complication costs (cost per event)		

VOC	£1,567	National Schedule of NHS Cost (SA36A-C, Sickle-Cell Anaemia with Crisis) (241)
Acute chest syndrome	£5,221	National Schedule of NHS Cost (DZ15M, Asthma with Interventions) plus cost of exchange RBC transfusion (241)
Stroke	£3,700	National Schedule of NHS Cost (AA35A-F, Stroke) (241)
Acute kidney injury	£1,985	National Schedule of NHS Cost (LA07H-P, Acute Kidney Injury with Interventions) (241)National Schedule of NHS Cost (LA07H-P, Acute Kidney Injury with Interventions) (241)
Pulmonary embolism	£2,065	National Schedule of NHS Cost (DZ09J-Q, Pulmonary Embolus) (241)
Acute infections	£4,490	National Schedule of NHS Cost (WJ01A-J, Sepsis) plus cost of exchange RBC transfusion (241)
Gallstones	£6,401	National Schedule of NHS Cost (DAPS04, RD40Z-RD43Z, GA10H-N, GB05F-GB09F), covering disease diagnostics and management (241)
Leg ulcers	£9,264	Guest et al., 2018(243), inflated to 2022 costs
Chronic complication costs (monthly cost per complication)		
Pulmonary hypertension	£314	National Schedule of NHS Cost (EB15A-C, Pulmonary Hypertension) (241)
Chronic kidney disease	£201	National Schedule of NHS Cost (LA08G-P, Chronic Kidney Disease) (241)
Avascular necrosis	£114	National Schedule of NHS Cost (HD24D-H, Non-Inflammatory, Bone or Joint Disorders) (241)
Post-stroke	£39	National Schedule of NHS Cost (VC04Z, Rehabilitation for Stroke) (241)
Neurocognitive impairment	£24	National Schedule of NHS Cost (MHCC18-21, Cognitive impairment or dementia) (241)

Retinopathy	£85	National Schedule of NHS Cost (BZ24D-G, Non-Surgical Ophthalmology) (241)
Heart failure	£174	National Schedule of NHS Cost (EB03A-E, Heart Failure or Shock) (241)
Liver complications	£181	National Schedule of NHS Cost (GC01D-F, Liver Failure Disorders) (241)
Other conditions		
Infertility (one-time IVF cost)		
Female (IVF)	£1,473 (weighted average of £2,631.56 for females and £5,565.08 for males)	NHS fertility centre (237)
Infertility (monthly cost of sperm/oocyte storage)		
Male	£18.60	NHS fertility centre (237)
Female	£18.60	NHS fertility centre (237)

Abbreviations: AE, adverse event; GvHD, Graft-versus-host disease; NHS, national health services; RBC, red blood cell; VOC, vaso-occlusive crisis.

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

Health state costs are comprised of complication costs (VOCs, acute complications, chronic complications and infertility) and monitoring costs (including post-transplant monitoring costs). These costs are detailed in the previous sub-sections.

B.3.5.6. Adverse reaction unit costs and resource use

AE costs for exa-cel are captured in transplantation or transplantation-related hospitalisation costs, as those AEs were assumed to occur during the procedure hospitalisation. AE costs were estimated based on the monthly rates of recurring AEs described in Section B.3.3.5 and the unit cost of treating AEs is summarised in Table 48 below. The cost of a Grade 3+ AE was assumed to be equal to the cost of a single physician visit based on the National Schedule of NHS Costs (241).

Table 48: Adverse reaction unit costs and HRU

Treatment	Unit cost	Reference
Unit cost of treating a grade 3+ AE	£168	National Schedule of NHS Cost (service code 303, Clinical Haematology) (241)

Abbreviations: AE, adverse event; NHS, National Health Service.

B.3.5.7. Miscellaneous unit costs and resource use

B.3.5.8.1 Terminal care costs

The base-case analysis includes a one-time cost of terminal care (£12,149), in accordance with the average costs for end-of-life care reported by Personal Social Services Research Unit (244).The base-case analysis includes a one-time cost of terminal care (£12,149), in accordance with the average costs for end-of-life care reported by Personal Social Services Research Unit (244).

B.3.5.8.2 Societal costs

In the societal perspective scenario analysis, costs associated with patient productivity, caregiver burden, out-of-pocket and other indirect costs were considered (Table 49).

Due to the severity of the condition and the significant time associated with managing disease, SCD patients are less likely to be employed than the general (non-SCD) population, and those who are employed are known to miss work (absenteeism) and experience decreased productivity when at work (presenteeism).

The model estimates the proportion of the cohort that is employed based on the Drahos et al., 2022 study, which reported that 23% of patients with SCD (who experienced an average of 5.9 VOCs per year) were receiving/awaiting disability payments or on leave from work due to SCD (5). The model assumed that patients who were functionally cured would have the same level of employment as the general (non-SCD) population.

Rates of absenteeism and presenteeism for patients with SCD were informed by Rizio et al., 2020, which reported that patients with SCD who experienced more frequent VOCs (≥4 per year) had a higher overall productivity loss than those experiencing less frequent VOCs (0-3 per year) (107). Therefore, productivity losses (absenteeism and presenteeism) were modelled based on annual number of VOCs (0-3 VOCs per year, ≥4 VOCs per year). Patients who were functionally cured were assumed to have no productivity loss due to SCD. Additionally, SCD patients who were unemployed due

to the disease (calculated as the difference between the rate of employment in the general population and the rate for patients with SCD) were assumed to have 100% absenteeism.

Caregiver burden was estimated based on the number of VOC events experienced by the patients while age ≤26 years. Each VOC event was assumed to be associated with seven days of work missed, as per Bradt *et al*. (2020), which assumed that each VOC event was associated with seven days of missed school in adolescents with SCD (198).

The impact of treatment on out-of-pocket costs for patients with SCD is estimated as a percentage of the health state costs in the model. Health state costs include the complication costs (VOCs, acute complications, chronic complications and infertility) and monitoring costs (including post-transplant monitoring costs). Therefore, treatments that reduce health state costs by reducing complications would be associated with lower patient out-of-pocket costs. However, given the lack of patient out-of-pocket costs in the UK, these costs were not included in the societal perspective scenario analysis.

Table 49: Indirect costs

Variable	Value	Reference
General population inputs		
Population below retirement age who are employed (%)	75.5	ONS employment rate (245)
Average number of working hours per week	33.2	ONS Annual Survey of Hours and Earnings (246)
Mean employment start age (years)	18	Assumption
Mean retirement age (years)	68	State Pension Age (247)
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 (246)
Patient productivity inputs		
SCD patient employment rates (%)		
Functionally cured	75.5	Assumed same as general (non-SCD) population, Office for

		National Statistics, Employment rate (245)
0-3 VOCs per year	63.9	Assumed to be the midpoint of employment rate for functionally cured SCD patients and ≥4 VOCs per year
≥4 VOCs per year	52.2	Drahos et al., 2022[a] (5)
Cost per month of unemployment due to SCD	£2,591	Assumed equal to 100% absenteeism
Absenteeism (%)		
Functionally cured	0	Assumption
0-3 VOCs per year	21.9	Rizio et al., 2020 (248)
≥4 VOCs per year	35.0	Rizio et al., 2020 (248)
Presenteeism		
Functionally cured	0	Assumption
0-3 VOCs per year	42.8	Rizio et al., 2020 (248)
≥4 VOCs per year	53.1	Rizio et al., 2020 (248)
Caregiver burden inputs		
Patient caregiver up to age (years)	26	Beaudoin et al., 2022 (194)
Workdays missed per VOC event	7.0	Number of school days missed by patient as per Bradt et al., 2020 (198)
Patient out-of-pocket costs		
Out-of-pocket costs as percentage of health state costs (%)	0.0	Assumption
Other indirect costs (monthly)		
Functionally cured	£0	Assumption
0-3 VOCs per year	£0	
≥4 VOCs per year	£0	

Key: ONS, Office for National Statistics; SCD, sickle cell disease; VOC, vaso-occlusive crisis
Notes:
[a] Calculated as the difference between general population employment rate (75.5%) and proportion of patients with SCD receiving/awaiting disability payments or on leave from work due to SCD (23.3%).

B.3.6 Severity

Exa-cel meets the criteria for a 1.2 severity modifier at the base case discount rate of 3.5% and a 1.7 modifier at a 1.5% discount rate. The QALY shortfall was calculated using the economic model discounted QALY projection for SoC using the baseline characteristics of the CLIMB SCD-121 FAS population, which is considered to be generalisable to the UK population that will be offered exa-cel.

The QALY shortfall was calculated relative to the age- and gender- matched UK population using the online QALY shortfall calculator tool (249), using the reference case MVH value set and HSE 2014 survival model.

Table 50: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	44.2% female	B.3.2.1
Starting age	21.2 years	B.3.2.1

It is not possible to provide a summary list of QALY shortfall from previous evaluations in SCD as the crizanlizumab appraisal did not include a QALY shortfall analysis, whilst the shortfall analysis was redacted for the voxelotor appraisal.

Table 51: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
Uncomplicated SCD	0.81 (0.04)	[redacted]
Complications	Time varying	[redacted]

Note: Health state values are presented before application of disutilties

Table 52: 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%	34.09	9.81	24.28 (71.22%)
3.5%	22.36	8.24	14.12 (63.15%)

B.3.7 Uncertainty

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

- Durability of absence of VOCs and/or 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.2.1, B.3.6 and B.3.12.1).

The uncertainties described in Table 53 could be addressed through a period of managed access. At present, the main source of clinical evidence is the index CLIMB SCD-121 study in SCD 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 15-year post-authorisation safety study (PASS), with a possible expansion in scope to collect UK patient data via EBMT for 3 years, in order to further augment the totality of data collected under a managed access agreement.

Table 53: List of uncertainties and the data that could be collected to resolve them

Clinical uncertainty	Outcome data	Data source
Durability of VOC-free status	• Time period VOC-free following exa-cel infusion • Time period free from inpatient hospitalisation for severe VOCs following exa-cel infusion	CLIMB SCD-121, CLIMB-131, EBMT Registry
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 SCD-121, CLIMB-131, EBMT Registry
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 SCD-121, 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

Key: SCD: sickle cell disease; VOC: vaso-occlusive crisis.

Table 54: Overview of data source

Study	A Long-term Follow-up Study of Subjects With β-thalassemia 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 SCD-121)
Intervention(s)	Exa-cel
Comparator(s)	N/A
Outcomes	• **Severe VOCs** • **Inpatient hospitalisations for severe VOCs** • **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 SCD-121 (as described in Section B.2)
Trial start date	September 2018
Data cut submitted to NICE	June 2023 (D120 data cut-off; database lock 16 April 2023)
Anticipated data cut after a period of managed access	Future data cuts will be submitted as they become available

Key: HbF: fetal haemoglobin; SCD: sickle cell disease.
Notes: Outcomes in bold are those directly used in the economic modelling.

Table 55: Overview of data source

Registry	European Society for Blood and Marrow Transplantation (EBMT)
Type of registry	**Long term registry-based study of patients with beta-thalassaemia or SCD treated with exa-cel**
Population	Patients with sickle cell disease, treated with exa-cel in participating centres reporting data to EBMT, will be eligible to enrol from the date of approval of exa-cel through to the end of the enrolment period (approximately 3 years)
Relevant data items collected	**Number of severe VOC events pre- and post-transplant (to be defined as acute pain events, acute chest syndrome events, priapism events, or splenic sequestration events):** • Time from exa-cel infusion to most recent VOC **Haemoglobin measures pre- and post-transplant:** • 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 PASS study duration: baseline, Day 100, Month 6, Year 1 and annually (Years 2-15). 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 SCD 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. For the PASS study, 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 PASS 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]) and final clinical study report after all patients have reached 15 year follow up (Year 18). 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

Proposed Data Source to gather evidence for Managed Access Agreement

It is anticipated that the CLIMB SCD-121 and CLIMB-131 studies will fulfil most of the data gap requirements, with the latter as the main source of supportive long-term outcomes data, and further gaps to be filled with data from the EBMT.

The EBMT was established in 1970s and is an established data source on haematopoietic stem cell transplant (HSCT) 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 (250).

The EBMT registry is the proposed data source in UK, France, Germany, and Italy for Vertex's regulatory mandated post-authorisation surveillance study (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 expanding 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.

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 sickle cell disease (SCD) patients ≥ 12 years of age and treated with exa-cel at any of the authorised treatment centres in the UK. These data will feed into the EBMT via the BSBMTCT registry on a 'consented'(i.e. non-compulsory) basis. 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 PASS 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 SCD 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 [ref], 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 experiences no VOC events after 2 years of

exa-cel treatment, with sustained HbF levels and engraftment plus improved iron status, that they are likely to maintain a VOC-free status and, in turn, less likely to encounter further disease complications and subsequent organ damage. Table 56 presents estimated numbers of patients that are predicted to have undergone therapy with exa-cel and engrafted over the initial five years.

Table 56: Forecast of Patients Commencing Engraftment

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

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. Vertex will also provide additional data collection resources for centres. Patients will also be followed up by their haemoglobinopathy team with respect to long term sickle cell 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 SCD 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.

B.3.9 Distributional cost-effectiveness analysis

Distributional cost-effectiveness analyses (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 (251).

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 L: DCEA methods.

It is important to emphasise that the DCEA weights are based on the pre-intervention quality-adjusted life expectancy (QALE) shortfall between IMD groups of the general population. 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 this submission, the DCEA shortfall value, therefore, does not represent a disease-specific modifier.

The DCEA also focuses on defining deprivation using IMD weights for several reasons. Firstly, SCD 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 (252). SCD patients are more likely to live in a more deprived area of the UK, with 72.4% of SCD patients identified in the Vertex BoI study living in the two most deprived quintiles according to the Index for Multiple Deprivation (IMD) (4, 253). 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 SCD prevalence across ethnic minorities whom, in turn, are also most likely to be disproportionately affected by socio-economic deprivation (4, 253). We also judged the available ethnicity data, collated from the CPRD-HES database, to be inadequate for an analysis based on ethnicity in the SCD 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 (4, 253). Therefore, 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 SCD population.

The above reasoning is supported by Cookson et al. (2020) (251), 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 SCD-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 (4, 253). Moreover, 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 (4, 252-254).

Our DCEA approach also assesses equity and efficiency in health at a population-level. The decision to conduct an aggregate approach was based on several factors too. Firstly, 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).

Moreover, conducting a full DCEA approach would necessitate estimating the opportunity costs across varying ethnicities and other potential health inequality proxies with high accuracy. As noted above, this is challenging within the context of SCD, 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) (251), 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.

Finally, the value for the aversion to inequality in the exa-cel DCEA was informed by the data from Robson M., et al. 2017 (255). An SLR of inequality aversion values for the UK has also been conducted (256). 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, our final choice 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 (years of life in full health (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. Although there is a more recent source for an Atkinson inequality aversion value in England (titled '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'), we have several concerns regarding the source of this value and its applicability to the submission, which we lay out below.

Firstly, based on our review and interpretation of the paper, the 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 (257).

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. Nevertheless, we would like to emphasise that the aversion to inequality value is fully flexible to user input and can be adjusted to consider alternative scenario values.

More details of the DCEA methods can be found in Appendix L: DCEA methods.

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

B.3.10.1. Summary of base-case analysis inputs

Table 57: Summary of variables applied in the economic model

	Base case	Upper 95% CI	Lower 95% CI	Include in PSA?	Distribution	Reference to section in submission
Cohort Inputs						
Demographics						
Age (years)	21.2	25.44	16.96	Y	Normal	B.3.2.1
Weight ratio of SCD/general population	1	N/A	N/A	N	Beta	B.3.2.1
Female (%)	44	62	27	Y	Beta	B.3.2.1
Proportion <18 years old (%)	27.9	N/A	N/A	N	N/A	B.3.2.1
Baseline clinical characteristics						
Frequency of VOC (mean per month)	0.35	0.42	0.28	Y	Gamma	B.3.2.1
Proportion of patients with baseline chronic complications						
Pulmonary hypertension	0	N/A	N/A	N	Beta	B.3.2.1
Chronic kidney disease	0	N/A	N/A	N	Beta	B.3.2.1
Post-stroke	0	N/A	N/A	N	Beta	B.3.2.1
Avascular necrosis	0	N/A	N/A	N	Beta	B.3.2.1
Retinopathy	14.3	N/A	N/A	N	Beta	B.3.2.1
Heart failure	0	N/A	N/A	N	Beta	B.3.2.1
Neurocognitive impairment	2.9	N/A	N/A	N	Beta	B.3.2.1
Liver disease	0	N/A	N/A	N	Beta	B.3.2.1
Baseline utilisation						
Hydroxycarbamide	63.8	77	51	Y	Beta	B.3.2.1
RBC transfusion	16	19	13	Y	Beta	B.3.2.1

Iron chelation therapy (among those receiving RBCT)	34.6	35%	34%	Y	Beta	B.3.2.1
Desferrioxamine (DFO)	6.1	N/A	N/A	N	Dirichlet	B.3.2.1
Deferasirox (DFX)	89.8	N/A	N/A	N	Dirichlet	B.3.2.1
Deferiprone (DFP)	4.1	N/A	N/A	N	Dirichlet	B.3.2.1
DFO+DFX	0	N/A	N/A	N	Dirichlet	B.3.2.1
DFO+DFP	0	N/A	N/A	N	Dirichlet	B.3.2.1
DFX+DFP	0	N/A	N/A	N	Dirichlet	B.3.2.1
Clinical Inputs						
Exa-cel						
Treatment procedure phase						
Duration from mobilisation to engraftment (months)	12	N/A	N/A	N	Gamma	B.3.3.1
Treatment withdraw (%)	19.0	28.9	14.03	Y	Beta	B.3.3.1
Initial engraftment success (%)	100	N/A	N/A	N	Beta	B.3.3.1
Repeated treatment after failed initial engraftment (%)	0	N/A	N/A	N	Beta	B.3.3.1
Second engraftment success (%)	100	N/A	N/A	N	Beta	B.3.3.1
Post engraftment phase						
Functionally cured (%)	96.6	77	100	Y	Beta	B.3.3.1
VOC reduction (%)	0.0	0.0	0.0	Y	Beta	B.3.3.1
Relative effect on VOC frequency among improved (non-cured) patients	0.00	0.00	0.00	Y	Beta	B.3.3.1
Complication risk inputs						
Acute complications						
Stroke						
Monthly rate when VOC = 0	0.0021	0.0031	0.0012	Y	Beta	B.3.3.2
HR by VOC occurrence	2.26	2.63	1.94	Y	Log Normal	B.3.3.2
Monthly rate among patients cured from SCD	0.0001	0.000	0.000	Y	Beta	B.3.3.2
Acute chest syndrome						

Monthly rate when VOC = 0	0.0003	0.001	0.000	Y	Beta	B.3.3.2
HR by VOC occurrence	58.67	68.55	50.21	Y	Log Normal	B.3.3.2
Monthly rate among patients cured from SCD	0.0000	0.0	0.0	Y	Beta	B.3.3.2
Acute infections						
Monthly rate when VOC = 0	0.0197	0.023	0.017	Y	Beta	B.3.3.2
HR by VOC occurrence	2.26	2.63	1.94	Y	Log Normal	B.3.3.2
Monthly rate among patients cured from SCD	0.0002	0.000	0.000	Y	Beta	B.3.3.2
Acute kidney injury/infarction						
Monthly rate when VOC = 0	0.0012	0.002	0.001	Y	Beta	B.3.3.2
OR by VOC occurrence	2.20	2.92	1.66	Y	Log Normal	B.3.3.2
Monthly rate among patients cured from SCD	0.0003	0.000	0.000	Y	Beta	B.3.3.2
Gallstones						
Monthly rate when VOC = 0	0.0027	0.004	0.002	Y	Beta	B.3.3.2
HR by VOC occurrence	2.26	2.63	1.94	Y	Log Normal	B.3.3.2
Monthly rate among patients cured from SCD	0.0005	0.001	0.000	Y	Beta	B.3.3.2
Pulmonary embolism						
Monthly rate when VOC = 0	0.0011	0.002	0.001	Y	Beta	B.3.3.2
HR by VOC occurrence	2.82	3.59	2.22	Y	Log Normal	B.3.3.2
Monthly rate among patients cured from SCD	0.0004	0.000	0.000	Y	Beta	B.3.3.2
Leg ulcers						
Monthly rate when VOC = 0	0.0083	0.010	0.007	Y	Beta	B.3.3.2
HR by VOC occurrence	2.26	2.63	1.94	Y	Log Normal	B.3.3.2
Monthly rate among patients cured from SCD	0.0002	0.000	0.000	Y	Beta	B.3.3.2
Chronic complications						
Chronic kidney disease						
Monthly risk when VOC = 0	0.120%	0.144%	0.096%	Y	Beta	B.3.3.2
OR by VOC occurrence	3	6.00	1.50	Y	Log Normal	B.3.3.2
Monthly risk among patients cured from SCD	0.009%	0.011%	0.007%	Y	Beta	B.3.3.2
Pulmonary hypertension						
Monthly risk when VOC = 0	0.067%	0.133%	0.024%	Y	Beta	B.3.3.2

HR by VOC occurrence	4.12	5.41	3.14	Y	Log Normal	B.3.3.2
Monthly risk among patients cured from SCD	0.002%	0.002%	0.001%	Y	Beta	B.3.3.2
Avascular necrosis						
Monthly risk when VOC = 0	0.227%	0.339%	0.138%	Y	Beta	B.3.3.2
HR by VOC occurrence	4.12	5.41	3.14	Y	Log Normal	B.3.3.2
Monthly risk among patients cured from SCD	0.002%	0.002%	0.001%	Y	Beta	B.3.3.2
Heart failure						
Monthly risk when VOC = 0	0.063%	0.075%	0.050%	Y	Beta	B.3.3.2
HR by VOC occurrence	4.12	5.41	3.14	Y	Log Normal	B.3.3.2
Monthly risk among patients cured from SCD	0.007%	0.008%	0.006%	Y	Beta	B.3.3.2
Neurocognitive impairment						
Monthly risk when VOC = 0	0.171%	0.205%	0.137%	Y	Beta	B.3.3.2
HR by VOC occurrence	4.12	5.41	3.14	Y	Log Normal	B.3.3.2
Monthly risk among patients cured from SCD	0.008%	0.010%	0.007%	Y	Beta	B.3.3.2
Post-stroke						
Proportion with severe stroke that incur long-term costs/disutility	35%	37%	33%	Y	Beta	B.3.3.2
Sickle retinopathy						
Monthly risk when VOC = 0	0.042%	0.050%	0.033%	Y	Beta	B.3.3.2
HR by VOC occurrence	4.12	5.41	3.14	Y	Log Normal	B.3.3.2
Monthly risk among patients cured from SCD	0.019%	0.022%	0.015%	Y	Beta	B.3.3.2
Liver complications						
Monthly risk when VOC = 0	0.041%	0.049%	0.033%	Y	Beta	B.3.3.2
HR by VOC occurrence	4.12	5.41	3.14	Y	Log Normal	B.3.3.2
Monthly risk among patients cured from SCD	0.008%	0.010%	0.007%	Y	Beta	B.3.3.2
Infertility						
Fertile age (years)						
Start	16	N/A	N/A	N	N/A	B.3.3.3
End	51	N/A	N/A	N	N/A	B.3.3.3
Prevalence in general population, by gender						

Male	16.9%	N/A	N/A	Y	Beta	B.3.3.3
Female	23.7%	N/A	N/A	Y	Beta	B.3.3.3
Increased risk of infertility related to treatments						
Exa-cel						
Male	1.24	0.99	1.49	Y	Log Normal	B.3.3.3
Female	1.57	1.26	1.88	Y	Log Normal	B.3.3.3
Mortality inputs						
Transplant-related mortality						
Instant mortality (rate)						
Transplantation-related mortality	0.00%	0	0	Y	Beta	B.3.3.4
Engraftment failure mortality	25%	20%	30%	Y	Beta	B.3.3.4
SCD cured mortality						
HR adjustment applied to general mortality	1.25	1.36	1.15	Y	Log Normal	B.3.3.4
SCD-related mortality						
Annual SCD-specific mortality by age (rate)						
0 years old	0.13%	N/A	N/A	N	N/A	B.3.3.4
1-4 years old	0.04%	N/A	N/A	N	N/A	B.3.3.4
5-9 years old	0.03%	N/A	N/A	N	N/A	B.3.3.4
10-14 years old	0.03%	N/A	N/A	N	N/A	B.3.3.4
15-19 years old	0.07%	N/A	N/A	N	N/A	B.3.3.4
20-24 years old	0.16%	N/A	N/A	N	N/A	B.3.3.4
25-34 years old	0.23%	N/A	N/A	N	N/A	B.3.3.4
35-44 years old	0.47%	N/A	N/A	N	N/A	B.3.3.4
45-54 years old	0.70%	N/A	N/A	N	N/A	B.3.3.4
55-64 years old	1.12%	N/A	N/A	N	N/A	B.3.3.4
65-74 years old	0.68%	N/A	N/A	N	N/A	B.3.3.4
75+ years old	8.47%	N/A	N/A	N	N/A	B.3.3.4
VOC-specific mortality						
HR by VOC occurrence	1.56	2.05	1.19	Y	Log Normal	B.3.3.4

Complication-dependent mortality						
HR by acute complication						
Acute chest syndrome	1.27	1.99	0.81	Y	Log Normal	B.3.3.4
Acute renal failure	9.50	12.66	7.13	Y	Log Normal	B.3.3.4
Pulmonary embolism	2.75	3.61	2.10	Y	Log Normal	B.3.3.4
Leg ulcers	1.66	2.47	1.12	Y	Log Normal	B.3.3.4
Acute infection	1.00	1.20	0.80	Y	Log Normal	B.3.3.4
Mortality rate post-event						
Stroke	7.7%	9.2%	6.2%	Y	Beta	B.3.3.4
HR by chronic complication						
Chronic kidney disease	9.57	11.48	7.66	Y	Log Normal	B.3.3.4
Pulmonary hypertension	12.57	15.08	10.06	Y	Log Normal	B.3.3.4
Heart failure	12.57	15.08	10.06	Y	Log Normal	B.3.3.4
Liver complications	2.53	4.70	1.36	Y	Log Normal	B.3.3.4
Infertility mortality						
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
Cost inputs						
Drug or transplant costs						
Exa-cel						
Acquisition price	[redacted]	[redacted]	[redacted]	N	Gamma	B.3.5.1
Discount	[redacted]	[redacted]	[redacted]	N	N/A	B.3.5.1
Hydroxycarbamide						
Cost per unit	£0.10	N/A	N/A	N	Gamma	B.3.5.1
Unit strength	500	N/A	N/A	N	N/A	B.3.5.1
Dose (mg/kg)	15	N/A	N/A	N	N/A	B.3.5.1
Administrations per month	30.4	N/A	N/A	N	N/A	B.3.5.1
Administration costs per month	£0	N/A	N/A	Y	Gamma	B.3.5.1
Blood transfusion costs						

Number of transfusions per month	0.7	N/A	N/A	N	N/A	B.3.5.2
Number of RBC units per administration	10.0	N/A	N/A	N	N/A	B.3.5.2
Cost per RBC unit	£261	N/A	N/A	N	N/A	B.3.5.2
Administration cost per transfusion	£90	N/A	N/A	N	N/A	B.3.5.2
Iron chelation costs						
Deferoxamine (DFO)						
Cost per unit	£4.66	£3.7	£5.6	Y	Gamma	B.3.5.2
Unit strength	500	N/A	N/A	N	N/A	B.3.5.2
Dose (mg/kg)	41.16	N/A	N/A	N	N/A	B.3.5.2
Administration per month	22.4	N/A	N/A	N	N/A	B.3.5.2
Administration costs per dose	£0	N/A	N/A	N	Gamma	B.3.5.2
Deferasirox (DFX)						
Cost per unit	£4.20	£3.36	£5.04	Y	Gamma	B.3.5.2
Unit strength	90	N/A	N/A	N	N/A	B.3.5.2
Dose (mg/kg)	14	N/A	N/A	N	N/A	B.3.5.2
Administration per month	30.44	N/A	N/A	N	N/A	B.3.5.2
Administration costs per dose	£0	N/A	N/A	N	Gamma	B.3.5.2
Deferiprone (DFP)						
Cost per unit	£1.30	N/A	N/A	N	Gamma	B.3.5.2
Unit strength	500	N/A	N/A	N	N/A	B.3.5.2
Dose (mg/kg)	75	N/A	N/A	N	N/A	B.3.5.2
Administration per month	30.4	N/A	N/A	N	N/A	B.3.5.2
Administration costs per dose	£0	N/A	N/A	N	N/A	B.3.5.2
Transplant-related costs						
Pre-transplant costs (Exa-cel)						
Mobilisation						
Mobilisation cycles	2.2	N/A	N/A	N	N/A	B.3.5.1
Plerixafor daily dose (mg/kg)	0.24	N/A	N/A	N	N/A	B.3.5.1
Plerixafor length (days)	4	N/A	N/A	N	N/A	B.3.5.1
Plerixafor cost per unit	£4,880	N/A	N/A	N	N/A	B.3.5.1

Plerixafor unit strength	24	N/A	N/A	N	N/A	B.3.5.1
Hospitalisation for harvesting procedure	£5,375	N/A	N/A	N	N/A	B.3.5.1
Pre-transplantation RBC transfusion costs						
Number of exchange transfusions	5	N/A	N/A	N	N/A	B.3.5.1
Total RBC transfusion costs	£13,488	N/A	N/A	N	N/A	B.3.5.1
Other pre-transplantation costs						
Exa-cel	0	N/A	N/A	N	N/A	B.3.5.1
Other transplantation-related costs						
Hospitalisation costs for procedure	£25,387	N/A	N/A	N	N/A	B.3.5.1
Monthly post-transplantation monitoring costs						
Number of years to apply post-transplant monitoring costs	15	N/A	N/A	N	N/A	B.3.5.3
Year 1	£100	N/A	N/A	N	N/A	B.3.5.3
Year 2	£100	N/A	N/A	N	N/A	B.3.5.3
Year 3	£82	N/A	N/A	N	N/A	B.3.5.3
Year 4	£82	N/A	N/A	N	N/A	B.3.5.3
Year 5+	£82	N/A	N/A	N	N/A	B.3.5.3
Complication costs						
Acute complication costs						
Cost per VOC event	£1,567	N/A	N/A	N	N/A	B.3.5.4
Chronic complication costs						
Monthly cost per condition						
Pulmonary hypertension	£314	N/A	N/A	N	N/A	B.3.5.4
Chronic kidney disease	£201	N/A	N/A	N	N/A	B.3.5.4
Avascular necrosis	£114	N/A	N/A	N	N/A	B.3.5.4
Post-stroke	£39	N/A	N/A	N	N/A	B.3.5.4
Neurocognitive impairment	£24	N/A	N/A	N	N/A	B.3.5.4
Retinopathy	£85	N/A	N/A	N	N/A	B.3.5.4
Heart failure	£174	N/A	N/A	N	N/A	B.3.5.4
Liver complications	£181	N/A	N/A	N	N/A	B.3.5.4

Monitoring costs						
Lab/test/physician visit frequency						
Haematological tests/labs	0.50	N/A	N/A	N	N/A	B.3.5.3
Renal tests/labs	0.33	N/A	N/A	N	N/A	B.3.5.3
Hepatic tests/labs	0.33	N/A	N/A	N	N/A	B.3.5.3
Lactate dehydrogenase test	0.33	N/A	N/A	N	N/A	B.3.5.3
Fetal haemoglobin lab	0.33	N/A	N/A	N	N/A	B.3.5.3
Physician visits	0.33	N/A	N/A	N	N/A	B.3.5.3
Unit costs						
Haematological tests/labs	£2.79	N/A	N/A	N	N/A	B.3.5.3
Renal tests/labs	£1.10	N/A	N/A	N	N/A	B.3.5.3
Hepatic tests/labs	£1.10	N/A	N/A	N	N/A	B.3.5.3
Lactate dehydrogenase test	£1.10	N/A	N/A	N	N/A	B.3.5.3
Fetal haemoglobin lab	£1.10	N/A	N/A	N	N/A	B.3.5.3
Physician visit	£167.58	N/A	N/A	N	N/A	B.3.5.3
Total monthly lab/test costs	£58.72	N/A	N/A	N	N/A	B.3.5.3
Fertility preservation costs						
One-time retrieval surgery	£1,787	N/A	N/A	N	N/A	B.3.5.1
Monthly storage costs	£19	N/A	N/A	N	N/A	B.3.5.1
AE costs						
One-time AE costs						
Exa-cel	£0	N/A	N/A	N	N/A	B.3.5.6
Terminal care						
One-time costs	£12,149	N/A	N/A	N	N/A	B.3.5.3
Utility inputs						
Base utilities						
Uncomplicated SCD	0.81	0.72	0.88	Y	Beta	B.3.4.1
Functionally cured	0.92	0.81	0.99	Y	Beta	B.3.4.1
Disutilities (decrement in QoL)						

Treatment with Exa-cel in transplant year	-0.11	N/A	N/A	N	Beta	B.3.4.4
Graft failure (affects transplantation year)	-0.4	-0.32	-0.48	Y	Beta	B.3.4.4
Infertility	-0.058	-0.070	-0.046	Y	Beta	B.3.4.4
Acute complications						
VOC	-0.18	-0.22	-0.15	Y	Beta	B.3.4.4
Acute chest syndrome	-0.56	-0.67	-0.45	Y	Beta	B.3.4.4
Stroke	-0.565	-0.68	-0.45	Y	Beta	B.3.4.4
Acute kidney injury	-0.14	-0.17	-0.11	Y	Beta	B.3.4.4
Pulmonary embolism	-0.05	-0.08	-0.03	Y	Beta	B.3.4.4
Acute infections	-0.16	-0.19	-0.13	Y	Beta	B.3.4.4
Gallstones	-0.12	-0.14	-0.10	Y	Beta	B.3.4.4
Leg ulcers	-0.11	-0.13	-0.09	Y	Beta	B.3.4.4
Chronic complications						
Pulmonary hypertension	-0.21	-0.25	-0.17	Y	Beta	B.3.4.4
Chronic kidney disease	-0.14	-0.17	-0.11	Y	Beta	B.3.4.4
Avascular necrosis	-0.05	-0.08	-0.03	Y	Beta	B.3.4.4
Post-stroke	-0.13	-0.16	-0.10	Y	Beta	B.3.4.4
Neurocognitive impairment	-0.05	-0.06	-0.04	Y	Beta	B.3.4.4
Retinopathy	-0.05	-0.08	-0.03	Y	Beta	B.3.4.4
Heart failure	-0.12	-0.36	-0.01	Y	Beta	B.3.4.4
Liver complications	-0.05	-0.08	-0.03	Y	Beta	B.3.4.4
Age- and gender-dependent utility adjustment						
Intercept	0.95	N/A	N/A	N	N/A	B.3.4.6
Age (years)	-0.0002587	N/A	N/A	N	N/A	B.3.4.6
Age^2	-0.0000332	N/A	N/A	N	N/A	B.3.4.6
Male	0.02	N/A	N/A	N	N/A	B.3.4.6

Key: ICT, iron chelation therapy; NHS, National Health Service; PSS, personal social services.

B.3.10.2. Assumptions

Table 58: Key model assumptions

Model parameters	Assumptions
Duration of complications	Acute complications are assumed to last for only one model cycle and not accumulate. Chronic complications are considered permanent conditions that are assumed to last until death once developed.
Mortality	Mortality is assumed to be affected by age, gender, patients' VOC status, frequency of VOCs, occurrence of SCD-related complications, transplantation, and engraftment failure (exa-cel only).
Adverse events	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 disabilities.
Treatment withdrawals and treatment failure's 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 KOL feedback.

Key: AE, adverse event; GvHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; ICT, Iron chelation therapy; NHS, National Health Service; RBC, red blood cell; SCD, sickle cell disease; SoC, standard of care; VOC, vaso-occlusive crisis.

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 59 to Table 62. As NICE considers inequality or unfairness in the distribution of health to be an important factor in decision-making (201), we conducted a DCEA to quantify the distribution of health inequalities in SCD and the potential impact on exa-cel, which is summarised in section B.3.9. We report, as a co-base case, the ICERs including modifiers to the incremental costs and incremental QALYs based on appropriate DCEA methodology to reflect the importance of inequity in decision-making.

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 33.

This *de novo* economic evaluation examined the cost-effectiveness of exa-cel in severe SCD. The model predicted that, over a lifetime horizon, patients treated with exa-cel had a substantial increase in survival of [redacted] years compared to SoC. Patients treated with exa-cel experienced approximately [redacted] less VOCs over the lifetime horizon compared to patients treated with SoC. Further, the lifetime burden of SCD-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] and the incremental QALYs were [redacted], which yielded an ICER of [redacted] per discounted QALY gained.

Table 59: 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				[redacted]		[redacted]	[redacted]	[redacted]

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

Table 60: Base-case 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]
DCEA-weighted incremental results				[redacted]		[redacted]	[redacted]	[redacted]

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

Table 61: 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]	[redacted]	[redacted]
DCEA-weighted NHB			[redacted]	[redacted]	[redacted]	[redacted]

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

Table 62: 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]	[redacted]	[redacted]
DCEA-weighted NHB			[redacted]	[redacted]	[redacted]	[redacted]

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

B.3.12 Exploring uncertainty

A range of sensitivity analyses were carried out including probabilistic sensitivity analyses (PSA), one-way sensitivity analysis (OWSA) and scenario analyses.

B.3.12.1. Probabilistic sensitivity analysis

A PSA was performed to explore the uncertainty around key model parameters. 1000 iterations were run for the PSA, 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 base case. This demonstrates that potential uncertainty in the modelling inputs do not have a significant impact on the ICER or cost effectiveness of exa-cel in SCD.

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

Table 63: 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]

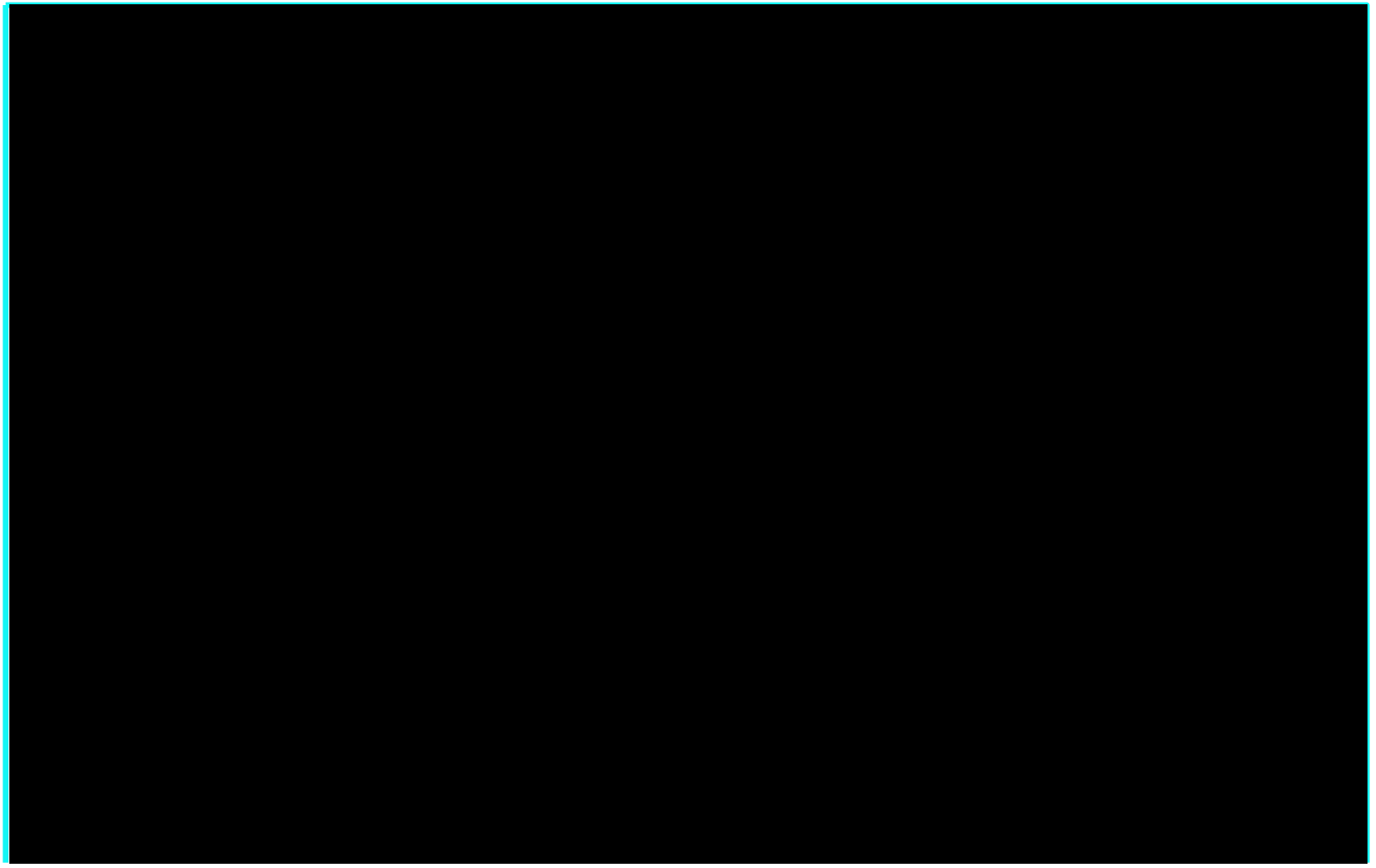
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DCEA, distributional cost-effectiveness analysis

Table 64: 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]

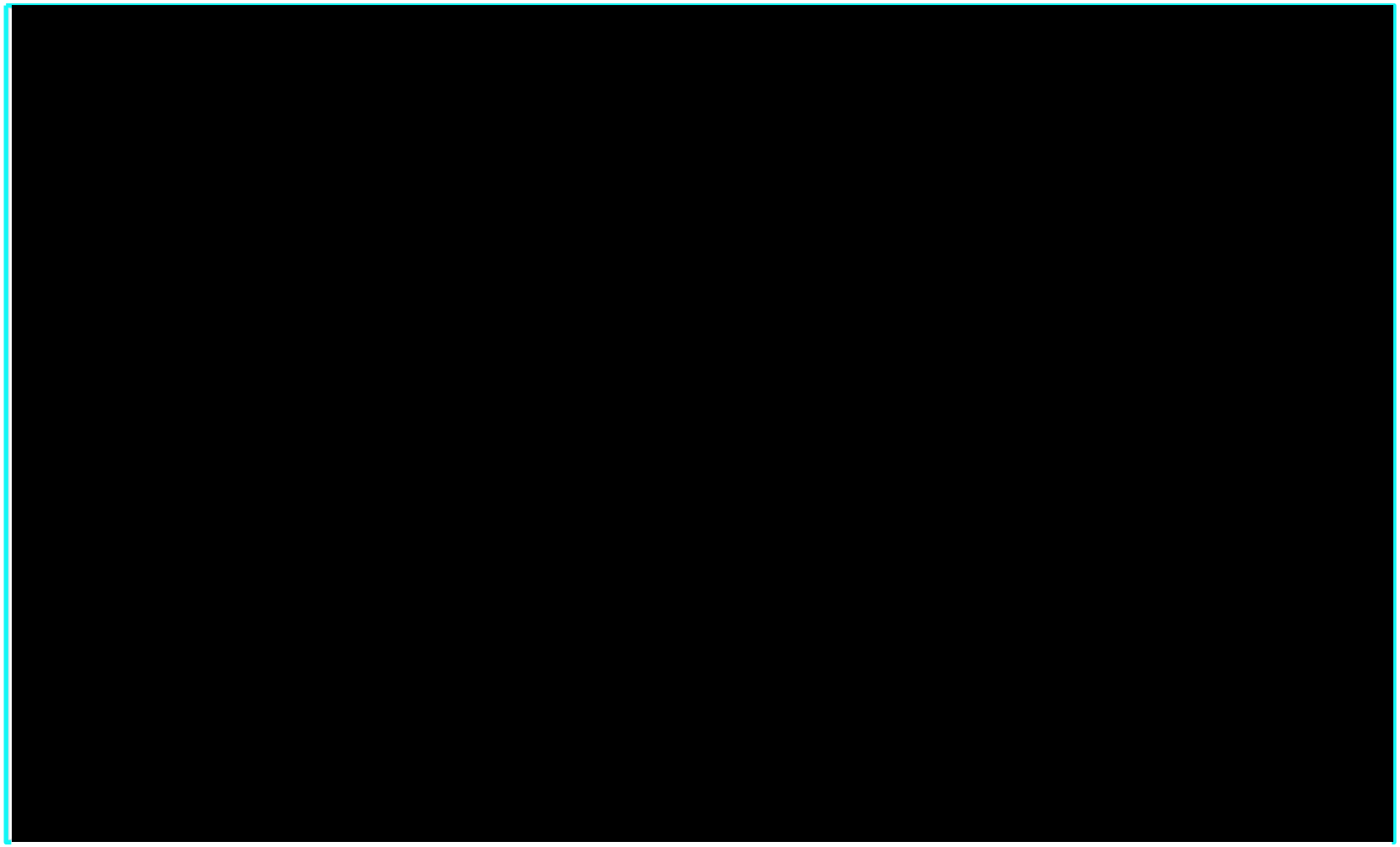
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; DCEA, distributional cost-effectiveness analysis

Figure 28: Cost-effectiveness acceptability curve, 1.5% discount rate (DCEA and severity modified)



Key: DCEA, Distributional cost-effectiveness analysis

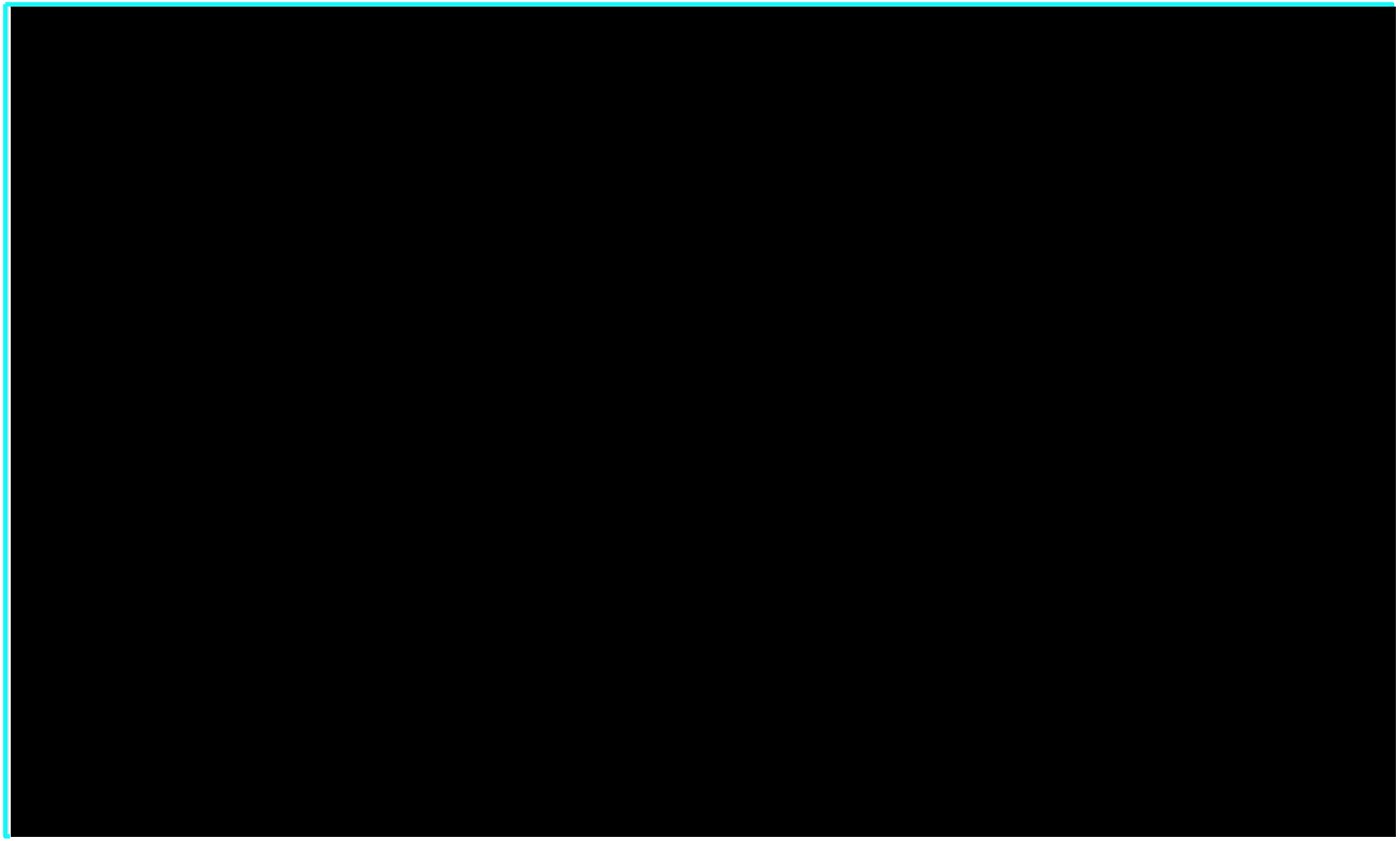
Figure 29: Cost-effectiveness acceptability curve, 3.5% discount rate (DCEA and severity modified)



Key: DCEA, Distributional cost-effectiveness analysis

Figure 30: Cost-effectiveness acceptability curve, 1.5% discount rate (severity modified)

Figure 31: Cost-effectiveness acceptability curve, 3.5% discount rate (severity modified)



B.3.12.2. Deterministic sensitivity analysis

In each deterministic sensitivity analysis 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 utilities used for the cured SCD patients and uncomplicated SCD patients.

At a discount rate of 3.5%, the most sensitive parameters remained largely similar to the base case scenario.

Figure 32: OWSA results, 1.5% discount rate (severity and DCEA modified)

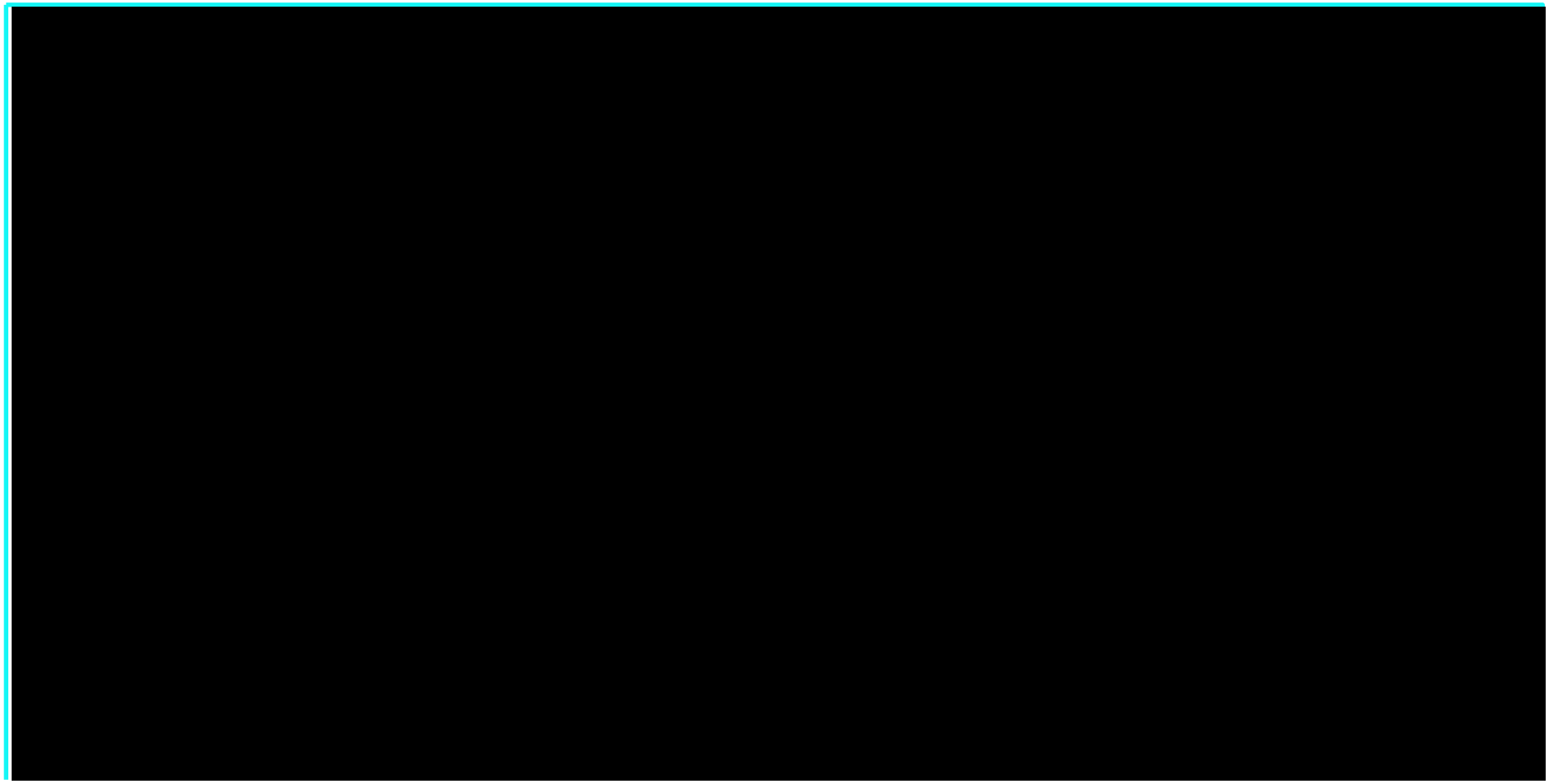


Figure 33: OWSA results, 3.5% discount rate (severity and DCEA modified)

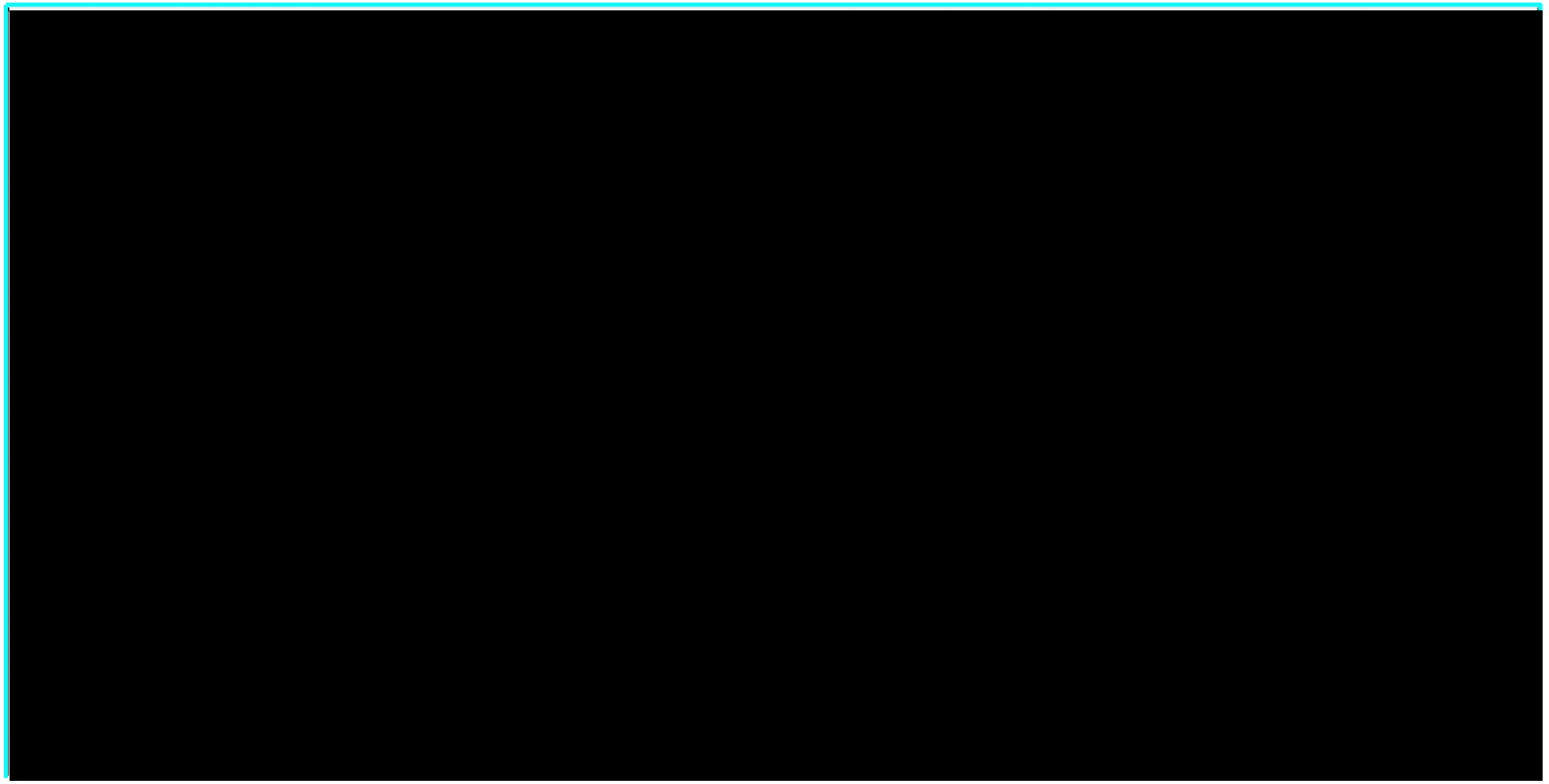


Figure 34: OWSA results, 1.5% discount rate (Severity modified)

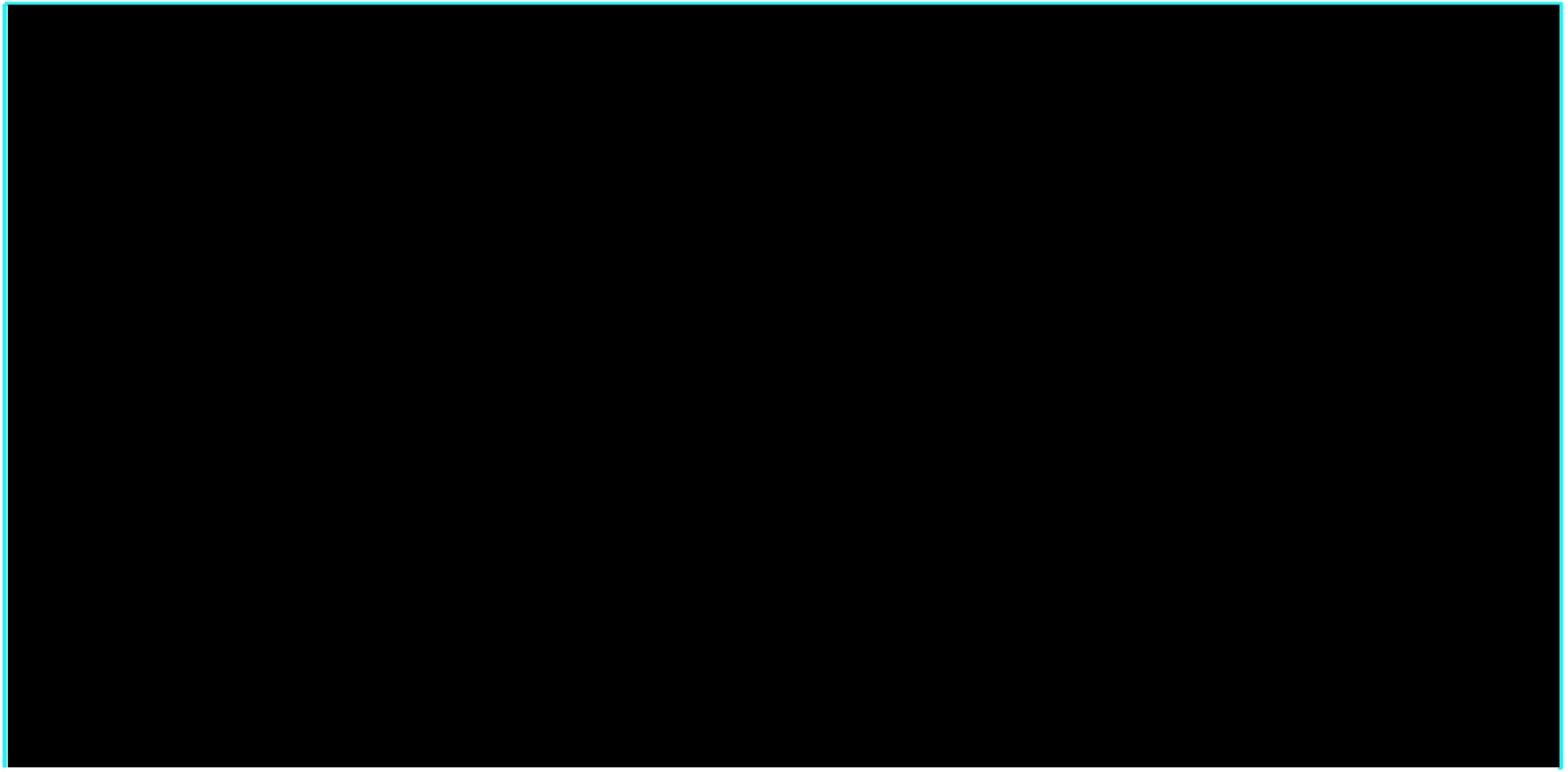


Figure 35: OWSA results, 3.5% discount rate (Severity modified)

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 were higher baseline VOCs per year and cost per VOC event.

At a discount rate of 3.5%, the most impactful scenarios were largely similar to the base case scenarios most impactful variables.

Table 65: 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]
Baseline age of 21.2 years informed by the CLIMB SCD-121 trial	Baseline age of 12 years	[redacted]	[redacted]	[redacted]
Baseline number of VOCs is 4.2 VOCs per year informed by the CLIMB SCD-121 trial	Baseline number of VOCs is 2 VOCs per year	[redacted]	[redacted]	[redacted]
	Baseline number of VOCs is 5.84 VOCs per year	[redacted]	[redacted]	[redacted]
	Baseline number of VOCs is 9.5 VOCs per year	[redacted]	[redacted]	[redacted]
Functionally cured SCD patients have the same risk of developing complications as the general (non-SCD) population	Functionally cured SCD patients have an increased risk (1.25) compared to the general (non-SCD) population	[redacted]	[redacted]	[redacted]
Cost per VOC event is £1,567	Cost per VOC event is £4,401 based on Pizzo et al., 2015	[redacted]	[redacted]	[redacted]
Interaction between disutilities of	Interaction between disutilities of complications is additive			

complications is multiplicative				
Carer utility is excluded	Carer utility is included	[redacted]	[redacted]	[redacted]
Age-specific SCD mortality estimates are applied	SCD HR adjustment to general population mortality rates is applied	[redacted]	[redacted]	[redacted]
Mortality inputs (hazard ratios) for SCD-related complications are: CKD: 9.57; pulmonary hypertension: 12.57; heart failure: 12.57	Mortality inputs (hazard ratios) for SCD-related complications are: CKD: 3.60; pulmonary hypertension: 2.34; heart failure: 1.51	[redacted]	[redacted]	[redacted]
Interaction between mortality from different complications is multiplicative	Interaction between mortality from different complications is additive	[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 66: 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]
Baseline age of 21.2 years informed by the CLIMB SCD-121 trial	Baseline age of 12 years	[redacted]	[redacted]	[redacted]
Baseline number of VOCs is 4.2 VOCs per year informed by the CLIMB SCD-121 trial	Baseline number of VOCs is 2 VOCs per year	[redacted]	[redacted]	[redacted]
	Baseline number of VOCs is 5.84 VOCs per year	[redacted]	[redacted]	[redacted]
	Baseline number of VOCs is 9.5 VOCs per year	[redacted]	[redacted]	[redacted]
Functionally cured SCD patients have the same risk of developing complications as the general (non-SCD) population	Functionally cured SCD patients have an increased risk (1.25) compared to the general (non-SCD) population	[redacted]	[redacted]	[redacted]
Cost per VOC event is £1,567	Cost per VOC event is £4,401 based on Pizzo et al., 2015	[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]
Age-specific SCD mortality estimates are applied	SCD HR adjustment to general population mortality rates is applied	[redacted]	[redacted]	[redacted]
Mortality inputs (hazard ratios) for SCD-related complications are: CKD: 9.57; pulmonary hypertension: 12.57; heart failure: 12.57	Mortality inputs (hazard ratios) for SCD-related complications are: CKD: 3.60; pulmonary hypertension: 2.34; heart failure: 1.51	[redacted]	[redacted]	[redacted]
Interaction between mortality from different complications is multiplicative	Interaction between mortality from different complications is additive			

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 67: 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]
Baseline age of 22.5 years informed by the CLIMB SCD-121 trial	Baseline age of 12 years	[redacted]	[redacted]	[redacted]
Baseline number of VOCs is 4.2 VOCs per year informed by the CLIMB SCD-121 trial	Baseline number of VOCs is 2 VOCs per year	[redacted]	[redacted]	[redacted]
	Baseline number of VOCs is 5.84 VOCs per year	[redacted]	[redacted]	[redacted]
	Baseline number of VOCs is 9.5 VOCs per year	[redacted]	[redacted]	[redacted]
Functionally cured SCD patients have the same risk of developing complications as the general (non-SCD) population	Functionally cured SCD patients have an increased risk (1.25) compared to the general (non-SCD) population	[redacted]	[redacted]	[redacted]
Cost per VOC event is £1,567	Cost per VOC event is £4,401 based on Pizzo et al., 2015	[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]
Age-specific SCD mortality estimates are applied	SCD HR adjustment to general population mortality rates is applied	[redacted]	[redacted]	[redacted]
Mortality inputs (hazard ratios) for SCD-related complications are: CKD: 9.57; pulmonary hypertension: 12.57; heart failure: 12.57	Mortality inputs (hazard ratios) for SCD-related complications are: CKD: 3.60; pulmonary hypertension: 2.34; heart failure: 1.51	[redacted]	[redacted]	[redacted]
Interaction between mortality from different complications is multiplicative	Interaction between mortality from different complications is additive			

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 68: 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]
Baseline age of 22.5 years informed by the CLIMB SCD-121 trial	Baseline age of 12 years	[redacted]	[redacted]	[redacted]
Baseline number of VOCs is 4.2 VOCs per year informed by the CLIMB SCD-121 trial	Baseline number of VOCs is 2 VOCs per year	[redacted]	[redacted]	[redacted]
	Baseline number of VOCs is 5.84 VOCs per year	[redacted]	[redacted]	[redacted]
	Baseline number of VOCs is 9.5 VOCs per year	[redacted]	[redacted]	[redacted]
Functionally cured SCD patients have the same risk of developing complications as the general (non-SCD) population	Functionally cured SCD patients have an increased risk (1.25) compared to the general (non-SCD) population	[redacted]	[redacted]	[redacted]
Cost per VOC event is £1,567	Cost per VOC event is £4,401 based on Pizzo et al., 2015	[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]
Age-specific SCD mortality estimates are applied	SCD HR adjustment to general population mortality rates is applied	[redacted]	[redacted]	[redacted]
Mortality inputs (hazard ratios) for SCD-related complications are: CKD: 9.57; pulmonary hypertension: 12.57; heart failure: 12.57	Mortality inputs (hazard ratios) for SCD-related complications are: CKD: 3.60; pulmonary hypertension: 2.34; heart failure: 1.51	[redacted]	[redacted]	[redacted]
Interaction between mortality from different complications is multiplicative	Interaction between mortality from different complications is additive	[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.

B.3.13 Subgroup analysis

No relevant subgroups have been identified who are likely to benefit more or less from exa-cel treatment. Thus, no subgroup analyses were conducted as part of this economic evaluation.

B.3.14 Benefits not captured in the QALY calculation

A large proportion of the SCD 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 treatment of sickle cell crises. These are likely to have knock-on consequences for the future success and employment of adolescents with SCD.

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

The model does not capture any productivity benefits such as improved employment rates of adults. A multi-country, cross-sectional survey across six geographical regions, including the UK, asked 2,145 patients about the impact of SCD on children, adolescents, and adults (258). It shows that 57% of patients from high income countries have reduced their working hours and 35% of them have lost their jobs completely due to SCD (258). Furthermore, the same study showed that 56% of patients from high income countries reported that SCD had a high impact on achievement at school, and 42% stated that SCD decreased motivation at school (258). Another study showed the societal benefits after HSCT treatment as healthy patients were able to be more productive which resulted in lower benefit payments and higher tax contributions (259).

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 SCD 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 for the SoC arm by comparing the model's predicted survival output with real-world estimates of survival reported in the literature. As exa-cel has not been approved for the treatment of SCD, there is limited evidence to assess face validity for this treatment. An analysis of the UK HES database from 2009 to 2018 by Piel *et al*, (2021) found the mean age at death for patients with SCD in England to be 46.7 years (73). Additionally, Vertex conducted an analysis of the mortality of patients with SCD with recurrent VOCs utilising CPRD/HES data from 2008–2018, and found the mean age of death in the SCD population was approximately 40 years of age (4). The mean age of death for patients treated with SoC was predicted to be approximately 44 years in the cost-effectiveness model.

External validation was conducted against the published economic assessment of SCD treatments conducted by the Institute for Clinical and Economic Review (198).

In addition, the prevalence of chronic complications predicted by the current model was compared with subgroup results from an analysis of US and UK claims data conducted by Vertex (4). Prevalence estimates were largely similar across most conditions (differences of <15%), except for the prevalence of neurocognitive impairment (47.6% in current model vs 14.0% and 9.6% in US and UK analyses, respectively). This substantial difference is likely due to underreporting of the condition. The datasets only capture neurocognitive impairment that is associated with a medical claim/record, and thus might not capture less

severe cases (4). It is to be noted that the prevalence predicted by the model were predicted at the end of the model time horizon. Furthermore, the prevalence of chronic complications predicted by the model were validated by external clinical experts who considered the estimates to be reasonable.

Further external validation of the model against the NICE submission of crizanlizumab (ID1406) was attempted; however, this was challenging since the crizanlizumab model results were redacted (150).

B.3.16 Interpretation and conclusions of economic evidence

As described in Section B.1.3.5, there remains a substantial unmet need for treatments that can address the huge burden posed by severe SCD, reducing the occurrence of acute pain events, chronic complications, and associated reduction in life expectancy. Exa-cel is projected to result in [redacted] less VOCs over the lifetime horizon relative to SoC. The expectation is this would also significantly reduce the need for hospitalisations. Support for this comes from the pivotal CLIMB SCD-121 study, where 40 of 41 patients with ≥60 days of follow-up after the last RBC transfusion for post-transplant support or SCD management remained free from inpatient hospitalisation for VOCs after exa-cel infusion throughout CLIMB SCD-121 and CLIMB-131, with a duration of 1.3 to 43.6 months.

Mean age at death in a cohort of severe SCD patients in the UK was 40.2 years (4). Exa-cel is modelled to increase life expectancy by [redacted] years compared to SoC. In doing so, exa-cel provides a paradigm shift in the management of SCD, and helps to address the health inequalities that persist, as described in Section 1.4.

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 limitation could lead to failure to adequately address health inequalities in the SCD population. The current submission endeavours to quantity the impact of exa-cel on health inequalities in SCD patients by applying published methods and the associated, published, weightings to incremental costs and QALYs.

Data for exa-cel was informed by the ongoing CLIMB SCD-121 trial (publicly available data presented at the EHA congresses in 2022 and 2023), which included 31 patients with SCD ages 12 to 34 years (162). The trial population is considered to be representative of the population expected to be treated for SCD in the UK. At the time of the most recent data-cut of the CLIMB SCD-121 trial, 28 of 29 patients with SCD were functionally cured after exa-cel infusion (169). Exa-cel may therefore provide a breakthrough solution for patients 12 years of age and older with recurrent VOCs who have β^S/β^S, β^S/β^0 or β^S/β^+, for whom a HLA-matched related HSC donor is not available.

B.4 References

1. Medicine and Healthcare Products Regulatory Agency. Guidance: Orphan Medicinal Products 2020 [Available from: .
2. Zaidi AU, Glaros AK, Lee S, Wang T, Bhojwani R, Morris E, et al. A systematic literature review of frequency of vaso-occlusive crises in sickle cell disease. Orphanet Journal of Rare Diseases. 2021;16(1).
3. Udeze C, Ly, N. F., Ingleby, C. et al. Mortality and clinical complications among patients with sickle cell disease with recurrent VOCs in England. British Journal of Haematology. 2023.
4. Vertex Pharmaceuticals Inc. Data on file. Sickle Cell Disease with recurrent VOCs and Transfusion-dependent β-thalassaemia: Economic and Clinical Burden of Disease in England. 2023.
5. Drahos J, Boateng-Kuffour A, Calvert M, Valentine A, Mason A, Pakbaz Z, et al. Health-Related Quality of Life, Disease Impacts, and Health Equity Concerns in Adults with Sickle Cell Disease with Recurrent Vaso-Occlusive Crises: Preliminary Results from a Global Longitudinal Survey. Blood. 2022;140(Supplement 1):1387-8.
6. Badawy SM, Beg U, Liem RI, Chaudhury S, Thompson AA. A systematic review of quality of life in sickle cell disease and thalassemia after stem cell transplant or gene therapy. Blood Adv. 2021;5(2):570-83.
7. Vertex Pharmaceuticals Inc. Data on File. Exa-cel Efficacy and Safety Update (16 April 2023). 2023.
8. St Martin A, Hebert KM, Serret-Larmande A, Jouhet V, Hughes E, Stedman J, et al. Long-term Survival after Hematopoietic Cell Transplant for Sickle Cell Disease Compared to the United States Population. Transplant Cell Ther. 2022;28(6):325 e1- e7.
9. Ngo DA, Aygun B, Akinsheye I, Hankins JS, Bhan I, Luo HY, et al. Fetal haemoglobin levels and haematological characteristics of compound heterozygotes for haemoglobin S and deletional hereditary persistence of fetal haemoglobin. British journal of haematology. 2012;156(2):259-64.
10. Sankaran VG, Orkin SH. The switch from fetal to adult hemoglobin. Cold Spring Harb Perspect Med. 2013;3(1):a011643-a.
11. Alsultan A, Ngo DA, Farrell JJ, Akinsheye I, Solovieff N, Ghabbour HA, et al. A functional promoter polymorphism of the δ-globin gene is a specific marker of the Arab-Indian haplotype. Am J Hematol. 2012;87(8):824-6.
12. Vertex Pharmaceuticals Inc. Data on file. Exa-cel UK HTA Advisory Board. 2022.
13. Rylatt A. No One's Listening: An Inquiry into the Avoidable Deaths and Failures of Care for Sickle Cell Patients in Secondary Care. 2021.
14. Frangoul H, Altshuler D, Cappellini MD, Chen Y-S, Domm J, Eustace BK, et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia. New England Journal of Medicine. 2020;384(3):252-60.
15. Bank A. Regulation of human fetal hemoglobin: new players, new complexities. Blood. 2006;107(2):435-43.
16. Conley CL, Weatherall DJ, Richardson SN, Shepard MK, Charache S. Hereditary persistence of fetal hemoglobin: a study of 79 affected persons in 15 Negro families in Baltimore. Blood. 1963;21:261-81.
17. Steinberg M. Targeting fetal hemoglobin expression to treat β hemoglobinopathies. Expert Opinion on Therapeutic Targets 2022;26(4):347-59.
18. Steinberg MH, Chui DH, Dover GJ, Sebastiani P, Alsultan A. Fetal hemoglobin in sickle cell anemia: a glass half full? Blood. 2014;123(4):481-5.

19. Adli M. The CRISPR tool kit for genome editing and beyond. Nat Commun. 2018;9(1):1911.
20. Barman NC, Khan NM, Islam M, Nain Z, Roy RK, Haque A, et al. CRISPR-Cas9: A Promising Genome Editing Therapeutic Tool for Alzheimer's Disease-A Narrative Review. Neurol Ther. 2020;9(2):419-34.
21. Kenyon M, Babic A. The European Blood and Marrow Transplantation Textbook for Nurses. 2018.
22. Wingard JR, Hsu J, Hiemenz JW. Hematopoietic stem cell transplantation: an overview of infection risks and epidemiology. Infect Dis Clin North Am. 2010;24(2):257-72.
23. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;4:18010.
24. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. Lancet. 2017;390(10091):311-23.
25. Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. New England Journal of Medicine. 2017;376(16):1561-73.
26. Dormandy E, James J, Inusa B, Rees D. How many people have sickle cell disease in the UK? J Public Health (Oxf). 2018;40(3):e291-e5.
27. National Health Service. National Haemoglobinopathy Registry Annual Data Report 2019/20. Available at https://nhr.mdsas.com/wp-content/uploads/2021/01/2020_12_NHR_AnnualReport201920_Final.pdf. 2020.
28. Adekile AD, Akbulut N, Azab AF, Al-Sharida S, Thomas D. The Sickle β-Thalassemia Phenotype. J Pediatr Hematol Oncol. 2017;39(5):327-31.
29. Ashley-Koch AOoGaDP, National Center for Environmental Health, Centers for Disease Control and PreventionAtlanta, GA;Yang, Q.;Birth Defects and Genetic Diseases Branch, Division of Birth Defects and Developmental Disabilities, National Center for Environmental Health, Centers for Disease Control and PreventionAtlanta, GA;Olney, R. S.;Birth Defects and Genetic Diseases Branch, Division of Birth Defects and Developmental Disabilities, National Center for Environmental Health, Centers for Disease Control and PreventionAtlanta, GA. Sickle Hemoglobin (Hb S) Allele and Sickle Cell Disease: A HuGE Review. American Journal of Epidemiology. 2000;151(9):839-45.
30. Steinberg MH. Fetal Hemoglobin in Sickle Hemoglobinopathies: High HbF Genotypes and Phenotypes. Journal of clinical medicine. 2020;9(11):3782.
31. Darbari DS, Wang Z, Kwak M, Hildesheim M, Nichols J, Allen D, et al. Severe painful vaso-occlusive crises and mortality in a contemporary adult sickle cell anemia cohort study. PloS one. 2013;8(11):e79923-e.
32. Elmariah H, Garrett ME, De Castro LM, Jonassaint JC, Ataga KI, Eckman JR, et al. Factors associated with survival in a contemporary adult sickle cell disease cohort. Am J Hematol. 2014;89(5):530-5.
33. National Health Service. National Haemoglobinopathy Registry Annual Data Report 2020/21. Available at https://nhr.mdsas.com/wp-content/uploads/2022/03/NHR_DataReport2021.pdf. 2021.
34. National Heart Lung and Blood Institute. Evidence-Based Management of Sickle Cell Disease. Available at https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf 2014 [
35. National Health Service. The National Haemoglobinopathy Register. Available at https://nhr.mdsas.com/ [Available from: https://nhr.mdsas.com/.
36. de Montalembert M, Voskaridou E, Oevermann L, Cannas G, Habibi A, Loko G, et al. Real-Life experience with hydroxyurea in patients with sickle cell disease: Results from the prospective ESCORT-HU cohort study. Am J Hematol. 2021;96(10):1223-31.

37. Gardner RV. Sickle Cell Disease: Advances in Treatment. Ochsner J. 2018;18(4):377-89.
38. Matte A, Zorzi F, Mazzi F, Federti E, Olivieri O, De Franceschi L. New Therapeutic Options for the Treatment of Sickle Cell Disease. Mediterr J Hematol Infect Dis. 2019;11(1):e2019002-e.
39. Rai P, Ataga KI. Drug Therapies for the Management of Sickle Cell Disease. F1000Res. 2020;9:F1000 Faculty Rev-592.
40. Fitzhugh CD, Hsieh MM, Allen D, Coles WA, Seamon C, Ring M, et al. Hydroxyurea-Increased Fetal Hemoglobin Is Associated with Less Organ Damage and Longer Survival in Adults with Sickle Cell Anemia. PLoS One. 2015;10(11):e0141706.
41. Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E, et al. Pain in Sickle Cell Disease. New England Journal of Medicine. 1991;325(1):11-6.
42. Eltzschig HK, Eckle T. Ischemia and reperfusion-from mechanism to translation. Nat Med. 2011;17(11):1391-401.
43. Ochocinski D, Dalal M, Black LV, Carr S, Lew J, Sullivan K, et al. Life-Threatening Infectious Complications in Sickle Cell Disease: A Concise Narrative Review. Frontiers in Pediatrics. 2020;8.
44. Sundd P, Gladwin MT, Novelli EM. Pathophysiology of Sickle Cell Disease. Annu Rev Pathol. 2019;14:263-92.
45. da Silva Junior GB, Daher EDF, da Rocha FAC. Osteoarticular involvement in sickle cell disease. Rev Bras Hematol Hemoter. 2012;34(2):156-64.
46. McGann PT, Nero AC, Ware RE. Current management of sickle cell anemia. Cold Spring Harb Perspect Med. 2013;3(8).
47. Alkindi S, Panjwani V, Al-Rahbi S, Al-Saidi K, Pathare AV. Iron Overload in Patients With Heavily Transfused Sickle Cell Disease-Correlation of Serum Ferritin With Cardiac T2(*) MRI (CMRTools), Liver T2(*) MRI, and R2-MRI (Ferriscan®). Front Med (Lausanne). 2021;8:731102.
48. Chaparro CM, Suchdev PS. Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. Ann N Y Acad Sci. 2019;1450(1):15-31.
49. Howard J. Sickle cell disease: when and how to transfuse. Hematology Am Soc Hematol Educ Program. 2016;2016(1):625-31.
50. Novelli EM, Gladwin MT. Crises in Sickle Cell Disease. Chest. 2016;149(4):1082-93.
51. Brandow AM, Zappia KJ, Stucky CL. Sickle cell disease: a natural model of acute and chronic pain. Pain. 2017;158 Suppl 1(Suppl 1):S79-s84.
52. Nolan VG, Zhang Y, Lash T, Sebastiani P, Steinberg MH. Association between wind speed and the occurrence of sickle cell acute painful episodes: results of a case-crossover study. Br J Haematol. 2008;143(3):433-8.
53. Veluswamy S, Shah P, Denton CC, Chalacheva P, Khoo MCK, Coates TD. Vaso-Occlusion in Sickle Cell Disease: Is Autonomic Dysregulation of the Microvasculature the Trigger? J Clin Med. 2019;8(10).
54. Osunkwo I, Andemariam B, Minniti CP, Inusa BPD, El Rassi F, Francis-Gibson B, et al. Impact of sickle cell disease on patients' daily lives, symptoms reported, and disease management strategies: Results from the international Sickle Cell World Assessment Survey (SWAY). American journal of hematology. 2021;96(4):404-17.
55. Niihara Y, Miller ST, Kanter J, Lanzkron S, Smith WR, Hsu LL, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. New England Journal of Medicine. 2018;379(3):226-35.

56. Inusa B, James J, Rajkovic-Hooley O, Bailey T, Medalla G, Taylor B. UK Patient Perceptions on the Symptomatic and Emotional Burden of Vaso-Occlusive Crises Resulting From Sickle Cell Disease. British Journal of Haematology. 2020.
57. Gardner K, Douiri A, Allman M, Drasar E, Awogbade M, Thein SL. Survival in Sickle Cell Disease: Data from a Well-Resourced, National Health System Setting. Blood. 2015;126(23):71.
58. Bailey M, Abioye A, Morgan G, Burke T, Disher T, Brown S, et al. Relationship between Vaso-Occlusive Crises and Important Complications in Sickle Cell Disease Patients. Blood. 2019;134(Supplement_1):2167-.
59. Castro O, Brambilla DJ, Thorington B, Reindorf CA, Scott RB, Gillette P, et al. The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. Blood. 1994;84(2):643-9.
60. Vichinsky EP, Styles LA, Colangelo LH, Wright EC, Castro O, Nickerson B. Acute chest syndrome in sickle cell disease: clinical presentation and course. Cooperative Study of Sickle Cell Disease. Blood. 1997;89(5):1787-92.
61. Howard J, Hart N, Roberts-Harewood M, Cummins M, Awogbade M, Davis B. Guideline on the management of acute chest syndrome in sickle cell disease. British Journal of Haematology. 2015;169(4):492-505.
62. Morgan G, Burke T, Herquelot E, Lamarsalle L, Brown S, Bonner A, et al. PSY27 AN EXAMINATION OF THE BURDEN OF SICKLE CELL DISEASE AMONG ADULTS IN ENGLAND. Value in Health. 2019;22:S906.
63. Jain S, Bakshi N, Krishnamurti L. Acute Chest Syndrome in Children with Sickle Cell Disease. Pediatr Allergy Immunol Pulmonol. 2017;30(4):191-201.
64. Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, et al. Causes and Outcomes of the Acute Chest Syndrome in Sickle Cell Disease. New England Journal of Medicine. 2000;342(25):1855-65.
65. Allareddy V, Roy A, Lee MK, Nalliah RP, Rampa S, Allareddy V, et al. Outcomes of acute chest syndrome in adult patients with sickle cell disease: predictors of mortality. PloS one. 2014;9(4):e94387-e.
66. Arnold S, Jin Z, Weinberg A, Bishop J, Sands S, Licursi M, et al. Allogeneic Stem Cell Transplantation for Children with Sickle Cell Disease Achieves Quality of Life Similar to Normal Children and Is Cost Effective. Biology of Blood and Marrow Transplantation. 2014;20(2):S79.
67. Cecchini J, Fartoukh M. Sickle cell disease in the ICU. Curr Opin Crit Care. 2015;21(6):569-75.
68. Olujohungbe A, Burnett AL. How I manage priapism due to sickle cell disease. British Journal of Haematology. 2013;160(6):754-65.
69. National Institute for Health and Care Excellence. Clinical Knowledge Summaries: What are the complications of sickle cell disease? 2021 [Available from: https://cks.nice.org.uk/topics/sickle-cell-disease/background-information/complications/.
70. Sickle Cell Society. Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK 2018 [Available from: https://www.sicklecellsociety.org/wp-content/uploads/2018/05/Standards-for-the-Clinical-Care-of-Adults-with-Sickle-Cell-in-the-UK-2018.pdf.
71. Idris IM, Galadanci JA, Abba A, Mashi SA, Uzoma A, Bonnet KR, et al. Cross Sectional Survey of Priapism and Sexual Dysfunction in 353 Men with Sickle Cell Disease. Blood. 2019;134(Supplement_1):2302-.
72. Alvaia MA, Maia HAAdS, Nelli AdM, Guimarães COS, Carvalho ESdS, Netto JMB, et al. Prevalence of priapism in individuals with sickle cell disease and implications on male sexual function. Einstein (Sao Paulo). 2020;18:eAO5070-eAO.

73. Piel FB, Jobanputra M, Gallagher M, Weber J, Laird SG, McGahan M. Co-morbidities and mortality in patients with sickle cell disease in England: A 10-year cohort analysis using hospital episodes statistics (HES) data. Blood Cells Mol Dis. 2021;89:102567.
74. Kane I, Nagalli S. Splenic Sequestration Crisis. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.
75. Ladu AI, Aiyenigba AO, Adekile A, Bates I. The spectrum of splenic complications in patients with sickle cell disease in Africa: a systematic review. Br J Haematol. 2021;193(1):26-42.
76. Boga C, Ozdogu H. Pregnancy and sickle cell disease: A review of the current literature. Critical Reviews in Oncology/Hematology. 2016;98:364-74.
77. Knight M, Bunch K, Patel R, Shakespeare J, Kotnis R, Kenyon S, et al. MBRRACE-UK: Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2018-20. 2022.
78. Venkataraman A, Adams RJ. Neurologic complications of sickle cell disease. Handb Clin Neurol. 2014;120:1015-25.
79. DeBaun MR, Kirkham FJ. Central nervous system complications and management in sickle cell disease. Blood. 2016;127(7):829-38.
80. Jorgensen DR, Metti A, Butters MA, Mettenburg JM, Rosano C, Novelli EM. Disease severity and slower psychomotor speed in adults with sickle cell disease. Blood Adv. 2017;1(21):1790-5.
81. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular Accidents in Sickle Cell Disease: Rates and Risk Factors. Blood. 1998;91(1):288-94.
82. Jitraruch S, Fitzpatrick E, Deheragoda M, Deganello A, Mieli-Vergani G, Height S, et al. Autoimmune Liver Disease in Children with Sickle Cell Disease. J Pediatr. 2017;189:79-85.e2.
83. Coats T, Gardner K, Thein SL. Gallstones in Sickle Cell Disease: A Single Institution Experience. Blood. 2014;124(21):4939-.
84. Lacaille F, Allali S, de Montalembert M. The Liver in Sickle Cell Disease. Journal of Pediatric Gastroenterology and Nutrition. 2021;72(1).
85. Fitzhugh CD, Lauder N, Jonassaint JC, Telen MJ, Zhao X, Wright EC, et al. Cardiopulmonary complications leading to premature deaths in adult patients with sickle cell disease. Am J Hematol. 2010;85(1):36-40.
86. Gladwin MT. Cardiovascular complications and risk of death in sickle-cell disease. Lancet. 2016;387(10037):2565-74.
87. Voskaridou E, Christoulas D, Terpos E. Sickle-cell disease and the heart: review of the current literature. Br J Haematol. 2012;157(6):664-73.
88. Mehari A, Klings ES. Chronic Pulmonary Complications of Sickle Cell Disease. Chest. 2016;149(5):1313-24.
89. Mehari A, Alam S, Tian X, Cuttica MJ, Barnett CF, Miles G, et al. Hemodynamic predictors of mortality in adults with sickle cell disease. Am J Respir Crit Care Med. 2013;187(8):840-7.
90. Adesina O, Brunson A, Keegan THM, Wun T. Osteonecrosis of the femoral head in sickle cell disease: prevalence, comorbidities, and surgical outcomes in California. Blood Adv. 2017;1(16):1287-95.
91. Smith WR, Penberthy LT, Bovbjerg VE, McClish DK, Roberts JD, Dahman B, et al. Daily assessment of pain in adults with sickle cell disease. Ann Intern Med. 2008;148(2):94-101.

92. Thompson WE, Eriator I. Pain control in sickle cell disease patients: use of complementary and alternative medicine. Pain Med. 2014;15(2):241-6.
93. Ataga KI, Derebail VK, Archer DR. The glomerulopathy of sickle cell disease. Am J Hematol. 2014;89(9):907-14.
94. Nath KA, Hebbel RP. Sickle cell disease: renal manifestations and mechanisms. Nat Rev Nephrol. 2015;11(3):161-71.
95. Sharpe CC, Thein SL. Sickle cell nephropathy - a practical approach. Br J Haematol. 2011;155(3):287-97.
96. McPherson Yee M, Jabbar SF, Osunkwo I, Clement L, Lane PA, Eckman JR, et al. Chronic kidney disease and albuminuria in children with sickle cell disease. Clin J Am Soc Nephrol. 2011;6(11):2628-33.
97. Ephraim RK, Osakunor DN, Cudjoe O, Oduro EA, Asante-Asamani L, Mitchell J, et al. Chronic kidney disease is common in sickle cell disease: a cross-sectional study in the Tema Metropolis, Ghana. BMC Nephrol. 2015;16:75.
98. Cecchini J, Lionnet F, Djibré M, Parrot A, Stojanovic KS, Girot R, et al. Outcomes of adult patients with sickle cell disease admitted to the ICU: a case series*. Crit Care Med. 2014;42(7):1629-39.
99. Gardner K, Bell C, Bartram JL, Allman M, Awogbade M, Rees DC, et al. Outcome of adults with sickle cell disease admitted to critical care - experience of a single institution in the UK. Br J Haematol. 2010;150(5):610-3.
100. van Tuijn CFJ, Schimmel M, van Beers EJ, Nur E, Biemond BJ. Prospective evaluation of chronic organ damage in adult sickle cell patients: A seven-year follow-up study. Am J Hematol. 2017;92(10):E584-E90.
101. Steinberg MH, McCarthy WF, Castro O, Ballas SK, Armstrong FD, Smith W, et al. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. Am J Hematol. 2010;85(6):403-8.
102. Mayes S, Baker A. Family Resilience and Chronic Illness: SpringerLink; 2017.
103. Inusa B, James J, Rajkovic-Hooley O, Medalla G, Taylor B. Patients' and Health Care Professionals' Perspectives on Treatment Goals in Sickle Cell Disease –A UK Perspective: Results From the International Sickle Cell World Assessment Survey (SWAY). British Journal of Haematology. 2020.
104. McClish DK, Penberthy LT, Bovbjerg VE, Roberts JD, Aisiku IP, Levenson JL, et al. Health related quality of life in sickle cell patients: the PiSCES project. Health Qual Life Outcomes. 2005;3:50.
105. Anie KA. Psychological complications in sickle cell disease. Br J Haematol. 2005;129(6):723-9.
106. Toumi ML, Merzoug S, Boulassel MR. Does sickle cell disease have a psychosomatic component? A particular focus on anxiety and depression. Life Sci. 2018;210:96-105.
107. Rizio AA, Bhor M, Lin X, McCausland KL, White MK, Paulose J, et al. The relationship between frequency and severity of vaso-occlusive crises and health-related quality of life and work productivity in adults with sickle cell disease. Qual Life Res. 2020;29(6):1533-47.
108. Bulgin D, Tanabe P, Jenerette C. Stigma of Sickle Cell Disease: A Systematic Review. Issues Ment Health Nurs. 2018;39(8):675-86.
109. Correll DJ. The Measurement of Pain: Objectifying the Subjective. In Pain Management (second edition)2007. 197-211 p.
110. Drahos J. Health-related quality of life impacts associated with sickle cell disease in the United States and United Kingdom: a qualitative assessment. Oral Presentation. International Society for Quality of Life Research. 2023.

111. Barcelos G, Besser M, O'Flaherty E, O'Sullivan S, Bourke S, Oluboyede Y, et al. PCR116 Quality of Life of and Economic Burden on Caregivers of Individuals With Sickle Cell Disease in the UK and France: A Cross-Sectional Survey. Value in Health. 2022;25(12):S1-S546.
112. van den Tweel XW, Hatzmann J, Ensink E, van der Lee JH, Peters M, Fijnvandraat K, et al. Quality of life of female caregivers of children with sickle cell disease: a survey. Haematologica. 2008;93(4):588-93.
113. Jobanputra M, Gallagher M, Weber J, Laird SG, McGahan M, Piel FB. Hospital Resource Usage and Costs for Patients With Sickle Cell Disease in England: a 10-year Cohort Analysis 2021 [Available from: https://assets.researchsquare.com/files/rs-920004/v1/d301dc5c-206d-4fbd-8d44-f9ca77397c6d.pdf?c=1667991570.
114. Desai RJ, Mahesri M, Globe D, Mutebi A, Bohn R, Achebe M, et al. Clinical outcomes and healthcare utilization in patients with sickle cell disease: a nationwide cohort study of Medicaid beneficiaries. Ann Hematol. 2020;99(11):2497-505.
115. Pizzo E, Laverty AA, Phekoo KJ, AlJuburi G, Green SA, Bell D, et al. A retrospective analysis of the cost of hospitalizations for sickle cell disease with crisis in England, 2010/11. Journal of public health (Oxford, England). 2015;37(3):529-39.
116. Shah N, Bhor M, Xie L, Paulose J, Yuce H. Medical Resource Use and Costs of Treating Sickle Cell-related Vaso-occlusive Crisis Episodes: A Retrospective Claims Study. J Health Econ Outcomes Res. 2020;7(1):52-60.
117. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N, et al. Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. British Journal of Haematology. 2017;176(2):179-91.
118. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N, et al. Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion. British Journal of Haematology. 2017;176(2):192-209.
119. Qureshi A, Kaya B, Pancham S, Keenan R, Anderson J, Akanni M, et al. Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. Br J Haematol. 2018;181(4):460-75.
120. [TA743]. NTag. NICE Technology appraisal guidance [TA743]. Crizanlizumab for preventing sickle cell crises in sickle cell disease. 2021 [cited 2021. Evidence-based recommendations on crizanlizumab for preventing sickle cell crises in people aged 16 or over with sickle cell disease.]. Available from: https://www.nice.org.uk/guidance/ta743.
121. National Institute for Health and Care Excellence. CG143 Sickle cell disease: managing acute painful episodes in hospital 2012 [Available from: https://www.nice.org.uk/guidance/cg143.
122. European Medicines Agency. Adakveo. 2023.
123. National Institute for Health and Care Excellence. Crizanlizumab for preventing sickle cell crises in sickle cell disease. Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10470. 2020.
124. National Institute for Health and Care Excellence. Voxelotor for treating sickle cell disease. Available at https://www.nice.org.uk/guidance/proposed/gid-ta10505. 2021.
125. Vertex Pharmaceuticals. Data on file. Vertex Haemoglobinopathies Virtual UK Advisory Board Meeting. 2021.
126. NHS England. Clinical Commissioning Policy: Allogenic Haematopoietic Stem Cell Transplantation for adults with sickle cell disease. 2019.
127. NHS England. Clinical Commissioning Policy: Allogeneic haematopoietic stem cell transplantation for adults with sickle cell disease 2020 [Available from: https://www.england.nhs.uk/publication/allogeneic-haematopoietic-stem-cell-transplantation-for-adults-with-sickle-cell-disease/.

128. British Society of Blood and Marrow Transplantation and Cellular Therapies. UK Paed BMT HSCT Indications Table 2015 [Available from: https://bsbmtct.org/indications-table/.
129. National Haemoglobinopathy Panel (NHP). National Haemoglobinopathy Panel Guidelines. Available at https://www.nationalhaempanel-nhs.net/nhpguidelines 2022 [
130. South Thames Sickle Cell & Thalassaemia Network (STSTN). Haemoglobinopathy Coordinating Centres. Available at http://www.ststn.co.uk/haemoglobinopathy-coordinating-centres/ 2020 [
131. Society SC. Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK. Available at https://www.sicklecellsociety.org/wp-content/uploads/2018/05/Standards-for-the-Clinical-Care-of-Adults-with-Sickle-Cell-in-the-UK-2018.pdf 2018 [
132. Society SC. Sickle Cell Disease in Childhood Standards and Recommendations for Clinical Care. Available at https://www.sicklecellsociety.org/wp-content/uploads/2019/11/SCD-in-Childhood_Final-version-1.pdf 2019 [
133. Gluckman E, Cappelli B, Bernaudin F, Labopin M, Volt F, Carreras J, et al. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. Blood. 2017;129(11):1548-56.
134. British Society of Blood and Marrow Transplantation and Cellular Therapy. UK & ROI Transplant Activity Table by Disease 2021 [Available from: https://bsbmtct.org/activity/2021/.
135. McGann PT, Ware RE. Hydroxyurea Therapy for Sickle Cell Anaemia. Expert Opinion on Drug Safety. 2015;14(11):1-20.
136. Nevitt SJ, Jones AP, Howard J. Hydroxyurea (hydroxycarbamide) for sickle cell disease. Cochrane Database Syst Rev. 2017;4(4):CD002202-CD.
137. NHR Information service. Number of Patients by Diagnosis 2019 [Available from: http://nhr.mdsas.com/wp-content/uploads/2019/04/NumberPatientsDiagnosis.pdf.
138. National Institute for Health and Care Excellence. Final appraisal document: Crizanlizumab for preventing sickle cell crises in sickle cell disease. Available at https://www.nice.org.uk/guidance/ta743/documents/final-appraisal-determination-document 2021 [
139. Chou ST. Transfusion therapy for sickle cell disease: a balancing act. Hematology Am Soc Hematol Educ Program. 2013;2013:439-46.
140. Tormey CA, Hendrickson JE. Routine non-ABO blood group antigen genotyping in sickle cell disease: the new frontier in pretransfusion testing? Transfusion. 2015;55(6pt2):1374-7.
141. Campbell-Lee SA, Kittles RA. Red Blood Cell Alloimmunization in Sickle Cell Disease: Listen to Your Ancestors. Transfusion Medicine and Hemotherapy. 2014;41(6):431-5.
142. Gragert L, Eapen M, Williams E, Freeman J, Spellman S, Baitty R, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med. 2014;371(4):339-48.
143. Shah N, Bhor M, Xie L, Halloway R, Arcona S, Paulose J, et al. Evaluation of Vaso-occlusive Crises in United States Sickle Cell Disease Patients: A Retrospective Claims-based Study. J Health Econ Outcomes Res. 2019;6(3):106-17.
144. Shah N, Beenhouwer D, Broder MS, Bronte-Hall L, De Castro LM, Gibbs SN, et al. Development of a Severity Classification System for Sickle Cell Disease. ClinicoEconomics and Outcomes Research. 2020;Volume 12:625-33.
145. Vertex Pharmaceuticals Inc. Data on file. Vertex Internal Forecasts (2021-2022). 2022.

146. Payne AB, Mehal JM, Chapman C, Haberling DL, Richardson LC, Bean CJ, et al. Trends in Sickle Cell Disease-Related Mortality in the United States, 1979 to 2017. Ann Emerg Med. 2020;76(3s):S28-s36.
147. Elguero E, Délicat-Loembet LM, Rougeron V, Arnathau C, Roche B, Becquart P, et al. Malaria continues to select for sickle cell trait in Central Africa. Proc Natl Acad Sci U S A. 2015;112(22):7051-4.
148. Global Health Data Exchange. GBD Results Tool 2019 [Available from: http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/4de92fcc7248e0cb8937ce7e383e735c.
149. GBD Sickle Cell Disease Collaborators. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000-2021: a systematic analysis from the Global Burden of Disease Study 2021. Lancet Haematol. 2023.
150. National Institute for Health and Care Excellence. Committee papers: Crizanlizumab for preventing sickle cell crises in sickle cell disease. Available at https://www.nice.org.uk/guidance/ta743/documents/committee-papers 2020 [
151. Kirby T. Evidence Mounts on the Disproportionate Effect of COVID-19 on Ethnic Minorities. The Lancet Respiratory Medicine. 2020;8:547-8.
152. Razai MS, Kankam HKN, Majeed A, Esmail A, Williams DR. Mitigating ethnic disparities in covid-19 and beyond. BMJ. 2021;372:m4921.
153. UK Parliament. Sickle Cell Diseases: Health Services. Available at https://questions-statements.parliament.uk/written-questions/detail/2019-05-21/256974 2019 [
154. Jenerette C, Brewer C. Health-Related Stigma in Young Adults with Sickle Cell Disease. Journal of the National Medical Association. 2010;102(11):1050-5.
155. Idowu M, Badejoko S, Rowan P, Juneja HS. Occupational History for Forty Adults with Sickle Cell Disease Compared with Healthy Siblings. Blood. 2014;124(21):4937-.
156. Lee L, Smith-Whitley K, Banks S, Puckrein G. Reducing Health Care Disparities in Sickle Cell Disease: A Review. Public Health Rep. 2019;134(6):599-607.
157. da Cunha Gomes EG, Machado LAF, de Oliveira LC, Neto JFN. The erythrocyte alloimmunisation in patients with sickle cell anaemia: a systematic review. Transfus Med. 2019;29(3):149-61.
158. ClinicalTrials.gov. A Safety and Efficacy Study Evaluating CTX001 in Subjects With Severe Sickle Cell Disease. Available at https://www.clinicaltrials.gov/ct2/show/NCT03745287 2022 [
159. de la Fuente J, Locatelli F, Frangoul H, Corbacioglu S, Wall D, Cappellini M, et al. 5612617 EFFICACY AND SAFETY OF A SINGLE DOSE OF EXAGAMGLOGENE AUTOTEMCEL FOR TRANSFUSION-DEPENDENT-THALASSEMIA AND SEVERE SICKLE CELL DISEASE. HemaSphere. 2023;7(S1).
160. Frangoul H, Bobruff Y, Cappellini MD, Corbacioglu S, Fernandez CM, de la Fuente J, et al. Safety and Efficacy of CTX001™in Patients With Transfusion-Dependent β-Thalassemia or Sickle Cell Disease: Early Results From the CLIMB THAL-111 and CLIMB SCD-121 Studies of Autologous CRISPR-CAS9-Modified CD34+Hematopoietic Stem and Progenitor Cells 2020 [Available from: https://crisprtx.com/assets/uploads/2020-ASH-Presentation-Frangoul_CTX001-HEME.pdf.
161. Grupp S, Bloberger N, Campbell C, Carroll C, Hankins JS, Ho TW, et al. CTX001™ for Sickle Cell Disease: Safety and Efficacy Results from the Ongoing CLIMB SCD-121 Study of Autologous CRISPR-Cas9-Modified CD34+ Hematopoietic Stem and Progenitor Cells. The European Hematology Association; Virtual2021.

162. Locatelli F, Frangoul H, Corbacioglu S, Fuente J, Wall D, Cappellini MD, et al. Efficacy and Safety of a Single Dose of Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease. 27th Congress of the European Hematology Association (EHA); Virtual2022.
163. Soni S, Frangoul H, Bobruff Y, Cappellini MD, Corbacioglu S, Fernandez CM, et al. Safety and Efficacy of CTX001 in Patients with Transfusion-Dependent β-Thalassemia (TDT) or Sickle Cell Disease (SCD): Early Results from the Climb THAL-111 and Climb SCD-121 Studies of Autologous CRISPR-Cas9-Modified CD34+ Hematopoietic Stem and Progenitor Cells (HSPCs). Transplantation and Cellular Therapy. 2021;27(3, Supplement):S72-S3.
164. Frangoul H, Locatelli F, Bhatia M, Corbacioglu S, de la Fuente J, Wall D, et al., editors. Efficacy and Safety of a Single Dose of ExagamglogeneAutotemcelfor Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease. ASH; 2022.
165. Locatelli F, Lang P, Corbacioglu S, Li A, de la Fuente J, Wall D, et al., editors. Transfusion Independence and Elimination of Vaso-Occlusive Crises After Exagamglogene Autotemcel in Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease. EHA; 2023.
166. Vertex Pharmaceuticals Inc. Data on file. CLIMB SCD-121 Interim Clinical Study Report. 2022.
167. Vertex Pharmaceuticals Inc. Data on file. CLIMB-131 Interim Clinical Study Report. 2022.
168. Vertex Pharmaceuticals Inc. Data on file. Clinical Study Protocol: A Phase 1/2/3 Study to Evaluate the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (CTX001) in Subjects With Severe Sickle Cell Disease. Study Number: CTX001-121 Version 6.4 (EUR). 2021.
169. da Guarda CC, Yahouédéhou SCMA, Santiago RP, Neres JSdS, Fernandes CFdL, Aleluia MM, et al. Sickle cell disease: A distinction of two most frequent genotypes (HbSS and HbSC). PLOS ONE. 2020;15(1):e0228399.
170. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Adv. 2020;4(2):327-55.
171. Cahill CR, Leach JM, McClure LA, Irvin MR, Zakai NA, Naik R, et al. Sickle cell trait and risk of cognitive impairment in African-Americans: The REGARDS cohort. EClinicalMedicine. 2019;11:27-33.
172. Smith-Whitley K, Zhao H, Hodinka RL, Kwiatkowski J, Cecil R, Cecil T, et al. Epidemiology of human parvovirus B19 in children with sickle cell disease. Blood. 2004;103(2):422-7.
173. Vertex Pharmaceuticals Inc. Data on File. Exagamglogene Autotemcel (exa-cel) KRM CTX001-121/131 Day 120 Update. 2023.
174. Powars DR, Weiss JN, Chan LS, Schroeder WA. Is there a threshold level of fetal hemoglobin that ameliorates morbidity in sickle cell anemia? Blood. 1984;63(4):921-6.
175. Akinsheye I, Alsultan A, Solovieff N, Ngo D, Baldwin CT, Sebastiani P, et al. Fetal hemoglobin in sickle cell anemia. Blood. 2011;118(1):19-27.
176. Steinberg MH, Sebastiani P. Genetic modifiers of sickle cell disease. American journal of hematology. 2012;87(8):795-803.
177. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. Blood. 2014;124(3):344-53.
178. Henry EB, Barry LE, Hobbins AP, McClure NS, O'Neill C. Estimation of an Instrument-Defined Minimally Important Difference in EQ-5D-5L Index Scores Based on

Scoring Algorithms Derived Using the EQ-VT Version 2 Valuation Protocols. Value Health. 2020;23(7):936-44.
179. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.
180. Shah J, Shacham, S., Kauffman, M., Daniele, P., Tomaras, D. Health-related quality of life and utility outcomes with selinexor in relapsed/refractory diffuse large B-cell lymphoma. Future Oncology. 2021;17(11):1295-310.
181. Maziarz RT, Waller EK, Jaeger U, Fleury I, McGuirk J, Holte H, et al. Patient-reported long-term quality of life after tisagenlecleucel in relapsed/refractory diffuse large B-cell lymphoma. Blood Adv. 2020;4(4):629-37.
182. CADTH. CADTH Common Drug Review Clinical Review Report: LETERMOVIR (PREVYMIS). 2018.
183. McQuellon RP, Russell GB, Cella DF, Craven BL, Brady M, Bonomi A, et al. Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. Bone Marrow Transplant. 1997;19(4):357-68.
184. Norman RG, Sloan AJ, Wyrwich WK. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Journal Medical Care. 2003;41(5):582-92.
185. Keller S, Yang M, Treadwell M, Werner EM, Hassell KL. Patient reports of health outcome for adults living with sickle cell disease: development and testing of the ASCQ-Me item banks. Health Qual Life Outcomes. 2014;12(125):1-11.
186. Measures H. Meaningful Change for PROMIS® - Estimates for the magnitude of change that corresponds to “important” change are published. [Available from: https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/meaningful-change.
187. Pharmaceuticals V. Data on File. CTX001 SCD PRO Review for MAA D120 Update. 2023.
188. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017;376(5):429-39.
189. Vertex Pharmaceuticals Inc. Data on File. Exagamglogene Autotemcel (exa-cel) for the Treatment of Sickle Cell Disease: Indirect treatment comparison. 2023.
190. Howard J, Ataga KI, Brown RC, Achebe M, Nduba V, El-Beshlawy A, et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol. 2021;8(5):e323-e33.
191. Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. New England Journal of Medicine. 2019;381(6):509-19.
192. Pharmaceuticals V. Data on File. D120 Appendices - AEs Occuring in >5% Patients (Table 14.3.2.4.1). 2023.
193. ClinicalTrials.gov. A Long-term Follow-up Study in Subjects Who Received CTX001 (CLIMB-131). Available at https://clinicaltrials.gov/ct2/show/NCT04208529 2022 [
194. Beaudoin F, Richardson M, Richardson M, Synnott P, Lancaster V, Fluetsch N, et al. Betibeglogene Autotemcel for Beta Thalassemia: Effectiveness and Value; Evidence Report: Institute for Clinical and Economic Review; 2022 [Available from: https://icer.org/wp-content/uploads/2021/11/ICER_Beta-Thalassemia_Evidence-Report_060222-1.pdf.

195. Colombatti R, Sangarappillai C, Soriano M, Bestwick J, Hann W, Wieczorek K, et al. Severe Acute Complications of Sickle Cell Disease in Two Expert Referral Centers (UK and Italy): Natural History Studies Highlight Ongoing Unmet Need for Effective Disease Modifying or Curative Therapies. Blood. 2021;138:3093.
196. National Health Service. Overweight and obesity in adults and children data tables. Available at https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2019/health-survey-for-england-2019-data-tables 2019 [
197. Chawla A, Sprinz PG, Welch J, Heeney M, Usmani N, Pashankar F, et al. Weight status of children with sickle cell disease. Pediatrics. 2013;131(4):e1168-73.
198. Bradt P, Spackman E, Synnott PG, Chapman R, Beinfeld M, Rind DM, et al. Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value. Institute for Clinical and Economic Review, January 23, 2020 2021 [Available from: https://icer.org/wp-content/uploads/2021/02/ICER_SCD_Evidence-Report_031220-FOR-PUBLICATION.pdf.
199. Singh A, Minniti C. Leg Ulceration in Sickle Cell Disease: An Early and Visible Sign of End-Organ Disease. 2016.
200. Yeruva SL, Paul Y, Oneal P, Nouraie M. Renal Failure in Sickle Cell Disease: Prevalence, Predictors of Disease, Mortality and Effect on Length of Hospital Stay. Hemoglobin. 2016;40(5):295-9.
201. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2022 [
202. Wang HM, Worly BL. Inequities in Inpatient Obstetrics Pain Management and Evaluation: Age, Race, Mental Health, and Obesity. Matern Child Health J. 2023;27(3):538-47.
203. Vertex Pharmaceuticals Incorporated. Data on file SCD Complication inputs Targeted Literature Search. 2023.
204. American Academy of Ophthalmology. Sickle Cell Retinopathy. Available at https://eyewiki.org/Sickle_Cell_Retinopathy [
205. Stevenson E, Tanabe P, Knisely M, Masese R, Bulgin D, Preiss L, et al. Infertility and treatment-seeking practices among females and males with sickle cell disease in the Sickle Cell Disease Implementation Consortium registry. Pediatr Blood Cancer. 2023;70(7):e30356.
206. National Institute for Health and Care Excellence. Committee papers: Betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia. Available at https://www.nice.org.uk/guidance/gid-ta10334/documents/committee-papers 2020 [
207. Datta J, Palmer MJ, Tanton C, Gibson LJ, Jones KG, Macdowall W, et al. Prevalence of infertility and help seeking among 15 000 women and men. Hum Reprod. 2016;31(9):2108-18.
208. British Menopause Society. Menopause Practice Standards. 2022.
209. Office for National Statistics. National life tables, England & Wales (2018-2020). Available at https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables [
210. Fouzia N, Kulkarni UP, Devasia AJ, Korula A, Lakshmi KM, Abraham A, et al. Impact of Graft Versus Host Disease on Outcome of Allogeneic Haematopoietic Stem Cell Transplantation for Thalassemia Major - Comparison of Bone Marrow Vs Peripheral Blood Stem Cell Grafts. Blood. 2019;134:4537.

211. Brunson A, Lei A, Rosenberg AS, White RH, Keegan T, Wun T. Increased incidence of VTE in sickle cell disease patients: risk factors, recurrence and impact on mortality. Br J Haematol. 2017;178(2):319-26.
212. Gardner K, Douiri A, Drasar E, Allman M, Mwirigi A, Awogbade M, et al. Survival in adults with sickle cell disease in a high-income setting. Blood. 2016;128(10):1436-8.
213. Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. N Engl J Med. 2019;381(6):509-19.
214. US Food and Drug Administration. Oral L-Glutamine Powder For The Treatment of Sickle Cell Disease: Sponsor Briefing Document. Available at https://www.fda.gov/media/105731/download [updated 2017.
215. Hernandez Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. Pharmacoeconomics. 2023;41(2):199-207.
216. O'Brien SH, Hankins JS. Decision analysis of treatment strategies in children with severe sickle cell disease. J Pediatr Hematol Oncol. 2009;31(11):873-8.
217. Kofi AA, Hannah G, Lauren W, Mendwas D, Gabriel R, Gavin C. Patient self-assessment of hospital pain, mood and health-related quality of life in adults with sickle cell disease. BMJ Open. 2012;2(4):e001274.
218. Matza LS, Paramore LC, Stewart KD, Karn H, Jobanputra M, Dietz AC. Health state utilities associated with treatment for transfusion-dependent β-thalassemia. Eur J Health Econ. 2020;21(3):397-407.
219. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-18.
220. Krol M, Nap A, Michels R, Veraart C, Goossens L. Health state utilities for infertility and subfertility. Reprod Health. 2019;16(1):47.
221. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. Prim Care Respir J. 2007;16(1):22-7.
222. Jiao B, Basu A, Ramsey S, Roth J, Bender MA, Quach D, et al. Health State Utilities for Sickle Cell Disease: A Catalog Prepared From a Systematic Review. Value Health. 2022;25(2):276-87.
223. Ojelabi AO, Bamgboye AE, Ling J. Preference-based measure of health-related quality of life and its determinants in sickle cell disease in Nigeria. PLoS One. 2019;14(11):e0223043.
224. Drabinski A, Williams G, Formica C. PID7: OBSERVATIONAL EVALUATION OF HEALTH STATE UTILITIES AMONG A COHORT OF SEPSIS PATIENTS. Value in Health. 2001;4:130.
225. National Institute for Health and Care Excellence. Gallstone Disease: Diagnosis and Management of Cholelithiasis, Cholecystitis and Choledocholithiasis. London: National Institute for Health and Care Excellence (NICE); 2014.
226. Keogh AM, McNeil KD, Wlodarczyk J, Gabbay E, Williams TJ. Quality of life in pulmonary arterial hypertension: improvement and maintenance with bosentan. J Heart Lung Transplant. 2007;26(2):181-7.
227. Cherry MG, Greenhalgh J, Osipenko L, Venkatachalam M, Boland A, Dundar Y, et al. The clinical effectiveness and cost-effectiveness of primary stroke prevention in children with sickle cell disease: a systematic review and economic evaluation. Health Technol Assess. 2012;16(43):1-129.
228. Stites SD, Harkins K, Rubright JD, Karlawish J. Relationships Between Cognitive Complaints and Quality of Life in Older Adults With Mild Cognitive Impairment, Mild

Alzheimer Disease Dementia, and Normal Cognition. Alzheimer Dis Assoc Disord. 2018;32(4):276-83.
229. Office for National Statistics. Consumer Prices Index, Special Aggregate: 06 Health. Available at https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/l528 [
230. Jalkanen K, Aarnio E, Lavikainen P, Jauhonen HM, Enlund H, Martikainen J. Impact of type 2 diabetes treated with non-insulin medication and number of diabetes-coexisting diseases on EQ-5D-5 L index scores in the Finnish population. Health Qual Life Outcomes. 2019;17(1):117.
231. National Health Service. Stem cell and bone marrow transplants 2022 [updated 07 September 2022.
232. NHS trusts and NHS foundation trusts. National Cost Collection: National schedule of NHS costs. 2021/22.
233. Therrell BL, Jr., Lloyd-Puryear MA, Ohene-Frempong K, Ware RE, Padilla CD, Ambrose EE, et al. Empowering newborn screening programs in African countries through establishment of an international collaborative effort. J Community Genet. 2020;11(3):253-68.
234. NHS Blood and Transplant. Blood and Components - Contract Equivalent Cost per Item. 2023/24.
235. Human Fertilisation and Embryology Authority. Egg freezing. Available at https://www.hfea.gov.uk/treatments/fertility-preservation/egg-freezing 2023 [
236. Drugs and pharmaceutical electronic market information tool (eMIT). Available at https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit [Internet]. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.
237. National Health Service. Birmingham Women's Fertility Centre. Treatment charges in 2020. Available at https://bwc.nhs.uk/download.cfm?doc=docm93jijm4n1679 2022 [
238. The Joint Formulary Committee (JFC). The British National Formulary (BNF). 2023.
239. US Food and Drug Administration. Product Information for Adakveo. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761128s005lbl.pdf [
240. Cappellini MD, Farmakis D, Porter J, Taher A. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT). 4th Edition 2021 [Available from: https://www.thalassemia.org/wp-content/uploads/2021/06/TIF-2021-Guidelines-for-Mgmt-of-TDT.pdf.
241. National Health Service. National Cost Collection data Version 2 - HRG Data. Available at https://www.england.nhs.uk/national-cost-collection [
242. Exposto F, Hermans R, Nordgren Å, Taylor L, Sikander Rehman S, Ogley R, et al. Burden of pulmonary arterial hypertension in England: retrospective HES database analysis. Ther Adv Respir Dis. 2021;15:1753466621995040.
243. Guest JF, Fuller GW, Vowden P. Venous leg ulcer management in clinical practice in the UK: costs and outcomes. Int Wound J. 2018;15(1):29-37.
244. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2021 (Section 8.2). Available at https://www.pssru.ac.uk/pub/uc/uc2021/services.pdf 2021 [
245. Office for National Statistics. Employment rate (aged 16 to 64, seasonally adjusted): %. Available at

https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/timeseries/lf24/lms [updated 11 October, 2022.
246. Office for National Statistics. Annual Survey of Hours and Earnings time series of selected estimates. Available at https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/datasets/ashe1997to2015selectedestimates [updated 26 October, 2021.
247. GOV.UK. Second State Pension Age Review launches. Available at https://www.gov.uk/government/news/second-state-pension-age-review-launches [updated 7 January, 2022.
248. Rizio AA, Bhor M, Lin X, McCausland KL, White MK, Paulose J, et al. The relationship between frequency and severity of vaso-occlusive crises and health-related quality of life and work productivity in adults with sickle cell disease. Qual Life Res. 2020;29(6):1533-47.
249. Schneider P. MS L-KJ, Doran T., Gutacker N. QALY shortfall calculator 2021 [Available from: https://r4scharr.shinyapps.io/shortfall/.
250. European Medicines Agency. Qualification opinion on cellular therapy module of the European Society for Blood and Marrow Transplantation (EBMT) registry. 2019 [Available from: https://www.ebmt.org/sites/default/files/2019-03/EMA%20qualification%20opinion%20on%20Cellular%20therapy%20module%20of%20the%20EBMT%20Registry-28022019.pdf
251. Cookson R, Griffin S, Norheim OF, Culyer AJ. Distributional Cost-Effectiveness Analysis: Quantifying Health Equity Impacts and Trade-Offs: Oxford University Press; 2020 01 Oct 2020.
252. The King's Fund. The health of people from ethnic minority groups in England. Available at https://www.kingsfund.org.uk/publications/health-people-ethnic-minority-groups-england 2023 [
253. Li N, Udeze C, Ly NF, Ingleby FC, Fleming SD, Conner S, et al., editors. Mortality and clinical complications among patients with transfusion-dependent β-thalassemia in England. BSH; 2023.
254. United Kingdom Thalassaemia Society. Thalassaemia Asian Awareness Campaign. Available at https://ukts.org/3d-flip-book/asian-awareness/. 2002.
255. Robson M, Asaria M, Cookson R, Tsuchiya A, Ali S. Eliciting the Level of Health Inequality Aversion in England. Health Econ. 2017;26(10):1328-34.
256. McNamara S, Holmes J, Stevely AK, Tsuchiya A. How averse are the UK general public to inequalities in health between socioeconomic groups? A systematic review. Eur J Health Econ. 2020;21(2):275-85.
257. Robson M, O'Donnell O, Van Ourti T. Aversion to Health Inequality - Pure, Income-Related and Income Caused. Available at https://papers.tinbergen.nl/23019.pdf. 2023.
258. Osunkwo I, Manwani D, Kanter J. Current and novel therapies for the prevention of vaso-occlusive crisis in sickle cell disease. Ther Adv Hematol. 2020;11:2040620720955000.
259. Holdford D, Vendetti N, Sop DM, Johnson S, Smith WR. Indirect Economic Burden of Sickle Cell Disease. Value Health. 2021;24(8):1095-101.
260. National Institute for Health and Care Excellence. Voxelotor for treating sickle cell disease. Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10505/documents 2023 [
261. National Institute for Health and Care Excellence. NICE Technology appraisal guidance [TA743]. Crizanlizumab for preventing sickle cell crises in sickle cell disease. [cited 2021. Evidence-based recommendations on crizanlizumab for preventing sickle cell

crises in people aged 16 or over with sickle cell disease.]. Available from: https://www.nice.org.uk/guidance/ta743.
262. Wallen GR, Minniti CP, Krumlauf M, Eckes E, Allen D, Oguhebe A, et al. Sleep disturbance, depression and pain in adults with sickle cell disease. BMC Psychiatry. 2014;14:207-.
263. Rigano P, De Franceschi L, Sainati L, Piga A, Piel FB, Cappellini MD, et al. Real-life experience with hydroxyurea in sickle cell disease: A multicenter study in a cohort of patients with heterogeneous descent. Blood Cells Mol Dis. 2018;69:82-9.
264. Wolfson JA, Schrager SM, Coates TD, Kipke MD. Sickle-cell disease in California: a population-based description of emergency department utilization. Pediatric blood & cancer. 2011;56(3):413-9.
265. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N, et al. Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. British Journal of Haematology. 2017;176(2):179-91.
266. Vichinsky E, Neumayr L, Gold JI, Weiner MW, Kasten J, Truran D, et al. A Randomized Trial of the Safety and Benefit of Transfusion Vs. Standard Care In the Prevention of Sickle Cell-Related Complications In Adults: a Preliminary Report From the Phase II NHLBI Comprehensive Sickle Cell Centers (CSCC) Study of Neuropsychological Dysfunction and Neuroimaging Abnormalities In Neurologically Intact Adult Patients with Sickle Cell Disease. Blood. 2010;116(21):3221.
267. Kanter J, Walters MC, Krishnamurti L, Mapara MY, Kwiatkowski JL, Rifkin-Zenenberg S, et al. Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease. N Engl J Med. 2022;386(7):617-28.
268. Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Kantor E, Bao Y, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics. 2010;28(10):935-45.
269. Pharmaceuticals V. Data on File. D120 Appendices. 2023.
270. Scottish Medicines Consortium. Crizanlizumab 10mg/mL concentrate for solution for infusion (Adakveo®). Available at https://www.scottishmedicines.org.uk/media/6982/crizanlizumab-adakveo-final-june-2022-for-website.pdf 2022 [updated 10 June 2022.
271. Drummond MF, Sculpher MJ, Claxton K, Stoddard GL, Torrance GW. Methods for the Economic evaluation of Health Care Programmes. 4th ed: Oxford University Press; 2015.
272. Pharmaceuticals V. Data on File. Economic SLR Report. 2023.
273. Karnon J, Tolley K, Oyee J, Jewitt K, Ossa D, Akehurst R. Cost-utility analysis of deferasirox compared to standard therapy with desferrioxamine for patients requiring iron chelation therapy in the United Kingdom. Current medical research and opinion. 2008;24(6):1609-21.
274. Spackman E, Sculpher M, Howard J, Malfroy M, Llewelyn C, Choo L, et al. Cost-effectiveness analysis of preoperative transfusion in patients with sickle cell disease using evidence from the TAPS trial. European journal of haematology. 2014;92(3):249-55.
275. Besser M, Jarvis S, Hamlyn M, Brown J, Barcelos G, Beaubrun A, et al. 5613022 Societal burden of sickle cell disease in the UK: Empirical estimates of productivity loss and loss of future income using real-world evidence. HemaSphere. 2023;7(Suppl).
276. [SMC2438]. Scottish Medicines Consortium. Crizanlizumab 10mg/mL concentrate for solution for infusion (Adakveo®) [updated 10 June 2022. Available from: https://www.scottishmedicines.org.uk/media/6982/crizanlizumab-adakveo-final-june-2022-for-website.pdf.

277. Karnon J, Zeuner D, Ades AE, Efimba W, Brown J, Yardumian A. The effects of neonatal screening for sickle cell disorders on lifetime treatment costs and early deaths avoided: a modelling approach. Journal of Public Health. 2000;22(4):500-11.
278. Thomas V, Gruen R, Shu S. Cognitivebehavioural therapy for the management of sickle cell disease pain: Identification and assessment of costs. Ethnicity & health. 2001;6(1):59-67.
279. Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value in health. 2013;16(4):686-95.
280. Lubeck D, Agodoa I, Bhakta N, Danese M, Pappu K, Howard R, et al. Estimated life expectancy and income of patients with sickle cell disease compared with those without sickle cell disease. JAMA Network Open. 2019;2(11):e1915374-e.
281. Tsironi M. Quality of life of patients with haemoglobinopathies in periods of economic austerity. Thalassemia Reports. 2014;4(3):4881.
282. Lanzkron S, Crook N, Wu J, Hussain S, Curtis RG, Robertson D, et al. PRO66 Health-Related quality of life in persons with sickle cell disease. Value in Health. 2021;24:S209-S10.
283. Anie KA, Grocott H, White L, Dzingina M, Rogers G, Cho G. Patient self-assessment of hospital pain, mood and health-related quality of life in adults with sickle cell disease. BMJ open. 2012;2(4):e001274.
284. Nietert PJ, Abboud MR, Silverstein MD, Jackson SM. Bone marrow transplantation versus periodic prophylactic blood transfusion in sickle cell patients at high risk of ischemic stroke: a decision analysis. Blood, The Journal of the American Society of Hematology. 2000;95(10):3057-64.
285. Bailey M, Bonner A, Brown S, Thompson M. PRO91 REDUCTION IN HRQOL WITH INCREASING VOC FREQUENCY AMONG PATIENTS WITH SCD. Value in Health. 2020;23:S345.
286. Thom HZ, Shafrin J, Keeney E, Zhao LM, Joseph GJ, Bhor M, et al. Relationship between Vaso-Occlusive Crisis and Quality of Life: An Analysis of Patients with Sickle Cell Disease in the United States. Blood. 2019;134:4700.
287. Shafrin J, Thom HH, Keeney E, Gaunt DM, Zhao LM, Bhor M, et al. The impact of vaso-occlusive crises and disease severity on quality of life and productivity among patients with sickle cell disease in the US. Current Medical Research and Opinion. 2021;37(5):761-8.
288. O'Brien SH, Hankins JS. Decision analysis of treatment strategies in children with severe sickle cell disease. Journal of pediatric hematology/oncology. 2009;31(11):873.
289. Jiao B, Hankins JS, Devine B, Barton M, Bender M, Basu A. Application of validated mapping algorithms between generic PedsQL scores and utility values to individuals with sickle cell disease. Quality of Life Research. 2022;31(9):2729-38.
290. Love-Koh J, Cookson R, Claxton K, Griffin S. Estimating Social Variation in the Health Effects of Changes in Health Care Expenditure. Med Decis Making. 2020;40(2):170-82.
291. McNamara S, Holmes J, Stevely AK, Tsuchiya A. How averse are the UK general public to inequalities in health between socioeconomic groups? A systematic review. The European Journal of Health Economics. 2020;21(2):275-85.
292. King MT, Cella D, Osoba D, Stockler M, Eton D, Thompson J, et al. Meta-analysis provides evidence-based interpretation guidelines for the clinical significance of mean differences for the FACT-G, a cancer-specific quality of life questionnaire. Patient Relat Outcome Meas. 2010;1:119-26.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Exagamglogene autotemcel for treating severe sickle cell disease

[ID4016]

Summary of Information for Patients (SIP)

September 2023

File name	Version	Contains confidential information	Date
ID4016_Exa-cel_SCD_SIP_FINAL [noCON]	1.0	No	07/09/2023

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

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:

Patients with sickle cell disease aged 12 years or older who have regular acute pain events and complications (known as vaso-occlusive crises), do not have a family relative who can provide them with matching blood stem cells, and who are eligible to have a stem cell transplant using their own blood stem cells (known as autologous stem cell transplant). Further detail on the definition of vaso-occlusive crises can be found in B1.1 of the main submission (Document B).

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 mentioned in 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 Sickle Cell Society with some of their work creating educational resources for families and individuals impacted by sickle cell disease.

SECTION 2: Current landscape

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.

Sickle cell disease is an umbrella term referring to a group of inherited blood diseases caused by a mutation in a gene responsible for making haemoglobin, the protein that carries oxygen in red blood cells (1). People with sickle cell disease have unusually shaped red blood cells (known as sickle-shaped) which can cause problems since they do not live as long as healthy red blood cells and can block blood vessels. This results in patients suffering from various acute and chronic complications, including unpredictable episodes of severe pain, chronic severe anaemia and widespread organ damage.

People with sickle cell disease require hydroxycarbamide treatment and/ or regular blood transfusions with removal of excess iron in the blood (known as iron chelation therapy) to manage their symptoms (1). Patients and their families experience severe disruption to their lives; approximately 80% of adults surveyed experienced problems with daily activities because of their condition (3).

Low haemoglobin levels 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. Patients taking hydroxycarbamide must be monitored regularly, due to the risks associated with its use.

In the UK, there are an estimated 14,200 patients with sickle cell disease, of which approximately 11,580 are 12 years of age or above (4). People with this disease are more likely to die earlier than the general population, with a recent UK study reporting an average life expectancy of 40.2 years in patients with more severe disease (5). In addition, patients with sickle cell disease are more likely to develop other severe illnesses such as stroke, heart conditions, kidney failure, 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 sickle cell disease. All newborn babies are offered screening as part of the newborn heel prick blood spot screening programme, which is usually performed when they are 5 days old (6). 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:
    - 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.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

In England, a large proportion of sickle cell disease patients – particularly those who experience more frequent acute pain events - receive hydroxycarbamide treatment (7). Hydroxycarbamide does not cure sickle cell disease but can provide temporary relief of symptoms caused by acute and chronic complications of the disease. Around 90% of adults with sickle cell disease will have had at least one blood transfusion (2).

Lifestyle advice (known as supportive care) can also be provided to ensure people with sickle cell disease understand the importance of adequate hydration, regulating body temperature, preventing infections and relieving their pain with painkillers such as paracetamol and opioids (including morphine, fentanyl). In the clinical trial for the technology under review in this appraisal, 94.8% of patients had received treatment with opioids at baseline.

The first sickle cell disease therapy to be made available in England for 20 years was crizanlizumab, which was recommended by National Institute for Health and Care Excellence (NICE) in 2021 (8). However, the recent results from the Phase III study of crizanlizumab did not meet the primary endpoint. The European Medicines Agency (the organisation that provides medicine recommendations for Europe based on clinical and safety data) has therefore revoked the conditional marketing authorisation of crizanlizumab (9). Novartis, the company who manufacture crizanlizumab, will remove this treatment from the market.

In addition, voxelotor (another treatment for sickle cell disease), was not recommended by NICE according to the final draft guidance published in July 2023 (10). The combined withdrawal of crizanlizumab's marketing authorisation and rejection of voxelotor presents a substantial unmet need for a new treatment option.

The only treatment available that can cure sickle cell disease 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. In the UK, only 24 sickle cell disease patients underwent a stem cell transplant in 2021, most of which would have been paediatric patients (children) (11).

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 care. rs 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 group discussions conducted in the UK and USA reported that sickle cell disease impacts almost all aspects of daily life. Individuals living with sickle cell disease often reported a profound impact of the disease on their daily lives and structured their lives in a way to reduce the risk of pain attacks. The unpredictability of sickle cell disease symptoms and consequences had adverse effects on patients' educational attainment, work prospects, and social lives. Patients also cited loneliness/ isolation, experiencing depression and low mood, anxiety, and fear of living in pain (3).

In a global longitudinal survey, patients reported suffering daily from pain/discomfort (90%), anxiety/depression (74%), issues with usual activities (80%), issues with mobility (71%), and issues with self-care (47%). Over half of patients (59%) reported moderate to extreme pain or discomfort. In addition, the impact was felt through both absenteeism and presenteeism, with participants reporting missing approximately 9.8 hours of work in the past week due to sickle cell disease (12).

SECTION 3: The treatment

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 known as fetal haemoglobin (HbF), which is produced in all developing babies before birth. HbF stops being produced soon after birth, but exa-cel turns HbF production back on. Higher levels of HbF increase the overall haemoglobin levels in the body, which has been shown to improve the production and function of red blood cells. This means people with sickle cell disease may not experience acute pain events or require treatments to manage them.

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 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 sickle cell disease.

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.

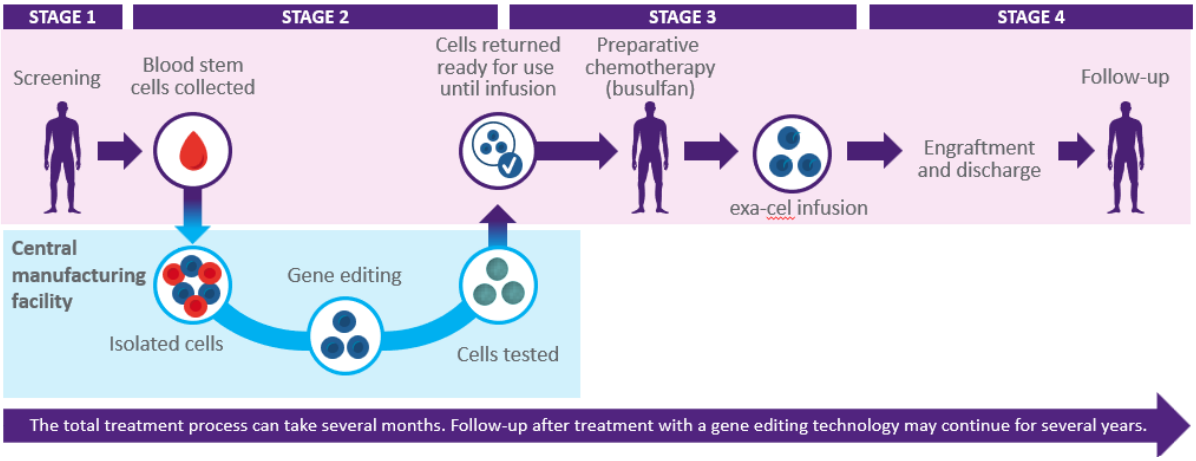
STAGE 2: After they are collected, the patient's blood stem cells will be sent to the manufacturing site where they are used to make exa-cel. It may take up to 6 months from the time the cells are collected to manufacture and test exa-cel before it is sent back to the patient's doctor.

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 and may reduce with increased experience. 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 (13, 14).



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 SCD-121 (previously known as CTX001-121) is an ongoing trial to assess the safety and efficacy of a single dose of exa-cel in patients aged 12-35 years with severe sickle cell disease. This study planned to dose approximately 45 patients with exa-cel and took place in 16 study centres across the USA, Canada, UK, France, Belgium, 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 SCD-121 was the number of patients who did not have any severe vaso-occlusive crises for at least 12 months in a row any time after exa-cel infusion. This outcome was known as 'VF12'. CLIMB SCD-121 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') were 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 35 patients with sickle cell disease who had received exa-cel by the time the trial data was analysed in September 2022, the majority had genotypes associated with severe disease, beta-

S/beta-S genotype. At the time of the data analysis, 17 sickle cell disease patients could be measured for the primary and key secondary endpoint, as they had >16 months of follow-up.

- 16 of 17 patients (94.1%) achieved the primary endpoint of not having any severe vaso-occlusive crises for at least 12 consecutive months after receiving exa-cel (VF12).
- All 17 patients achieved the key secondary endpoint of being free from hospitalisation for severe vaso-occlusive crises for at least 12 consecutive months after receiving exa-cel (HF12).
- On average, patients were free from severe vaso-occlusive crises for a duration of 18.7 months, and the longest single period of absence from vaso-occlusive crises was 36.5 months.
    - The one patient who did not achieve absence from severe vaso-occlusive crises (VF12) had a complex set of existing conditions, including a history of chronic pain. However, this patient remained free from hospitalisation for severe vaso-occlusive crises (HF12).
    - One patient who achieved absence from severe vaso-occlusive crises (VF12), had a vaso-occlusive crisis 22.8 months after receiving exa-cel. This was determined to be caused by a virus infection called parvovirus B19. The patient experienced a milder course of parvovirus infection than would be expected for a sickle cell disease patient; this patient has since recovered from the infection and been free from severe vaso-occlusive crises.
- Increases in total haemoglobin and fetal haemoglobin occurred early within the first few months and were maintained over time. In the analysis of all patients who received exa-cel, average fetal haemoglobin was more than 30% of the total haemoglobin concentration at Month 3, and remained at around 40% up to Month 24, with fetal 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.

The following patient reported outcome areas considered to be most important in sickle cell disease were:

- Pain (acute and chronic)
- Affect (emotional impact, sleep quality and tiredness)
- Functional (social, physical, and ability to think, work and manage the disease)

Patient reported outcomes in the CLIMB SCD-121 trial showed significant improvement in general well-being, quality of life and overall health status. EQ-5D-5L scores showed clinically meaningful improvements in overall health status from Month 6 onwards and at the beginning of the trial

('baseline'), EQ-5D-5L scores were reported to be lower than the average UK population score. This indicates that health-related quality of life was impaired before treatment with exa-cel. EQ-5D-5L was considered an appropriate tool for measuring health-related quality of life in the CLIMB SCD-121 trial since its elements capture the nature of the disease, including aspects such as pain intensity, pain relief and mobility limitations to assist the measurement of quality of life in sickle cell disease patients (15).

In addition, the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) tool is frequently used and validated in sickle cell disease. The ASCQ-Me tool includes emotional, social, stiffness, and sleep impact scores, which all demonstrated meaningful changes in the CLIMB SCD-121 trial from Month 6 to Month 24, indicating significant improvements in these scores after treatment with exa-cel.

According to the UK analysis of the Sickle Cell World Assessment Survey (SWAY), the most cited treatment goal for both patients and healthcare professionals was improvement in health-related quality of life (69% of patients versus 80% of healthcare professionals) (16). Patients reported impaired health-related quality of life in relation to physical well-being, with the physical functioning aspect being worse than or comparable to that of patients with other chronic diseases or cancer (17, 18). In addition to the significant burden imposed on patients, caregivers also experience negative impacts on their physical, mental, and social well-being. Caregivers of patients with sickle cell disease have been shown to have a lower quality of life compared to the general population (19, 20).

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 busulfan when it 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: nausea, inflammation or redness of the mouth (stomatitis) and vomiting.

No sickle cell disease patients had serious adverse events considered related to exa-cel. One patient had a fatal adverse event. However, this was not related to exa-cel, and was instead due to respiratory failure after COVID-19 infection.

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 sickle cell disease 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. Moreover, exa-cel has demonstrated a safety profile similar to existing 'conditioning medicines' and stem cell transplant procedures.

As a result of the increased haemoglobin blood concentration and fetal haemoglobin levels following exa-cel infusion, patients will experience less anaemia and fatigue associated with low haemoglobin. This eliminates the need for hydroxycarbamide and regular blood transfusions meaning 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. Both hydroxycarbamide and iron chelation medicines are associated with many side effects and patients find them unpleasant to take. The removal of the need to take these chronic medications can also save a lot of 'out of pocket' costs for patients who do not receive financial help with paying for their prescriptions.

As previously mentioned, the results from the Phase III study of crizanlizumab did not meet the primary endpoint. The European Medicines Agency (the organisation that provides medicine recommendations for Europe based on clinical and safety data) has therefore recommended removing their conditional approval for the market authorisation of crizanlizumab (9). In addition, voxelotor (another treatment for sickle cell disease), was not recommended by NICE according to the final draft guidance published in July 2023 (10). These recommendations reduce the available treatment options for addressing acute pain events in patients even further, therefore there remains a clear unmet need for a potentially curative therapy to transform the treatment landscape for sickle cell disease patients.

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 sickle cell disease 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 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.

3j) Value and economic considerations

Introduction for patients:

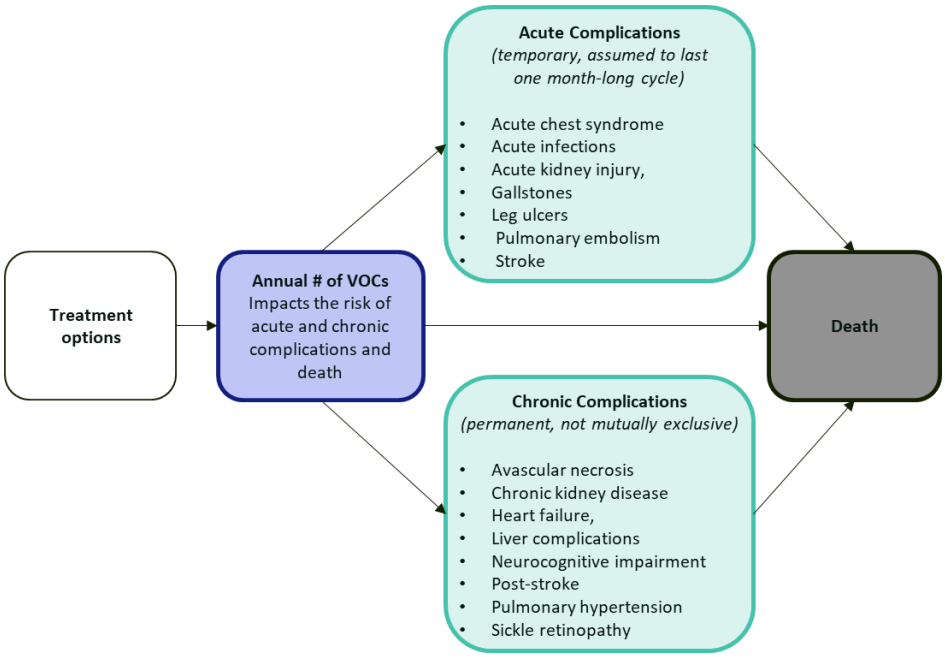
Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, 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.

The manufacturer of exa-cel built an economic model in Microsoft Excel to demonstrate the economic value of exa-cel when compared with current standard of care for eligible sickle-cell patients in the National Health Service. The economic model shows the different ways in which a patient's health can change throughout the rest of their life based on the absence of, or reduction of vaso-occlusive crisis frequency after having either exa-cel compared with current standard of care for sickle cell disease (treatment with hydroxycarbamide and/or chronic blood transfusions). The model compares the total costs (drug and healthcare resource use) generated by exa-cel and current standard of care as well as the survival and quality of life of the patient over their lifetime; these last two are combined to produce a measure called the quality-adjusted life year (QALY).

The below diagrams shows what acute and chronic complications the model captures:



The results of the economic model showed that patients treated with exa-cel initially have a reduction in their quality of life compared with current standard of care, due to the need for chemotherapy drugs to prepare the body for exa-cel, which are similar to those for patients who are given stem cell transplants currently in the NHS. However, following infusion with exa-cel, quality of life improves over time as the immune system recovers from the transplant procedure and the graft begins to generate normal red blood cells and haemoglobin. Within a few years of infusion, as frequency of vaso-occlusive crises decreases and blood markers improve, so does quality of life, hence more quality-adjusted life years are generated from the model.

Over the longer term, patients with normal red blood cells and haemoglobin are predicted to have far fewer acute and chronic complications over their lifetime than a sickle cell patient who does not receive exa-cel. This leads to higher survival and quality of life for exa-cel treated patients, and consequently higher quality-adjusted life years when compared with standard of care.

The results of the economic model showed that patients treated with exa-cel initially incur higher treatment costs compared with current standard of care, due to both the additional cost of exa-cel to the NHS but also the cost of the drugs and hospital stay that are required to administer it, which are similar to those for patients who are given stem cell transplants currently in the NHS. However, over the longer term there are significant cost savings to the NHS due to the reduction in frequency of vaso-occlusive crises and their management costs, as well as the cost of hydroxycarbamide and blood transfusions. Over the longer term, patients are predicted to have a much lower risk of acute and chronic complications, and hence cost the NHS less than they would do without exa-cel, as managing these complications, many of which are very serious, can be very costly to the NHS.

Altogether the model predicted higher costs over the treated patient's lifetime due to the cost of exa-cel and initial transplantation procedure, but also predicted higher survival and improved quality of life, and consequently, quality-adjusted life years.

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 sickle cell disease to achieve a disease-free state by treating the underlying cause of the disease. Exa-cel is expected to eliminate the acute pain events which occur in sickle cell disease patients, meaning that patients will also not need to regularly attend medical appointments.

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 in England sickle cell disease mainly affects individuals of African or Caribbean ethnicity (21). This is also supported by a UK burden of illness study, which found that most patients enrolled were Black (22). As shown by the COVID-19 pandemic, these individuals usually have poorer health outcomes, including higher rates of chronic disease and lower life expectancy when compared to other ethnicities such as White British (23, 24).

The All-Party Parliamentary Group (APPG) on Sickle Cell and Thalassaemia advocates for increased awareness and improved care for individuals living with sickle cell disease. In 2021, the APPG published a report based on information obtained from patients, clinicians and politicians, which highlighted an unfortunate pattern of many years of suboptimal care, stigmatisation as well as lack of understanding and prioritisation towards sickle cell disease patients (25).

The APPG report recommended that NICE revise their clinical guideline surrounding pain relief for sickle cell disease patients to include standards relating to pain management for an entire sickle cell crisis. Ultimately, the APPG report recommendations mentioned above were underpinned by two main insights. The first was a great sense of anger and frustration from patients contacted since many failings in sickle cell disease care highlighted in the past have not been properly acted upon (25).

In 2021, the APPG on Sickle Cell and Thalassaemia launched an inquiry following numerous high-profile examples of failings in care for SCD patients, including the tragic death of Evan Nathan Smith. This inquiry has contributed to increasing awareness of the challenges frequently faced by SCD patients when receiving appropriate care. For instance, no evidence was present in Evan's medical records showing the sickle cell team requested advice prior to a routine stent removal procedure, despite the increased risk of sepsis (blood poisoning caused by bacteria) present (25).

The second insight to arise from the APPG report was related to race, highlighting the deep inequalities shown towards sickle cell disease patients in terms of lack of disease understanding and awareness from healthcare professionals, and again failings when accessing treatment. Patients reported often having to educate healthcare professionals on the basics of the condition and are regularly treated with disrespect, not believed or listened to, and are dismissed as a priority case (25). Results from a survey in adult patients with sickle cell disease reported participants felt they had been treated unfairly due to their race whilst seeking care (67%) or requesting additional pain medication (65%) (3).

In addition, pregnancy in women with sickle cell disease is linked with maternal and fetal fatality rates as high as 11.4% and 20.0%, respectively (26). According to the Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries (MBRRACE) UK Report (2022), the risk of mothers dying in 2018-2020 was 3.7 times higher amongst women from Black ethnic backgrounds compared to White women (27).

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://toolbox.eupati.eu/resources/patient-toolbox/guidance-for-patient-involvement-in-industry-led-medicines-rd/
- 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

Adult Sickle Cell Quality of Life Measurement Information System – a patient-reported outcome measurement system that assesses the physical, social, and emotional impact of sickle cell disease on adults.
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.
Baseline – the beginning of a clinical trial/ study.
Co-morbidity – any illness that affects patients alongside their sickle cell disease.
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 generic, preference-based survey that asks patients to mark their health-related quality of life across 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 – the action of making the patient's blood stem cells move from the bone marrow into the blood stream using a *mobilisation* medicine.
Myeloablation – a method of decreasing bone marrow activity. Also known as *myeloablative conditioning.*
Neutrophil – a type 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.*
Vaso occlusive crisis – the most common clinical symptom of sickle cell disease, occurring when the blood supply for an organ is cut off.
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. Zaidi AU, Glaros AK, Lee S, Wang T, Bhojwani R, Morris E, et al. A systematic literature review of frequency of vaso-occlusive crises in sickle cell disease. Orphanet Journal of Rare Diseases. 2021;16(1).
2. Chou ST. Transfusion therapy for sickle cell disease: a balancing act. Hematology Am Soc Hematol Educ Program. 2013;2013:439-46.

3. Drahos J, Boateng-Kuffour A, Calvert M, Valentine A, Mason A, Pakbaz Z, et al. Health-Related Quality of Life, Disease Impacts, and Health Equity Concerns in Adults with Sickle Cell Disease with Recurrent Vaso-Occlusive Crises: Preliminary Results from a Global Longitudinal Survey. Blood. 2022;140(Supplement 1):1387-8.
4. National Health Service. National Haemoglobinopathy Registry Annual Data Report 2020/21. Available at https://nhr.mdsas.com/wp-content/uploads/2022/03/NHR_DataReport2021.pdf. 2021.
5. Udeze C, Ly, N. F., Ingleby, C. et al. Mortality and clinical complications among patients with sickle cell disease with recurrent VOCs in England. British Journal of Haematology. 2023.
6. Public Health England. Sickle cell and thalassaemia (SCT) screening: programme overview. 2013.
7. National Health Service. The National Haemoglobinopathy Register. Available at https://nhr.mdsas.com/ [Available from: https://nhr.mdsas.com/.
8. National Institute for Health and Care Excellence. Final appraisal document: Crizanlizumab for preventing sickle cell crises in sickle cell disease. Available at https://www.nice.org.uk/guidance/ta743/documents/final-appraisal-determination-document 2021
9. European Medicines Agency. Adakveo. 2023.
10. National Institute for Health and Care Excellence. Voxelotor for treating sickle cell disease. Available at https://www.nice.org.uk/guidance/proposed/gid-ta10505. 2021.
11. British Society of Blood and Marrow Transplantation and Cellular Therapy. UK & ROI Transplant Activity Table by Disease 2021 [Available from: https://bsbmtct.org/activity/2021/.
12. Drahos J. Health-related quality of life impacts associated with sickle cell disease in the United States and United Kingdom: a qualitative assessment. Oral Presentation. International Society for Quality of Life Research. 2023.
13. Frangoul H, Altshuler D, Cappellini MD, Chen Y-S, Domm J, Eustace BK, et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia. New England Journal of Medicine. 2021;384(3):252-60.
14. ClinicalTrials.gov. A Long-term Follow-up Study in Subjects Who Received CTX001 (CLIMB-131) 2022 [Available from: https://clinicaltrials.gov/ct2/show/NCT04208529.
15. Kofi AA, Hannah G, Lauren W, Mendwas D, Gabriel R, Gavin C. Patient self-assessment of hospital pain, mood and health-related quality of life in adults with sickle cell disease. BMJ Open. 2012;2(4):e001274.
16. Niihara Y, Miller ST, Kanter J, Lanzkron S, Smith WR, Hsu LL, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. New England Journal of Medicine. 2018;379(3):226-35.
17. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;4:18010.
18. McClish DK, Penberthy LT, Bovbjerg VE, Roberts JD, Aisiku IP, Levenson JL, et al. Health related quality of life in sickle cell patients: the PiSCES project. Health Qual Life Outcomes. 2005;3:50.
19. Barcelos G, Besser M, O'Flaherty E, O'Sullivan S, Bourke S, Oluboyede Y, et al. PCR116 Quality of Life of and Economic Burden on Caregivers of Individuals With Sickle Cell Disease in the UK and France: A Cross-Sectional Survey. Value in Health. 2022;25(12):S1-S546.
20. van den Tweel XW, Hatzmann J, Ensink E, van der Lee JH, Peters M, Fijnvandraat K, et al. Quality of life of female caregivers of children with sickle cell disease: a survey. Haematologica. 2008;93(4):588-93.
21. NHR Information service. Number of Patients by Diagnosis 2019 [Available from: http://nhr.mdsas.com/wp-content/uploads/2019/04/NumberPatientsDiagnosis.pdf.
22. National Institute for Health and Care Excellence. Committee papers: Crizanlizumab for preventing sickle cell crises in sickle cell disease. Available at https://www.nice.org.uk/guidance/ta743/documents/committee-papers 2020

23. Kirby T. Evidence Mounts on the Disproportionate Effect of COVID-19 on Ethnic Minorities. The Lancet Respiratory Medicine. 2020;8:547-8.
24. Razai MS, Kankam HKN, Majeed A, Esmail A, Williams DR. Mitigating ethnic disparities in covid-19 and beyond. BMJ. 2021;372:m4921.
25. Rylatt A. No One's Listening: An Inquiry into the Avoidable Deaths and Failures of Care for Sickle Cell Patients in Secondary Care. 2021.
26. Boga C, Ozdogu H. Pregnancy and sickle cell disease: A review of the current literature. Critical Reviews in Oncology/Hematology. 2016;98:364-74.
27. Knight M, Bunch K, Patel R, Shakespeare J, Kotnis R, Kenyon S, et al. MBRRACE-UK: Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2018-20. 2022.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

Clarification questions

October 2023

File name	Version	Contains confidential information	Date
ID4016_exa-cel_SCD_clarification_response [CON]	1.0	Yes	13 October 2023

Notes for company

Highlighting in the template

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

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

Section A: Clarification on effectiveness data

Literature searching (clinical effectiveness)

A1. Please can the company provide the reference list for the exa-cel company submission appendices?

Company response

As requested, a version of the CS Appendix including a bibliography is submitted alongside our clarification response.

A2. Please provide the search terms used for hand-searching of relevant congresses for the clinical systematic literature review (ran on 10/05/2022)?

Company response

Table 1: Keywords used for conference search

Sickle
Sickle Cell Disease
Sickle Cell Anaemia
Sickle Cell Anemia
Haemoglobinopath
Hemoglobinopath
Anaemia
Anemia

Note: Terms were searched individually

A3. Table 71 (CS Document B Appendix, page 65) provides a list of eight studies included in the clinical systematic literature review at eligibility screening that were prioritised for the ITC assessment. The PRISMA flow charts in Figure 36 and Figure 37 (CS Document B Appendix, page 64) reported that there were five studies prioritised for ITC feasibility assessment. Please confirm which number is correct?

Company response

Of the 52 studies included in the SLR for SCD, 5 were prioritised for data extraction and ITC feasibility assessment (Table 2) (1). Table 71 (CS Document B Appendix, Page 65) refers to associated publications of the CLIMB SCD-121 study of exa-cel, initially reported by Frangoul *et al* (2021) (2, 3).

Table 2: Summary of studies prioritised for the ITC assessment for SCD (n=5)

Lead author, year	Study name (trial ID)	Intervention	Geography (sample size)	Age range (mean or median)	VOC-related outcome
Vichinsky, 2010 (4)	NR	Blood transfusions vs Standard of care (RCT)	US (n=36)	21-55 years	Total number of VOCs
Ataga, 2017 (5)	SUSTAIN; NCT01895361	High-dose vs low-dose crizanlizumab vs Placebo + Standard of care (RCT)	US, Brazil, and Jamaica (n=198)	16-65 years	Acute episodes of pain that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral nonsteroidal anti-inflammatory drug. Calculated as the total number of crises × 365 ÷ (end date − date of randomization + 1)
Niihara, 2018 (6)	NCT01179217	L-Glutamine vs Placebo + Standard of care (RCT)	US (n=230)	5-58 years	Pain leading to treatment with a parenterally administered narcotic or

					ketorolac in an emergency department (or outpatient treatment center) or during hospitalisation
Howard, 2021 (7)	HOPE; NCT03036813	Voxelotor 1500 mg vs Voxelotor 900 mg vs Placebo + Standard of care (RCT)	Multi-national (n=274)	12-65 years	Any one of the following: acute painful crisis lasting at least 2 hours, requires opioids, ketorolac, or other analgesics prescribed in a medical setting (hospital, clinic, emergency room, or by telephone, episode ACS. Annualized incidence rate (the number of crises per person-year)
Kanter, 2022 (8)	HGB-206; NCT02140554	LentiGlobin (Zynteglo) (non-RCT)	US (n=43)	12-50 years	Event that included acute episodes of pain, ACS, acute hepatic sequestration, acute splenic sequestration, and acute priapism

Key: ACS: acute chest syndrome; RCT: randomised controlled trial; VOC: vaso-occlusive crisis.
Note: The standard of care/ control group in the three highlighted studies were included in the ITC assessment.

A4. Please can the company clarify which review articles you reviewed bibliographies for (as stated in the PRISMA flow for the original clinical systematic literature review)?

Company response

Four review articles were reviewed (Table 3). In addition to these articles, a review of publications listed on ClinicalTrials.gov was undertaken for included trials. One addition record was retrieved from this review (9).

Table 3: Review articles for bibliography review

Thom H, Jansen J, Shafrin J, Zhao L, Joseph G, Cheng HY, Gupta S, Shah N. Crizanlizumab and comparators for adults with sickle cell disease: a systematic review and network meta-analysis. BMJ Open. 2020 Sep 17;10(9):e034147. doi: 10.1136/bmjopen-2019-034147. PMID: 32948541; PMCID: PMC7500297 (10).
Sridharan K, Sivaramakrishnan G. Efficacy and safety of iron chelators in thalassemia and sickle cell disease: a multiple treatment comparison network meta-analysis and trial sequential analysis. Expert Rev Clin Pharmacol. 2018 Jun;11(6):641-650. doi: 10.1080/17512433.2018.1473760. Epub 2018 May 18. PMID: 29727586 (11).
Dick MH, Abdelgadir A, Kulkarni VV, Akram H, Chatterjee A, Pokhrel S, Khan S. Comparing the Safety and Efficacy of L-Glutamine, Voxelotor, and Crizanlizumab for Reducing the Frequency of Vaso-Occlusive Crisis in Sickle Cell Disease: A Systematic Review. Cureus. 2022 May 11;14(5):e24920. doi: 10.7759/cureus.24920. PMID: 35706735; PMCID: PMC9187358 (12).
Tucci F, Galimberti S, Naldini L, Valsecchi MG, Aiuti A. A systematic review and meta-analysis of gene therapy with hematopoietic stem and progenitor cells for monogenic disorders. Nat Commun. 2022 Mar 14;13(1):1315. doi: 10.1038/s41467-022-28762-2. PMID: 35288539; PMCID: PMC8921234 (13).

A5. In the section ‘Complete reference lists for included studies and excluded studies’ (CS Document B Appendix, page 66), it states that ‘Table 71 provides a list of studies included in the clinical SLR at eligibility screening and were prioritised for the ITC assessment, while Table 73 refers to the included studies not prioritised for the ITC assessment’; however, Table 71 (CS Document B Appendix, page 65) contains ‘Identified studies and associated publications for exa-cel in SCD’ (n=8), Table 73 (CS Document B Appendix, page 80) presents ‘Summary of studies prioritised for the ITC assessment for SCD (n=5)’, Table 80 (CS Document B Appendix, page 80) presents the summary of the studies prioritised for the ITC assessment for SCD (n=5)’.

a. Please can the company clarify what the data in Tables 71, 73 and 80 contain?

Company response

- Table 71 contains a list of identified studies and associated publications which were included in the SLR at eligibility screening (n=8). These studies were not prioritised for the ITC assessment.
- Table 73 contains a summary of studies prioritised for the ITC assessment for SCD (n=5).

- Table 74 (we assume the EAG are referring to Table 74 rather than Table 80, which reports subgroup analysis) contains a list of studies not prioritised for the ITC assessment for SCD, including a reason for exclusion.

b. Please can you clarify whether the studies reported in Table 74 were from the clinical SLR, update or both?

Company response

Studies reported in Table 74 were retrieved from the original clinical SLR.

A6. Priority Question: Table 12 (CS Document B, page 65) states that the CLIMB SCD-121 is being conducted across 16 study centres.

a. Please can the company clarify how many UK participants were enrolled in the CLIMB SCD-121 study.

Company response

[redacted] from the UK were enrolled in CLIMB SCD-121 at D120.

b. Please can the company clarify how many participants in the PES analysis (n=29) were from the UK?

Company response

[redacted] from the UK were included in the PES analysis at D120.

A7. Priority Question: The analysis of safety was conducted on 58 participants that started mobilisation, of which 43 participants received exa-cel. Please can the company provide explanation for the 15 participants included in the analysis of safety who had not received exa-cel infusion.

Company response

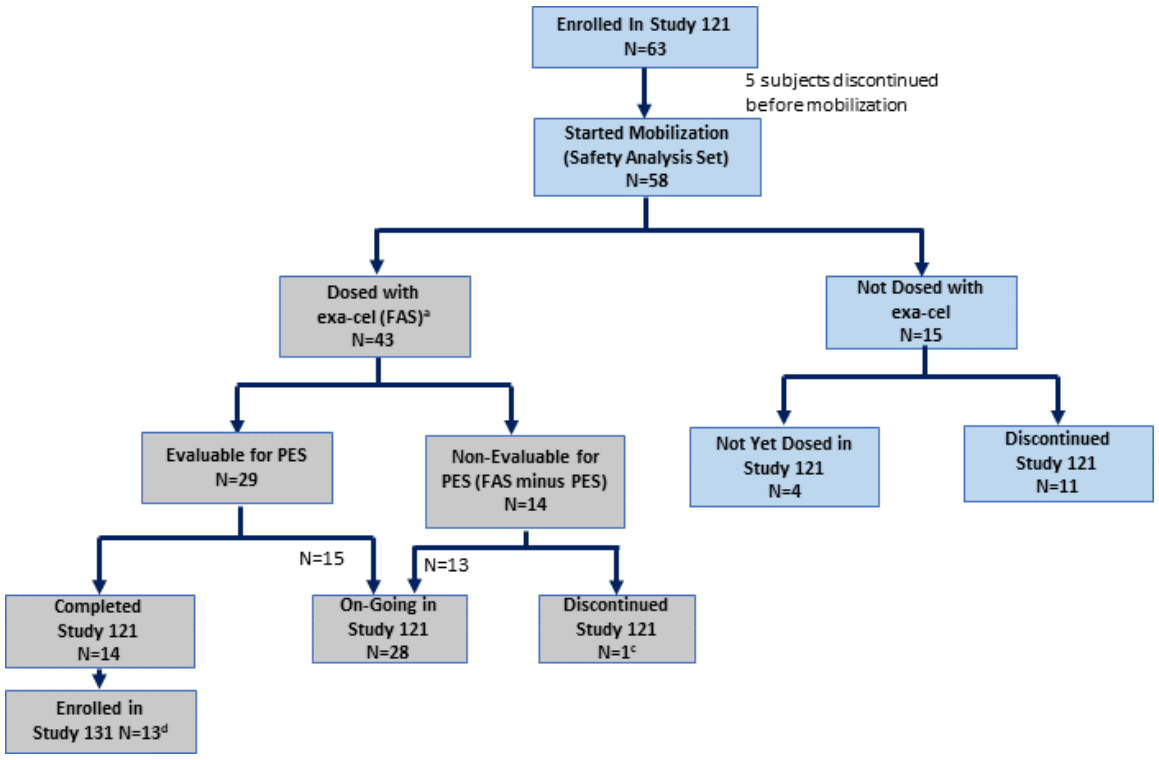
As the EAG state, at the time of D120 there were a total of 58 patients in the Safety Analysis Set (who had started mobilisation), of which 43 had been dosed with exa-cel. Of those yet to receive treatment with exa-cel, these can be broadly categorised as follows:

- Not yet dosed with exa-cel: 4 patients had not yet been dosed with exa-cel at the D120 cut-off. Of these, 1 patient has since been dosed, and 3 are planned to be dosed by Q4 2023.

- Discontinued CLIMB SCD-121: 11 patients discontinued CLIMB SCD-121 after starting mobilisation. Reason for discontinuation after starting mobilisation were: inadequate cell collections (6 patients), no longer met eligibility criteria for renal function (1 patient), non-compliance (1 patient), withdrew consent (2 patients), and psychological and physical stress (1 patient).

Patient disposition in CLIMB SCD-121 and CLIMB-131 (SCD only) at the D120 data cut-off is presented in Figure 1.

Figure 1: Patient disposition for CLIMB SCD-121 and CLIMB 131



Source: Figure 15, D120 report, data on file (14).
Abbrevations: exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; N: total number of patients; PES: Primary Efficacy Set
Notes: Patients listed as non-evaluable for PES are included in the FAS minus PES data set. For the 4 patients not yet dosed in Study 121 as of the data cutoff date, 1 patient has since been dosed and 3 are planned to be dosed by Q4 2023.

[a] The FAS included all patients who received exa-cel infusion.
[b] Reason for discontinuation after exa-cel: death due to COVID-19 infection that resulted in respiratory failure and was not related to exa-cel.
[c] Reason for discontinuation after starting mobilisation: inadequate cell collections (6 patients), no longer met eligibility criteria for renal function (1 patient), non-compliance (1 patient), withdrew consent (2 patients), and psychological and physical stress (1 patient).
[d] One patient enrolled in Study 131 after the data cutoff date.

A8. Priority Question: Please can the company provide clarification about the 20 participants in the enrolled set who did not receive exa-cel infusion?

Company response

Our response to A7 provides detail on the difference between the number of patients who had started mobilisation (Safety Analysis Set [n=58]) and the number who had received exa-cel infusion (Full Analysis Set [n=43]). There are a further 5 patients in the enrolled set (n=63). These 5 patients discontinued before mobilisation (Figure 1).

A9. Priority Question: Section 2.2.2 (Data on File D120 Report, page 15) states that three participants received a slightly lower than protocol specified minimum dose, due to previously having received exa-cel.

a. Please can the company provide additional information about the duration between the first and second dose.

Company response

Vertex would like to clarify that the wording 'patients who had previously received exa-cel' refers to patients who had received exa-cel prior to the adjustment to the exa-cel drug product calculation and does not mean that patients had more than one dose of exa-cel.

A total of 43 patients received exa-cel infusion at D120, with a median (range) dose of 4.7 (2.9 to 14.4) × 106 CD34+ cells/kg. Doses received for patients in the PES were generally similar to those received by patients in the FAS. Three patients received doses of 2.9 × 10^6 CD34+ cells/kg, this is slightly lower than the protocol specified minimum dose of 3.0 × 10^6 CD34+ cells/kg.

The reason for this is that early in the study, an adjustment was made to the exa-cel drug product calculation to account for the density coefficient of the final formulation medium and doses were recalculated, including for some patients who had previously received exa-cel. Upon recalculation, it was determined that 3 patients who had already received exa-cel in Study 121 received a dose of 2.9 × 106 CD34+ cells/kg (Study 121/Listing 16.2.5.1.5); which is lower than the protocol-specified minimum. In these 3 patients, neutrophil and platelet engraftment times and clinical

benefit were consistent with those who received the protocol-defined minimum dose or higher (≥3.0 × 10^6 CD34+ cells/kg) (Study 121/Listing 16.2.8.1).

No patients were dosed more than once.

b. Had these three participants experienced two VOC events per year for two consecutive years despite first a dose of exa-cel?

Company response

Please see our response to A9a, no patient received more than one dose of exa-cel.

A10. Priority Question: Please can the company clarify if people would require additional doses of exa-cel?

Company response

Please see our response to A9. Patients will not require additional doses of exa-cel. Exa-cel is a one-time treatment.

A11. Section B.2.3.2. (CS Document B, page 70) states that approximately 45 patients were planned to be dosed in the CLIMB SCD-121 pivotal study. Table 17 (CS Document B, page 78) states that 43 participants were included in the FAS analysis. However, section B.2.4.2. (CS Document B, page 80) states that 'With a total of 45 patients dosed…' Please can the company clarify the sample size?

Company response

As of D120, 43 patients had received exa-cel and were therefore included in the FAS (14). The text cited in Section B.2.4.2 relates to sample size considerations. As stated in the protocol, CLIMB SCD-121 may be expanded to include a total of up to approximately 45 patients dosed. This expanded sample size will provide an overall power of at least 95% to rule out a response rate of 50% or less for the primary efficacy endpoint when the true response rate is 80% for the primary efficacy endpoint. Assuming that the study will be expanded to a total of approximately 45 patients, 3 interim analyses (IAs) may be performed following a group sequential testing procedure. As described in our CS, the D120 data cut follows on from IA2 (14, 15).

A12. Priority Question: CS Document B, page 12 states there is variability in the definition of VOCs. Please can the company clarify how likely are licensing authorities to use the definition of VOC on page 12.

Company response

It was confirmed at the clarification call that by 'licensing authorities' the EAG are referring specifically to NICE.

As described in the CS, there is substantial variability in the definition of VOCs. In the broader scientific literature, VOC is typically used to refer to an acute pain crisis, whereas clinical trials often adopt a composite definition.

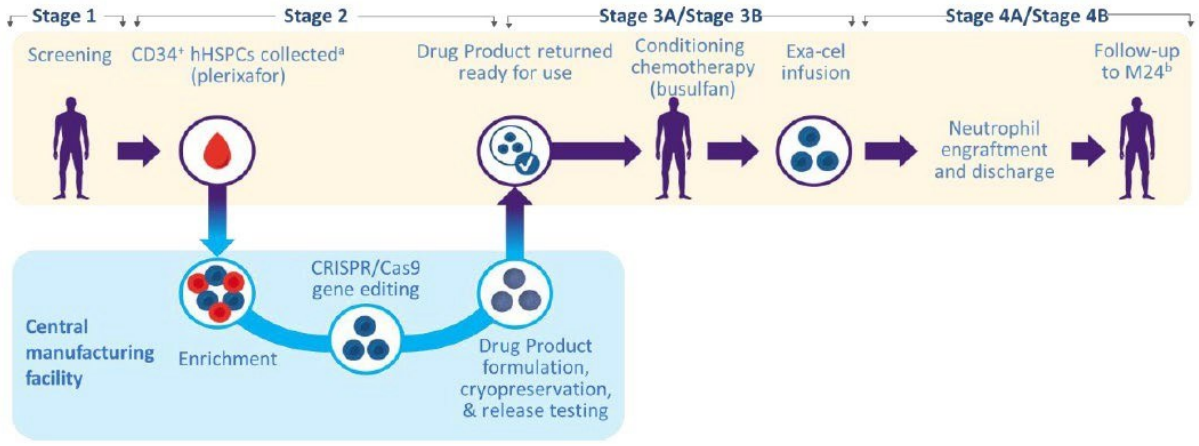
The final eligibility criteria for exa-cel, should reimbursement be achieved, will be subject to discussions between NICE and Vertex, and would be informed by CLIMB SCD-121, as well as the anticipated regulatory label and other stakeholders. It is possible that there may be wording in the summary of product characteristics or regulatory label that supports a decision on definition of VOC. However, at this stage, predicting the likelihood of NICE adopting a definition of VOC aligned to CLIMB SCD-121 would be purely speculative.

A13. Figure 3 (CS Document B, page 21) provides a schematic of the exa-cel treatment process. In stage 2, cells are frozen and tested. Please can the company provide details about what testing is?

Company response

As highlighted in Figure 2 below, cryopreservation and release testing are carried out on the isolated $CD34^+$ cells.

Figure 2: Exa-cel treatment process schematic



Key: CRISPR/ Cas9, clustered regularly interspaced short palindromic repeats-CRISPR associated 9 nuclease; HSPCs, haematopoietic stem and progenitor cells; M: month.
[a] Including collection of CD34+ cells as back-up for rescue therapy in the event of non-neutrophil engraftment with exa-cel.
[b] Patients were followed for approximately 2 years after the exa-cel infusion. All patients who received exa-cel were asked to enroll into the long-term follow-up study.
Source: Frangoul et al., (2020) (3).

This quality release panel includes viability, purity, content, potency, sterility, and other safety release tests. Quality release testing is performed on samples of edited cells and includes CD34+ cell purity analysis by flow cytometry, on-target editing frequency, post thaw cell count and viability as well as compendial sterility, mycoplasma and endotoxin testing. Some of the quality release tests require culturing CD34+ cells; they must grow and then differentiate, which is labour-intensive and takes many weeks.

A14. CS Document B, page 41 reports the mean (range) EQ-5D-5L utility score of 0.62 (0.29). Please can the company provide the range as stated?

Company response

The original source has been reviewed and page 41 should read ‘mean (8)’ instead of ‘mean (range)’ in relation to the EQ-5D-5L utility score of 0.62 (0.29) (16).

A15. Figure 10 (CS Document B, page 53) provides an epidemiological cascade for SCD in the UK. Of the 3,990 people with severe SCD (≥2 VOCs/year), how many of these are eligible for exa-cel treatment?

Company response

As depicted in the epi cascade (CS, Figure 10), Vertex expects that approximately 1,750 patients will be eligible for exa-cel in England, based on the anticipated regulatory label.

Of note, there are several additional clinical and real-world considerations for a gene-editing 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, it is likely that the number of exa-cel treated patients will only comprise a small proportion of the eligible SCD population.

A16. CS Document B, page 63 states that 'in response to a regulatory authority request…' Please can the company state which regulatory authority?

Company response

The D120 data cut was in response to a request from the Medicines and Healthcare products Regulatory Agency (MHRA).

A17. Table 12 (CS Document B, page 67) states that 'shipment of collected cells intended for manufacturing on the same day at 2°C to 8°C to the manufacturing facility.' Please can the company state if there is only one central manufacturing facility or if there are more, where are these located?

Company response

[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.

A18. In Table 18, (CS Document B, page 80) month was defined as 30 days. What part of the submission uses a 30-day month?

Company response

For patients who were lost to follow-up or died, safety or efficacy analyses were based on their available data before death or loss to follow-up and for these patients month was defined as 30 days (15). No other part of the submission uses a 30-day month.

A19. Figure 19 (CS Document B, page 94) provides a series of haemoglobin types. Please can the company define in terms of their polypeptide chains?

Company response

- HbF comprises two alpha and two gamma subunits.
- HbA comprises two alpha and two beta subunits.
- HbS comprises two alpha subunits.
- HbA2 comprises two alpha and two delta subunits.

A20. Figure 21 (CS Document B, page 97) reported the proportion of edited alleles in CD34+ bone marrow over time at D120 (%). Please can the company provide a legend for this figure?

Company response

Vertex have checked the cited figure against the D120 report, and can confirm that the figure legend is already present in the CS. This provides a similar level of detail to other figure legends, listing out abbreviations and noting any points where additional information is deemed to be required.

A21. Figure 22 (CS Document B, page 98) reported the proportion of edited alleles in peripheral blood cells over time at D120 (%). Please can the company provide a legend for this figure?

Company response

Vertex have checked the cited figure against the D120 report, and can confirm that the figure legend is already present in the CS. This provides a similar level of detail to other figure legends, listing out abbreviations and noting any points where additional information is deemed to be required.

A22. Section B.2.6.2.6. (CS Document B, page 99) reports a summary of haemolysis including the change in baseline lactose dehydrogenase (LDH). Please can the company clarify if this should be lactate dehydrogenase?

Company response

Thank you for pointing this out. To confirm, this should read lactate dehydrogenase (14).

Section B: Clarification on cost-effectiveness data

Literature searching (cost-effectiveness)

B1. Priority Question: The systematic literature review searches for cost-effectiveness, cost and healthcare resource use studies and health-related quality of life searches in Medline and the Cochrane Library are reported to have been undertaken on the Ovid platform. It is reported that the update searches for the clinical systematic literature review were undertaken using different platforms due to a change in database subscription. The searches for the economics and health-related quality of life were undertaken at the same time as the update searches (July 2023); however, the Medline and Cochrane searches for cost-effectiveness, cost and healthcare resource use studies and health-related quality of life searches uses syntax that is incompatible with Ovid and would impact the search results. Please clarify which interface was used to search Medline for the economics and health-related quality of life searches?

Company response:

Thank you for the opportunity to clarify. The statement relating to a change in database was an error in the CS. All searches were conducted in Medline (Ovid) and Embase (Elsevier). Vertex have explored the query relating to incompatible syntax, and have established that the issue relates to the erroneous use of a colon ':ab,ti' where '.ab,ti' should have been used. Updated searches with the syntax corrected, and details of any additional citations retrieved are provided as data on file, supplementary to our response, although we note that the difference in hits was minimal.

Population

B2. Section B.3.2.1. (CS Document B, page 136)

a. Please provide the rationale for not using the distribution of patient weight as per CLIMB SCD-121.

Company response

The CLIMB SCD-121 average weight cannot be used in the model given that a significant proportion transition from adolescents to adults over the model time horizon. Therefore, a weight ratio between the SCD cohort and general population was used to calculate cohort weight. At the time of submission, the weight ratio between the SCD cohort and general population had not been calculated and was thus based on clinical opinion.

Using the observed mean body weight from the CLIMB SCD-121 trial, we recalculate this weight ratio as [redacted]: the mean baseline weight of CLIMB SCD-121 trial patients ([redacted]) divided by the mean body weight of the age and gender matched UK general population (72.3kg) (15, 17). Implementing this scenario in the model has a negligible effect on the results. The DCEA and severity-modified ICER decreases by £10 ([redacted] to [redacted]). This has been included as an updated base case.

b. Please clarify the meaning of “baseline” in “At baseline, patients were assumed to experience an average of 4.2 VOCs per year (162).” And several other occurrences in this Section. Does “baseline” refer to the CLIMB SCD-121 population (all treated with exa-Cel) or to the model comparator, or as stated in Table 32, to overall model clinical inputs (i.e., both intervention and comparator)?

Company response

The term “baseline” in the text refers to patient characteristics, which are applied to both the intervention and comparator at baseline. However, key clinical baseline characteristics are also extrapolated forward throughout the model time horizon to represent clinical outcomes in the SoC arm, including the annual severe VOC rate of 4.2, the proportion receiving hydroxycarbamide, regular blood transfusions and ICT.

c. The report states that “No patient had any of the following complications at baseline: pulmonary hypertension, chronic kidney disease (trial criteria excluded estimated glomerular filtration rate (eGFR) <60ml/min), post-stroke,

heart failure, or liver disease since none of the conditions fall within the hepatic complications considered by the model." Please clarify how the statement above relates with the list of VOC-related complications included in the model (I "Model Inputs", Sheet "Introduction" of the model" and listed here below)

Risk of developing the following acute complications based on VOC frequency:

- Acute chest syndrome
- Stroke
- Acute infections
- Acute kidney injury/infarction
- Gallstones
- Pulmonary embolism
- Leg ulcers

Risk of developing the following chronic complications based on VOC frequency or occurrence of relevant acute complications:

- Chronic kidney disease
- Pulmonary hypertension
- Avascular necrosis
- Heart failure
- Neurocognitive impairment
- Post-stroke
- Sickle retinopathy
- Liver complications

Company response

Vertex understand from the EAG clarification call that this question related specifically to the hepatic disorders. The only hepatic disorders present at baseline (IA2 data cut, D120 data not available for medical history at time of analysis) were hepatomegaly [redacted] and post-cholecystectomy [redacted]. Neither of these conditions align with the hepatic conditions captured in the model, which are consistent with

those identified in the Vertex burden of illness (BoI) analysis and included hepatitis, cirrhosis, fibrosis, hepatic insufficiency, liver cancer and portal hypertension.

d. Please clarify whether the therapies stated as “Baseline clinical inputs” (Table 32, CS Document B, page 137), i.e., “The utilisation of hydroxycarbamide, RBC transfusions and iron chelation “patients treated with exa-cel are receiving additional supportive care including exchange transfusions to lower the risk of VOCs during the treatment phase therapy (ICT) at baseline was informed by CLIMB SCD-121 and the literature” refers to clinical trial data or to the model comparator, or to general model inputs as stated in the heading of Table 32.

   Table 32: Baseline clinical inputs [extract]

Hydroxycarbamide
RBC transfusion
Iron chelation therapy (among those receiving RBC transfusion)
DFO
DFX
DFP
DFO+DFX
DFO+DFP
DFX+DFP

Company response

As per our response to part b), the therapies stated as “Baseline clinical inputs” refer to patient treatment characteristics at baseline. These treatment characteristics are extrapolated forward throughout the model time horizon in the SoC arm. The RBC transfusions and iron chelation therapy (ICT) are applied to the proportion of patients requiring chronic blood transfusions at baseline, prior to treatment with exa-cel and requiring ongoing treatment as part of SoC. The study medical history did not collect information on the proportion of patients who required chronic blood transfusion to manage their SCD prior to trial entry, therefore this parameter and the ICT use for this patient cohort was sourced from the literature. Hydroxycarbamide use on the other hand was sourced from the CLIMB SCD-121 clinical study.

Model Structure

B3. Priority Question: Section B.3.2.2. states that "A Markov cohort state-transition model was developed in Microsoft Excel®". Please clarify whether the model is a Markov state-transition model or otherwise.

Company response

Vertex can confirm that the model structure is a Markov cohort state-transition model.

B4. Priority Question: Please clarify the match between the following statements:

- **"For exa-cel, only patients who are infused are included in the modelled cohort. Patients who withdraw from treatment prior to infusion or transplant in the clinical trial are assumed to withdraw prior to myeloablation, and these patients are not included in the modelled cohort. However, the costs of pre-mobilisation, mobilisation and apheresis for these patients are included as additional costs in the pre-transplantation costs" (CS Document B, page 140)**

- **"The exa-cel, treatment phase includes pre-mobilisation, mobilisation and apheresis, myeloablative conditioning and infusion, and engraftment. The treatment phase is assumed to last for 12 months, based on CLIMB SCD-121. Treatment withdrawal is defined as patients who were never dosed with exa-cel; thus, these patients were not analysed in the FAS or PES trial data. Eleven out of 58 patients withdrew from the exa-cel arm. Patients with engraftment failure from exa-cel were assumed not to receive any clinical benefits from exa-cel and would continue receiving SoC as per baseline" (CS Document B, page 151).**

- **Among modelled patients treated with exa-cel, all of whom achieved engraftment success (CS Document B, page 151).**

Company response

Patients who withdrew before infusion with exa-cel did so between stem cell harvest and myeloablation. The costs of these patients are captured via a cost uplift, by multiplying the cost of pre-treatment by the proportion of patients who withdrew and adding this value to the pre-treatment costs already applied to 100% of the model cohort. Outcomes of these patients are not included in the model, as per our response to question B5.

B5. Priority Question: Please clarify how the model incorporates the clinical course of disease for people who are never dosed (19% of the CLIMB SCD-121 patient population).

Company response

The model does not capture the clinical outcomes of patients who are not dosed with exa-cel; 100% of the cohort represents the outcomes of patients dosed with exa-cel.

B6. Priority Question: Section B.3.2.3. (CS Document B, page 150) Please provide a thorough definition of intervention and comparator. The Section states that exa-cel is the intervention, however the model assumes that for the first year, patients are not functionally cured; in this case, patients in the intervention still receiving SoC for the first year. Page 151 of CS Document B states that "patients treated with exa-cel are receiving additional supportive care including exchange transfusions to lower the risk of VOCs during the treatment phase", therefore the intervention appears to be "Exa-cel+ enhanced SoC" compared with SOC. Please clarify.

Company response

The model assumes that all patients receive 5 supportive transfusions: 2 pre-transplant and 3 post-transplant following treatment with exa-cel. A proportion of these are effectively double-counting transfusions received by the 16% chronically transfused patients referred to in question B2d, who would already be receiving transfusions as part of their SoC.

B7. Priority Question: The company stated that ITC were undertaken but not used in the model because the number of baseline VOCs among SCD patients on SOC incorporates efficacy associated with SoC.

a. Please can the company clarify if there is functionality in the model to use the results from the ITC?

Company response

The model does not have the functionality to use results from the ITC for SoC.

B8. Priority Question: Please can the company clarify how the severity of VOCs experienced by people are captured in the model?

Company response

The model only captures severe VOCs, in line with the CLIMB SCD-121 primary endpoint. The definition of "severe VOC" according to the CLIMB SCD-121 was (15):

- Acute pain event that requires a visit to a medical facility and administration of pain medications (opioids or IV NSAIDs) or RBC transfusions;
- Acute chest syndrome, as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever;
- Priapism lasting >2 hours and requiring a visit to a medical facility;
- Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in haemoglobin concentration of ≥2 g/dL.

The model therefore does not capture the disutility of less severe VOCs managed at home and may underestimate the benefit of exa-cel on quality of life.

B9. Table 33 (CS document B, page 141) outlines the features of the base-case economic analysis. The company stated that the justification for the one-month cycle length (with half-cycle correction) is to capture meaningful changes in patient disease history and treatment effects. Please can the company outline how patient history is being captured in the model?

Company response

The sentence should have read “patient disease natural history”; that is, the risk of development of comorbidities conditional on having SCD either with or without experiencing a VOC in each model cycle.

Model inputs

B10. Priority Question: Mortality inputs

a. Please clarify why the values for the 65-74 years old are lower than those for younger groups.

Table 39: Mortality inputs (obtained from CS Document B, pages 161-162)

Variable	Value	Reference
Annual SCD-specific mortality rate by age (%)		
0 years old	0.13	Bradt et al., 2020 (18)
1-4 years old	0.04	
5-9 years old	0.03	
10-14 years old	0.03	
15-19 years old	0.07	
20-24 years old	0.16	
25-34 years old	0.23	
35-44 years old	0.47	
45-54 years old	0.70	
55-64 years old	1.12	
65-74 years old	0.68	
75+ years old	8.47	

Company response

These data were replicated from Bradt et al., 2020., Table E2. Age-specific Annual Probability of Death – adjusted by risk factors p.180 (18). Data are reported in Table 4 below. The reason for the value being lower in the 65-74 years old group is unknown.

Table 4: Age-specific Annual Probability of Death – adjusted by risk factors

Age	Percent that die at each age	Probability of Death	Probability of Death (Annual)	Adjusted by Risk Factors
0 years old	1.5%	0.0150	0.0150	0.013

1-4 years old	2%	0.0203	0.0051	0.0004
5-9 years old	1.5%	0.0155	0.0031	0.0003
10-14 years old	1.5%	0.0158	0.0032	0.0003
15-19 years old	4%	0.0428	0.0087	0.0007
20-24 years old	8%	0.0894	0.0186	0.0016
25-34 years old	20%	0.2454	0.0278	0.0023
35-44 years old	27%	0.4390	0.0562	0.0047
45-54 years old	20%	0.5797	0.0820	0.0070
55-64 years old	11%	0.7586	0.1325	0.0111
65-74 years old	2%	0.5714	0.0812	0.0068
75+ years old	1.5%	1.0000	0.9688	0.0812

b. Please clarify how the “mortality rate for engraftment failure” (25%, here below) is applied in the model, given instances in the report that state there are no exa-cel transplant related deaths in the model.

Table 38: Mortality inputs

Instant mortality (rate)		
Engraftment failure (exa-cel) (%)	25.00	Assumption

Company response

The model accounts for two transplant-related mortality parameters. One is transplantation-related mortality, which is set to zero, as there were no exa-cel transplant-related deaths in the clinical study. The other is engraftment failure mortality, assumed to be 25% based on clinical expert input. Vertex confirm that this is not applicable in the model base case as there were no engraftment failures in the clinical study to date.

Resource use and costs

B11. Section B.3.5.1 Intervention and comparators costs and resource use

a. CS Document B, Page 171 states that "The cost of hospitalisation for exa-cel infusion is £5,375 and myeloablative conditioning is £25,387. This value is based on a weighted average of the NHS reference cost codes for autologous peripheral blood stem cell transplant tariff for 19 years and over (SA26A), and 18 years and under (SA26B) (233)." Please provide details of the weighting methodology.

Company response

The myeloablative conditioning cost of £25,387 was calculated based on a weighted average of adult vs paediatric HRG codes, as shown in Table 5 below. The weighting is determined by the proportion of patients in the FAS who were under 18 (28%).

Table 5: Weighted average calculation of myeloablative conditioning cost

HRG code	Unit cost	Weight
Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over [Elective Inpatient, SA26A]	£19,135	0.72 (Proportion ≥18 years old from 'D120 data from CLIMB SCD-121 (FAS, Table 15))
Peripheral Blood Stem Cell Transplant, Autologous, 18 years and under [Elective Inpatient, SA26B]	£41,535	0.28 (Proportion <18 years old from 'D120 data from CLIMB SCD-121 (FAS, Table 15))
Weighted Average:		£25,387

Please note that the calculations can be found in the model in the "Central data control" sheet, table B195:D198.

b. Table 42 (CS Document B, page 172): Exa-cel treatment and transplant related costs: please provide two separate tables, one for unit costs and one for resource consumption.

Company response

The unit costs are presented in Table 6 below.

Table 6: Exa-cel treatment and transplant related unit costs

Variable	Value	Reference/Source for assumption
Exa-cel acquisition costs		
Acquisition cost	[redacted]	Company
Discount	[redacted]	Company
Pre-transplant costs (exa-cel)		
Assessments during the pre-mobilisation period		
Haematology outpatient appointment, follow-up, unit cost	£209	Non-admitted face-to-face attendance, Follow-up, OP, Consultant Led, Clinical Haematology Service, Currency code: WF01A, Service Code: 303. NHS reference costs 2021-22 (19)
Brain MRI/MRA unit cost	£198	Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over, IMAG, Imaging: Outpatient, Currency code: RD02A. NHS reference costs 2021-22 (19)
DLCO (corrected) test unit cost	£141	Full Pulmonary Function Testing, DZ52Z, DADS. NHS reference costs 2021-22 (19)
Echocardiogram unit cost	£134	Simple Echocardiogram, 19 years and over, RD51A, IMAG. NHS reference costs 2021-22 (19)
Transcranial Doppler (TCD) ultrasound unit cost	£85	Weighted average of Ultrasound Scan with duration of 20 minutes and over, without and With Contrast, IMAG, Imaging: Outpatient, Currency code: RD42Z, RD43Z. NHS reference costs 2021-22 (19)
Fertility preservation		
One-time retrieval surgery	£1,787	Weighted average of CLIMB SCD-121 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 (19)

Monthly storage costs	£19	Price chart from an NHS fertility centre (20)
Mobilisation costs		
Mobilisation cost	£5,375	Peripheral Blood Stem Cell Harvest, APC, Elective Inpatients, Currency code: SA34Z. NHS reference costs 2021-22 (19)
Plerixafor cost per unit (vial)	£4,880	Plerixaform, BNF
Busulfan cost per unit (vial), scenario only	£169	Busulfan, eMIT
Pre-transplantation RBC transfusion costs		
RBC exchange costs per unit	£261	NHS Blood and Transplant price list (21)
Total RBC transfusion costs	£13,488	Calculated
Hospitalisation costs for procedure		
Hospitalisation cost for inpatient stay during exa-cel procedure	£25,387	NHS reference cost Elective Inpatient Peripheral Blood Stem Cell Transplant SA26A and SA26B HRG codes, weighted by CLIMB SCD-111 age distribution

The quantity of HRU is presented in Table 7 below.

Table 7: Exa-cel treatment and transplant related resource consumption

Variable	Value	Reference/Source for assumption
Pre-transplant unit costs (exa-cel)		
Assessments during the pre-mobilisation period		
Haematology outpatient appointment, follow-up, frequency	1	KOL
Brain MRI/MRA, frequency	1	KOL
DLCO (corrected) test frequency	1	KOL
Echocardiogram frequency	1	KOL
TCD ultrasound frequency	1	KOL
Fertility preservation		
Proportion of patients requiring fertility preservation	100%	Assumption
Mobilisation costs		
Mobilisation cost multiplier	2	Mobilisation in the NHS typically takes 1-2 days whereas 3 were required pre- exa-cel (22).
Plerixafor unit concentration (mg/1ml)	24	Plerixaform, BNF
Busulfan unit concentration (mg/10ml), scenario only	60	Busulfan, eMIT
Mobilisation HCRU		

Mobilisation cycles	2.2	CLIMB SCD-121
Plerixafor daily dose (mg/kg)	0.24	CLIMB SCD-121
Plerixafor treatment duration (days)	4	CLIMB SCD-121 (15)
Busulfan daily dose (mg/kg), scenario only	2.98	D120 data from CLIMB SCD-121
Busulfan treatment duration (days)	4	D120 data from CLIMB SCD-121 (14)
Pre-transplantation RBC transfusion costs		
Number of RBC transfusions required prior to exa-cel transfusion	5	Assumption

c. Cost of fertility preservation: Please provide details of weighting methodology.

Company response

The cost of fertility preservation of £1,787 was calculated based on a weighted average of two HRG codes, as shown in the table below. The weighting is based on the proportion of female (44%) vs. male patients in the FAS.

HRG code	Unit cost	Weight
Oocyte preservation - Oocyte Recovery, Gynaecology Service, OPROC, Currency code: MC12Z, Service Code: 502. NHS reference costs 2021-22	£3,350	0.44 (Female percentage in 'CTX001-111/121/131 (FAS))
Sperm preservation - Collection of Sperm, Urology Service, OPROC, Currency code: MC21Z, Service Code: 101. NHS reference costs 2021-22	£550	0.56 (male percentage in 'CTX001-111/121/131 (FAS))
Weighted Average:		£1,787

Please note that the calculations can be found in the model in the “Central data control” sheet, table B200:G202.

d. Table 42 (CS Document B, page 172), line as below: please clarify when this information is used?

Busulfan administration costs, applied in scenario, scenario only	£314	Busulfan, eMIT

Company response

The costs of myeloablation, including the cost of busulfan and its administration, are only included in a scenario analysis. In the base case we assume that these costs

are included in the NHS transplant tariff, based on clinical opinion and published information that the NHS transplant tariff includes patient management costs in the 30 days preceding the transplant, which would include myeloablation (23) .This scenario can be applied by choosing 'Yes' from the dropdown list in cell E81 on the 'Cost Inputs' sheet.

e. Table 42 (CS Document B, page172), line as below. Please provide details of weighting methodology.

Hospitalisation cost for inpatient stay during exa-cel procedure	£25,387	NHS reference cost Elective Inpatient Peripheral Blood Stem Cell Transplant SA26A and SA26B HRG codes, weighted by CLIMB SCD-111 age distribution

Company response

As per our response to B11a, the weighting is based on the proportion of patients aged under 18 (28%) in the FAS.

f. With relation to point B3 of this document, and CS Document B, page 151 states that patients are still treated with SoC in the first year alongside transplant, and that “patients treated with exa-cel are receiving additional supportive care including exchange transfusions to lower the risk of VOCs during the treatment phase”. Please provide an explanation for how the costs of SoC and “additional supportive care including exchange transfusions to lower the risk of VOCs” have been calculated and incorporated in the model.

Company response

As per our response to question B2d, the quantities of RBC transfusions and ICT for those patients receiving SoC were based on an assumption from the literature of the proportion of the model cohort chronically transfused at baseline.

The 5 additional pre-treatment exchange transfusions, fertility treatment and other imaging/diagnostic tests was based on clinical opinion. The 5 additional pre-treatment exchange transfusions were costed using the same assumptions as the chronically transfused patients, outlined in Table 8 below:

Table 8: Costings of the additional pre-treatment transfusions

Pre-transplantation RBC transfusion costs	Value	Source
RBC exchange costs per unit	£261	NHS Blood and Transplant price list (21)
Number of RBC units per administration	10	Assumptions based on NICE crizanlizumab STA [ID1406] (24)
Staff time	£49	Assumptions based on NICE crizanlizumab STA [ID1406] (24)
Disposables	£41	Assumptions based on NICE crizanlizumab STA [ID1406] (24)
Administration cost per transfusion	£90	Calculated: (Staff time + Disposables)
Number of RBC transfusions required prior to exa-cel transfusion	5	Includes 3 RBC transfusions pre-mobilisation and 2 RBC transfusions pre-transplantation. Assumption based on expert opinion.
Total RBC transfusion costs	£13,488	Calculated: (cost per unit * number of units + administration cost) * Number of transfusions

g. Table 46 (CS Document B, page 177). Please state resource consumption associated with the unit costs reported.

Company response

The ERG report of the Betibeglogene committee papers reported an annual post-transplantation monitoring cost of £1,128 for year 1 and 2 and £927 for year 3 and 4 as showing in Figure 3. As these were reported in 2018 cost values, we inflated to 2021 values by multiplying by an inflation adjustment factor of 1.0621 (=114.0/107.3), and then adjusted to monthly estimates to reflect our one-month cycle length by dividing by 12. This results in estimates of £99.84 per month for years 1 and 2 and £82.05 for years 3 and 4. The year 3/4 costs (£82.05) were conservatively applied for up to 15 years of post-transplant monitoring (i.e., years 3-15).

As the Betibeglogene NICE committee papers did not include the full company submission (i.e., Document B), we were unable to determine the resource

consumption associated with the unit costs reported, which were also absent from the EAG section.

Figure 3: screenshot of table 14: Summary of the costs included in the economic model from the ERG report of the Zynteglo NICE committee

Description of cost	Patients ≤18 years	Patients >18 years	Source
Zynteglo			
Zynteglo acquisition cost	[redacted]	[redacted]	bluebird bio, includes PAS
Pre-transplant cost	£27,057	£27,130	
Transplant-related costs	£34,539	£18,529	NHS Reference Costs[68]
Post-transplant monitoring costs – Years 1 & 2	£1,128	£1,128	NHS Reference Costs[68]
Post-transplant monitoring costs – Years 3 & 4	£927	£927	NHS Reference Costs[68]

B12. Please can the company provide the Cox model that was used to derive the hazard ratio of '1.56x' increased risk of death compared to patients with SCD without VOCs?

Company response

The Cox model was sourced from Shah et al 2019 (25) where Cox models were applied to examine the relationship between the frequency of VOCs and clinical endpoints. Patients who had a follow-up VOC had a 0.55 higher hazard of death than those without a follow-up VOC (95% CI [1.19-2.05]; p value=0.0014). Patients with VOC were also more likely to develop life-threatening complications including ACS (HR=58.67; 95% CI [50.21-68.55]; p value <0.0001), splenic sequestration (HR=34.99; 95% CI [30.65-63.13]; p value<0.0001), pulmonary hypertension (HR=4.12; 95% CI [3.14-5.41]; p value <0.0001), pulmonary embolism (HR=2.82; 95% CI [2.21-3.58]; p value<0.0001), and stroke (HR=2.26; 95% CI [1.94-2.63]; p value <0.0001)

Health-related quality of life

B13. Priority Question: Section B.3.4.1. Health-related quality of life data from clinical trials (CS Document B, page 164)

a. Please clarify how utility data were measured, and how clinical trial utility data were summarised and analysed, including any relevant presentation of the data, measures of variability, and full analysis methods and results, including goodness-of-fit statistics (Table 40 CS Document B, page 164).

Company response

As explained in section B.3.4.1 of the dossier, 5L utility values collected in the CLIMB SCD-121 study were mapped to the 3L UK value set using the Hernandez-Alava algorithm to generate utilities. There are no analysis methods to present, as the values shown in Table 40 of the submission represent simple summary statistics for those patients with available data at that timepoint at the time of the D120 data cut. The utility value of a "cured" patient was calculated as the baseline value of the cohort plus the mean change in utility of 0.11 after 24 months. Measures of uncertainty are presented in Table 40 as well as in Table 22 of the submission.

b. Please provide full characterisation of mapping methods used for utilities.

Company response

The UK index value was calculated from the EQ-5D-5L responses based on the Hernandez-Alava mapping algorithm at ADQS domain level. There was no published software package for SAS, so according to biostats' instructions, we created our only code based on table5v5.csv mapping instruction file, which could be downloaded from the R command and examples tab on https://www.sheffield.ac.uk/nice-dsu/methods-development/mapping-eq-5d-5l-3l.

c. Please provide summary baseline characteristics (including baseline utilities and country) for patients whose utility data were used in the model AND for patients whose data were discarded from the analyses.

Company response

Table 17 of the submission presented the baseline characteristics for the PES, which provided utility values for the model. Table 40 as well as in Table 22 of the submission provide the utilities at baseline. No data were 'discarded' from the analysis. Missing data at later timepoints is due to administrative censoring of patients who have not achieved the relevant length of follow-up. As explained in part

e), baseline characteristics of patients with administrative censoring are not available at the time of response.

The patient enrolment sites were spread across four countries: According to the FAS group in the most recent data cut, patient enrolment sites were distributed among four countries as follows: [redacted] (14).

d. Please provide the justification why patients who received exa-cel, modelled as “cured” at month 12, are assigned the utility value of month 24, instead than the value at month 12, also reported in data analyses.

Company response

The model was structured prior to availability of clinical data, into either cured or uncured, and at the time significant differences between month 12 and month 24 were not anticipated. HRQoL outcomes have been shown to improve as patients are further away from the time of HSCT in both longitudinal and cross-sectional studies (26). As the “cured” utility value is applied to the remainder of the time horizon, using the value at 12 months would underestimate long-term utility in the model.

e. Please provide baseline data for patients who are excluded from the utility data analysis at month 18 and 24.

Company response

As explained in part c), this data, which would require a post-hoc analysis, was unavailable at the time of the response. However, Vertex will strive to conduct this analysis ahead of technical engagement.

f. Please clarify how the utility value for VOC (-0.18) was calculated.

Company response

In the NICE crizanlizumab company submission, a VOC was associated with a 0.46 utility decrement incurred over 12 days (0.36 utility decrement during VOC which was assumed to last 2 days prior to hospitalization and 3 days during the hospitalization, and 0.10 decrement for 7 days post-hospitalization). Given the model uses month-long cycles, the disutility was adjusted to account for the proportion of

the month the VOC lasted: 0.46 disutility x (12 days / 30.4375 days per month) = 0.18 disutility per VOC in a month-long cycle.

g. Please exclude Section 3.4.5 (CS Document B, page 166) regarding caregiver disutility from the report.

Company response

As discussed at the EAG clarification call, caregiver disutility is included in scenario analyses only, therefore this section of the dossier is relevant, given NICE methods specify that carer utility can be considered as part of scenario analyses.

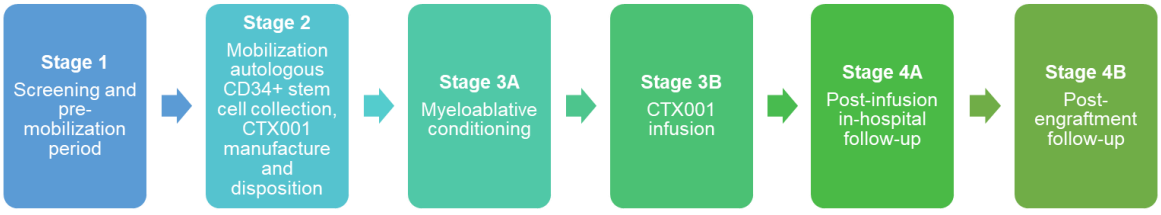
h. Please provide a model and model results that excludes caregiver disutilities from the base-case analyses.

Company response

The submitted model excludes caregiver disutilities in all base-case analyses. Vertex have only included caregiver disutility in two scenarios: a standalone caregiver disutility scenario and the societal perspective scenario. Caregiver disutilities can be included by switching the 'cdc_disutility_carer' parameter to a value of 2, in cell E105 of the 'Central data control' sheet. To exclude caregiver disutility, the user can switch the same cell back to a value of '1'.

B14. Priority Question: Patients withdrawal from CLIMB 121and costing of intervention. Figure 13 (CS Document B, page 69) provides a schematic of the therapeutic process involved in administering exa-cel in the CLIMB 121 study.

Figure 4: Exa-cel Treatment Process in Stages



Source: CLIMB SCD-121 Study Protocol (168).

Figure 13: CLIMB SCD-121 study design (from Document B, page 69)

CS Document B (Page 70) states that "At the time of D120, 63 patients were enrolled in the pivotal CLIMB SCD-121 clinical study (Stage 1, Fig 13). Of these, 43 patients had received exa-cel infusion (7)" (Stage 3B).

With respect to the statements in clarification question B14, please clarify the following:

a. **D120 being an administrative cut-off set by the regulator, please clarify whether all 63 patients enrolled are still in the trial – or if any have been withdrawn.**

Company response

At the time of the D120 cut off, as presented in Figure 1, of the 63 enrolled patients, 5 discontinued before mobilisation, and a further 11 patients discontinued prior to exa-cel treatment. A further patient discontinued after treatment with exa-cel, with the reason for discontinuation being death due to COVID-19 infection that resulted in respiratory failure and was not related to exa-cel.

b. Please clarify how many patients recruited to the study have reached (and are retained, or have failed (if any, therefore withdrawn) each of the therapeutic steps described in the Company Submission (Stage 2, Stage 3a, Stage 3b):

• **Mobilisation, autologous CD34+ stem cell collection, exa-cel manufacture and disposition (Figure 4; Stage 2):**	
• Stem cell mobilisation by apheresis for three consecutive days	• Number of patients who failed (withdrawn)
• Target collection of $CD34^+$ cells for manufacturing of exa-cel • Up to 3 cycles of mobilisation and apheresis, separated by ≥14 days	• Mean number of cycles of mobilisation per patient • Number of patients who failed to provide the minimum target quantity of cells for manufacture. It is assumed that for these patients, exa-cel would not be manufactures (please confirm or clarify if otherwise)
• Shipment of collected cells to manufacturing facility	• Assumed 100% success, please clarify of otherwise
• Manufacturing of exa-cel from collected $CD34^+$ cells	• Number of patients for whom the manufacture process did not provide sufficient quantity of exa-ecl for re-

	shipment (The ERG assumes that all productive processes are 100% efficient and successful, however there may be reasons for failure related with cell viability, i.e. cells of potentially insufficient quality to be imputed into the process, yield lower than expected, cells which failed to survive etc..)
• **Myeloablative conditioning (Figure 4; Stage 3A) and infusion of exa-cel (Figure 4; Stage 3B):**	
○ RBC transfusions for ≥8 weeks prior to planned conditioning to achieve a goal of HbS% <30% and maintaining total haemoglobin ≤11 g/dL	• Assumed 100% success, please clarify of otherwise
○ Conditioning (Stage 3A):	• Number of patients who started conditioning; number of patients who failed conditioning (if any)
○ Infusion of exa-cel (Stage 3B)	• Number of patients (if any) who failed to have sufficient quantities of exa-cel for infusion. If any, please specify whether any patients were reinfused with exa-el at sub-therapeutic dose (i.e. less than 3×10^6 $CD34^+$ cells/kg)

Company response

Table 9: Clarification of patient disposition at requested stages of treatment process

• **Mobilisation, autologous CD34+ stem cell collection, exa-cel manufacture and disposition (Figure 4; Stage 2):** 58 patients	
• Stem cell mobilisation by apheresis for three consecutive days	• 11 patients started mobilisation but have subsequently been discontinued from trial and have not been dosed with exa-cel. • Of these, 5 patients did not proceed to mobilisation because they withdrew consent/non-compliance/were no longer eligible • 6 patients did not proceed to conditioning as they did not achieve the minimum dose due to inability to manufacture drug product (low manufacturing yield or drug product did not meet release testing specifications)
• Target collection of $CD34^+$ cells for manufacturing of exa-cel	• Mean number of mobilisation cycles in whole cohort = 2.21 (SD 1.30). Median number of mobilisation cycles = 2.00 • 6 patients did not achieve the minimum dose due to inability to manufacture drug product (low

• Up to 3 cycles of mobilisation and apheresis, separated by ≥14 days	manufacturing yield or drug product did not meet release testing specifications)
• Shipment of collected cells to manufacturing facility	• 100%
• Manufacturing of exa-cel from collected $CD34^+$ cells	• 6 patients did not achieve the minimum dose due to inability to manufacture drug product (low manufacturing yield or drug product did not meet release testing specifications)
• **Myeloablative conditioning (Figure 4; Stage 3A) and infusion of exa-cel (Figure 4; Stage 3B): 43 patients**	
○ RBC transfusions for ≥8 weeks prior to planned conditioning to achieve a goal of HbS% <30% and maintaining total haemoglobin ≤11 g/dL	• 100%
○ Conditioning (Stage 3A):	• 43 patients started and completed conditioning. No patients failed conditioning.
○ Infusion of exa-cel (Stage 3B)	• Patients did not proceed with myeloablative conditioning until sufficient quantity of exa-cel had been manufactured and shipped to the centre. All patients who had myeloablative conditioning had sufficient quantities of exa-cel for infusion. • Three patients received doses of 2.9×10^6 $CD34^+$ cells/kg, this is slightly lower than the protocol specified minimum dose of 3.0×10^6 $CD34^+$ cells/kg • The reason for this is that early in the study, an adjustment was made to the exa-cel drug product calculation to account for the density coefficient of the final formulation medium and doses were recalculated, including for some patients who had previously received exa-cel. Upon recalculation, it was determined that 3 patients who had already received exa-cel in Study 121 received a dose 2.9×10^6 $CD34^+$ cells/kg; (Study 121/Listing 16.2.5.1.5) slightly lower than the protocol-specified minimum. In these 3 patients, neutrophil and platelet engraftment times and clinical benefit were consistent with those who received the protocol-defined minimum dose or higher (≥3.0×10^6 $CD34^+$ cells/kg) (Study 121/Listing 16.2.8.1). • The wording 'patients who had previously received exa-cel' refers to patients who had received exa-cel prior to the adjustment to the exa-cel drug product calculation and does not

	mean that patients had more than one dose of exa-cel

Resource use and costs

B15. Priority Question: Costing of exa-cel for patients who are not infused. With respect to the patient flow above (clarification question B14), and with respect to the statement "Pre-transplant costs included both mobilisation/apheresis costs and all other transplant preparation costs (e.g., labs, physician visits, transfusions). Patients who withdrew from treatment incur a pre-transplant cost but do not incur transplantation and treatment-related costs." (CS Document B, page 169), please clarify how costs of the intervention (exa-cel) have been modelled, specifically referring to:

a. Cost of manufacturing for patients who fail to successfully complete myeloablative conditioning.

Company response

Vertex assume the EAG means "do not proceed to myeloablative conditioning" given that once a patient has undergone myeloablation, they have to proceed to transplant as they have no white blood cells. [redacted]

b. Cost of infusion for patients for whom an insufficient quantity of exa-cel becomes available (according to minimum therapeutic dosage).

Company response

[redacted]

B16. Priority Question: Please can the company provide a model that excludes societal costs.

Company response

The model base case results are from the NHS and PSS perspective, which exclude the societal costs. The Societal perspective can be selected using the Control' sheet, Dropdown list in cell D10.

Assumptions

B17. Table 34 (CS document B, page 153) referenced expert opinion for an assumption about duration of treatment phase. Please can the company clarify why an assumption based on clinical expert opinion is made about the 12-month duration of treatment phase?

Company response

The treatment phase is assumed to last for 12 months, based on estimates of the different treatment phases in the CLIMB SCD-121 protocol. This duration was validated by expert opinion as being relevant to UK clinical practice, as explained in the text on page 151 of the submission.

Treatment effectiveness

B18. CS Document B, page 153 states that 'long-term efficacy following exa-cel is the most plausible outcome based on the published literature on SCD patients treated with allo-SCT.' Please can the company provide reference(s) to support this statement?

Company response

Martin et al, 2022 (27) reported that among 2-years survivors, the overall incidence of graft failure (leading to recurrent disease) that occurred beyond 2-years after transplantation was 7% (95% CI 5 – 9). When examined by donor type, the risk of graft failure beyond 2 years after transplantation was higher after alternative donor (HR 2.59, 95% CI 1.94 – 3.46, p<0.0001; 12% [95% CI 8–18]) compared to HLA-matched sibling transplantation (4% [95% CI 3–6]). 73% of patients with graft failure showed mixed donor chimerism, a risk factor not relevant to patients treated with exa-cel.

Results

B19. The EAG notes that the model overestimates the prevalence of neurocognitive impairment (CS Document B, page 230, 47.6% in the current model vs 14.0% and 9.6% in US and UK analyses, respectively). Please can the company clarify if there are other prevalence that might have been overestimated in the current model?

Company response

The prevalence of chronic complications predicted by the current model was compared with subgroup results derived from an analysis of US and UK claims data conducted by Vertex, as presented in Table 10 (28). The data indicates that the model only overestimates the prevalence of neurocognitive impairment, whereas the prevalence of all other conditions closely aligns, differing by less than 15%. Therefore, as of our current assessment, we do not believe there are any other prevalence estimates that have been overestimated in the model.

Table 10:Prevalence of chronic complications predicted by economic model compared to US and UK claims analyses

Complication	Proportion of patients who develop complications over a lifetime in model	US Burden of Illness Study prevalence (age ≥36) N=392	UK Burden of Illness Study prevalence (age ≥36) N=249
Chronic kidney disease	[redacted]	[redacted]	[redacted]
Pulmonary hypertension	[redacted]	[redacted]	[redacted]
Avascular necrosis	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]
Neurocognitive impairment	[redacted]	[redacted]	[redacted]
Post stroke*	[redacted]	N/A	N/A
Retinopathy	[redacted]	[redacted]	[redacted]
Liver complications	[redacted]	[redacted]	[redacted]

Abbreviations: SCD, sickle cell disease; UK, United Kingdom; US, United States. *Post stroke prevalence was not reported in the literature.

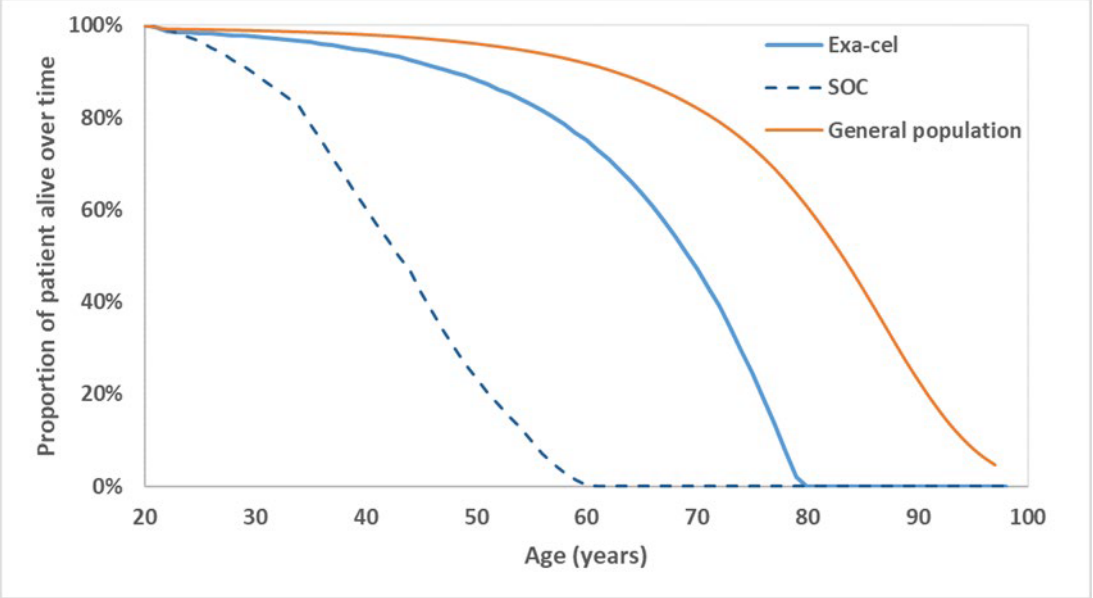
B20. Priority Question: Please can the company provide a graphical representation of overall survival from the model for participants receiving exa-cel and SoC, and UK general population matched to age and gender of the trial?

Company response

The overall survival graph is provided in Figure 5 below. It presents the survival of patients over time given each comparator. Over a lifetime horizon, patients treated with exa-cel had a substantial increase in survival of [redacted] years compared to SoC. The mean survival (i.e., age at death) of patients receiving exa-cel was [redacted] vs [redacted] years for patients treated with SoC.

Please note that this graph was reported in Appendix J1.1. It can also be found in the model, on the sheet 'Addl clinical results,' cell I37.

Figure 5: Survival extrapolation over time



B21. Priority Question: Please can the clarify how repeated treatment (cost inputs worksheet, cell D16) is being used in the model?

Company response

Vertex can confirm that the repeated treatment cost was not applied in the model.

Distributional cost-effectiveness analysis

B22. Section 3.9, CS Document B, page 193 states that "Firstly, 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." Please provide references or precedents that support of this statement.

a. Figure 43, CS Document B Appendix L, page 146: inequality aversion input. Please provide full methods and justification for how the value of "11" was obtained. Please justify the choice of this value.

Company response

The value for the aversion to inequality in the exa-cel DCEA was informed by the data from Robson M., et al. 2017 (29). A systematic literature review (SLR) of inequality aversion values for the UK has also been conducted (30). 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 (31, 32).

b. Figure 44, CS Document B Appendix L, page 147: eligible population shares. Please provide full methods and justification for how the values in the Table were derived.

Company response

These values are used for the IMD quintile distribution for the eligible treatment population. The values were derived from Vertex's Burden of Illness study data, discussed in B26 below.

c. Figure 45, CS Document B Appendix L, page 147: general population shares. Please provide full methods and justification for how the values in the Table were derived.

Company response

These values are based on Love-Koh et al. 2020 (33). Specifically, these values are taken from Table 2 of the article. These data were derived from Hospital Episode Statistics (27), 2012-2013. However, note that the cited figure is used as an example in the text. The base case source applied in the company CS is Love-Koh J., et al. 2023 (34), which used updated HES data.

d. Figure 46, CS Document B Appendix L, page 147: Quality-Adjusted Life Years. Please provide full methods and justification for how the values in the Table were derived.

Company response

These values have been mislabelled during editorial review. The figure should be titled as 'Quality-Adjusted Life Expectancy for IMD quintile'. These values were derived from Love-Koh J., et al. 2015 (35), Table 3 of the article. The authors state that to calculate QALEs, life expectancy is adjusted for HRQOL using the predicted utility scores for each age-sex-socioeconomic group, via the Sullivan method. Because the authors were unable to estimate HRQOL for people aged 0 to 15 years, they assumed that they experience the same average HRQOL as do those in the youngest age group for which the HRQOL could be estimated (16–19 years). It is thus relevant to note that obtaining QALE estimates is nearly the same as for life expectancy, except that years of life for each IMD group are multiplied, in each age interval, by the associated QALY weight for the general population.

e. CS Document B Appendix L, page 148. Lastly (not shown), the expected share of opportunity cost and the % of treatment uptake within each IMD

group (i.e., a value between 0-100% for each group). Please provide full methods and results for how these values are calculated.

Company response

Treatment uptake is assumed to be 100%. This is because the uptake proportions are assumed to be accounted for by the estimated treatment population size of 1750 patients, which includes the calculations for patient cascade.

For health opportunity costs, these values are derived from Love-Koh et al. 2020 (33). This source was used based on EAG feedback during the clarification process for exa-cel's beta-thalassemia submission, which occurred prior to the SCD dossier submission.

f. CS Document B Appendix L, page 148. The Appendix states "Given the progressive tax system and nationalised health insurance funding pool which characterises the UK health system". Please provide a justification and sources for this statement.

Company response

This is based on the health system structure of the UK, which is based on a patient's clinical need, requiring minimal out-of-pocket payments, where funding is derived from a national tax pool (36, 37).

g. CS Document B Appendix L, page 148. With respect to the statement "The weightings in the model base case, of each Index of Multiple Deprivation (IMD) group, are as follows: 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).". Please provide full methodology for how these values were obtained.

Company response

These are examples provided for an aversion value of 11. These values vary according to the aversion parameter value inputted by the user in the 'DCEA inputs' tab, cell C8. For a full list of different weights across IMD groups, please see the 'DCEA_weights' tab in the model. The data table provides a full table of different values that are used for aversion values from 0 to 20. The methodology for obtaining

each weight has already been described in full within the original CS, under the sub-heading ‘DCEA: weighting methods’ in Appendix L, Document B.

B23. On page 194 of CS Document B, the company stated that based on the recommendations of the external expert and the applicability of the study criteria, a value of 11 was chosen as the most appropriate and robust value for inequality aversion in England. It was further mentioned that a more recent source for an inequality aversion value is available.

a. Please can the company provide further information of the external expert?

Company response

The external expert consulted was Professor Richard Cookson, who advised on the source and use of the aversion value of 11 at the time of consultation.

b. Please can the company report the inequality aversion value from the Tinbergen Institute, 2023?

Company response

The value from this paper is 3.5. As stated in the original CS, 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 (38).

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.

Vertex 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.

B24. CS Document B, page 192. Reference 4 is to a study of beta-thalassemia in the UK [Vertex Pharmaceuticals Inc. Data on file. Sickle Cell Disease with recurrent VOCs and Transfusion-dependent β-thalassaemia: Economic and Clinical Burden of Disease in England. 2023]. The study seems to be the basis for all parameters of the DCEA.

a. Please clarify how is this study is relevant for this appraisal?

Company response

The BoI study includes data on both TDT and SCD (28). Therefore, data related to SCD patients are applied in the DCEA and model where relevant.

b. Please provide the UK-SCD BOI study, including all definitions used in the methods and data analyses, identification of sample, baseline characteristics and methods of attributing IMD status to each study participant.

Company response

Please see B26a.

B25. Figure 42 (CS Document B Appendix L, page 146).

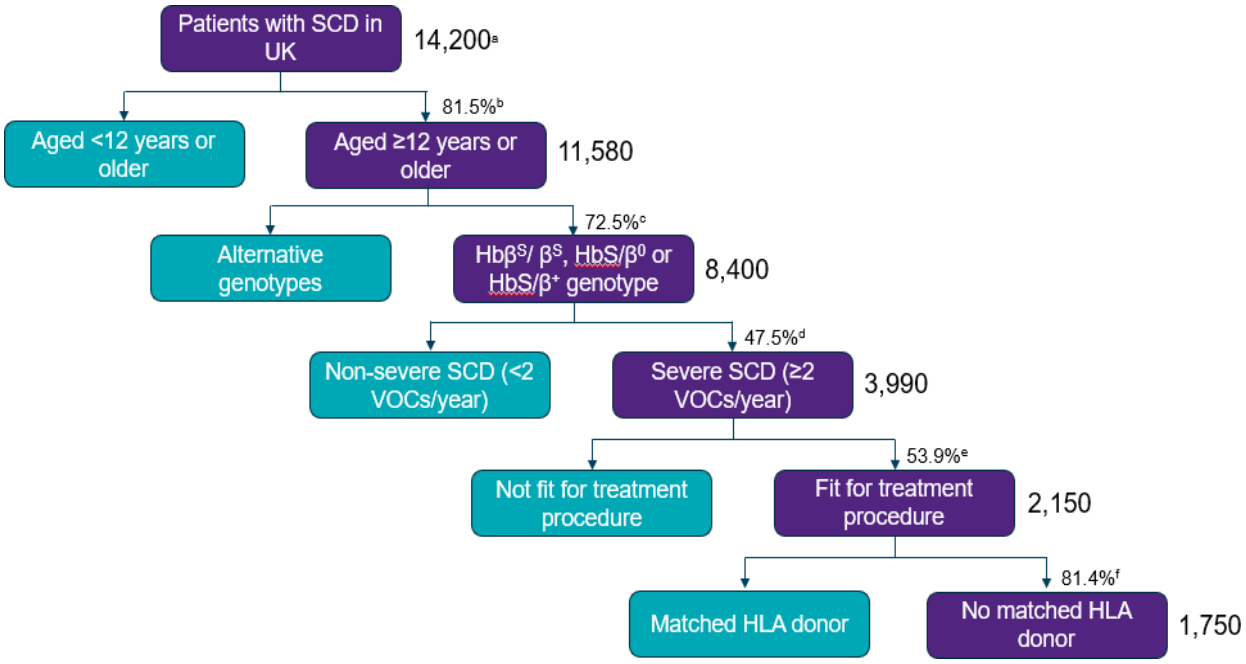
a. Please explain how the value of 1000 was obtained for the total eligible population size.

Company response

This input is incorrect and was an error in the original CS. The final eligible treatment population size for SCD in England is estimated to be 1750 patients. This is based

on Vertex's commercial forecast. Vertex have provided an updated value in the CQ model submission. Please see Figure 6 below for a detailed cascade analysis. Note that this change has minimal impact on the DCEA weighted ICER.

Figure 6: Epidemiological cascade for SCD in the UK



b. Please explain why the model file states a value of 1117 for the same parameter (DCEA Inputs worksheet, cell C4).

Company response

Please see response a., question B25 above.

B26. Model file, DCEA_weights worksheet. The model uses a distribution of IMD scores that appears unexplained.

a. Please provide methods of data collection for this study (assuming it is the same BOI study referred in clarification question B24b).

Company response

The Vertex BoI study aimed to understand the clinical and economic burden of sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs) and transfusion-dependent β-thalassaemia (TDT) in England (28).

Patients were identified using primary care records (Clinical Research Practice Database [CPRD]) linked with secondary care data sources (Hospital Episode Statistics [HES]) in England. The index date was the date the patient first meets disease severity criterion, i.e., the patient with a SCD diagnosis has ≥ 2 VOCs in the second consecutive year or the patient with β-thalassaemia diagnosis has ≥ 8 transfusions per year in the 2nd consecutive years within the study eligibility period (1st of July 2008 and 30th of June 2018). Patients could be indexed at any age. These patients were matched with individuals from the general population (i.e., without primary or secondary diagnosis of SCD or β-thalassaemia at any time in their medical record). Clinical and economic burdens (healthcare resource utilization [HCRU] and associated costs, and lifetime HCRU estimated costs) together with mortality outcomes were assessed during follow-up (timed from the index date until the earliest of end of the study period [30th June 2019], death, deregistration due to the patient leaving the practice, or the practice discontinuing its contribution to the database). For mortality and chronic complications, the rates were presented per 100 person-years. For HCRU and acute complications, the numbers of events per patient per year were presented. Proportions of patients with events were also reported.

1,117 patients with SCD with recurrent VOCs (N=5,585 matched controls) and 237 TDT patients (N=1,184 matched controls) who met the severity and inclusion/exclusion criteria were included in this study. In the SCD with recurrent VOCs cohort, patients had substantial clinical complications (e.g., cardiopulmonary complications [30%] and bone and joint problems [26%]) and recurrent VOCs (mean of 5.84 VOCs PPPY, n=1,117). Furthermore, economic outcomes were 22 times higher in the SCD with recurrent VOC cohort compared to the matched general population (mean total HCRU costs £12,472.01 PPPY; n = 1,009 vs £669.77 PPPY; n = 5,292, respectively). The mean costs for VOC-related hospitalisations PPPY increased with the number of VOCs and accounted for most secondary HCRU costs. Mortality was significantly higher in patients with SCD with recurrent VOCs compared to the matched general population (0.78 deaths per 100 person-years vs 0.16 deaths per 100 person-years, respectively).

Similarly, in the TDT cohort, patients experienced substantial clinical complications including endocrine complications and bone disorders (58%), urinary tract complications (18%), mental health problems (15%), any cardiac and cardiopulmonary complications (14%), liver complications (14%) and splenomegaly (11%). Furthermore, economic outcomes were significantly higher in the TDT cohort compared to the matched general population (mean total HCRU costs £13,617.35 PPPY; n=214 vs £615.09 PPPY; n=1,123, respectively). Mortality was significantly higher in patients with TDT compared to the matched general population (1.19 deaths per 100 person-years vs 0.2 deaths per 100 person-years, respectively).

b. Please provide full operationalisation of how the distribution of IMD groups was obtained.

Company response

IMD scores were calculated based on the area that a patient lives. IMD a composite measure derived from several indicators covering different aspects ('domains') of material socio-economic deprivation: income, employment, education and skills, health, housing, crime, access to services, and living environment. The overall composite index, the Index of Multiple Deprivation (IMD), is calculated as a weighted sum of the domain indices for small areas of England and represented as five quintiles (Q1 being the least deprived and Q5 the most deprived). The IMD score itself was calculated by CPRD and generated for each patient identified linked for the UK BOI (note database was CPRD linked to HES) based on their geography. These scores were then shared by CPRD in deciles, which were then categorized into quintiles for reporting based on the study methods.

c. Please provide full operationalisation of how IMD class was attributed, i.e., which patient-level data were used, whether patient level data on the components of IMD were obtained directly from patients' data or otherwise, for example, via assumptions made by treating physicians.

Company response

The UK BOI reported the IMD groups based on quintiles (Q1 – Q5). As noted above this is patient-level data based on the specific area a patient lives. The specific

calculation was conducted by CPRD at a patient-level and then shared based on deciles, which were then reported as quintiles.

B27. Please explain why the proportion of the general population by IMD group (Appendix L, Figure 45) 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).

B28**.** 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

According to company submission records and a review of Vertex's original CS model version, this source was used as the base case QALE by IMD quintile distribution. If this, however, does not align with the version submitted to the EAG, we provided a user option switch to select this source in the original CS. This source was incorporated prior to submission based on feedback during the clarification process for exa-cel's beta-thalassemia submission.

B29. 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

As above, according to company records, we have applied this source in the original CS. The user can select this source in the ‘DCEA Inputs’ sheet, cell I12.

Section C: Textual clarification and additional points

C1. Please can the company provide the reference to support the sentence that there is precedent for applying a severity modifier and implementing a 1.5% discount rate in the HST appraisal of Onasemnogene abeparvovec for treating spinal muscular atrophy?

Company response

The Company was referring to onasemnogene abeparvovec in HST15. This is described in the committee papers as having been applied, albeit below the full QALY weighting of 1.86 to account for considerable uncertainty in the model.

As described in the Final Appraisal Document for HST15, the committee considered *'that it was likely that the alternative 1.5% discounting rate was intended to cover situations similar to this (that is, when costs are incurred upfront, but benefits are accrued over a longer period).*'. It was agreed that the committee would use the 1.5% discount rate for decision making.

As such, HST15 provides precedent for the application of a QALY weighting alongside the non-reference discount rate. The QALY weighting applicable in HSTs is not awarded under the same criteria as STAs, being underpinned by undiscounted QALY gain. However, as the potential QALY gain is, by definition, determined by the initial QALY shortfall on current SoC, there is considerable overlap with the criteria of the severity modifier.

Conversely, the severity modifier is determined by discounted QALY gain, which penalises chronic conditions with a gradual increase in morbidity and mortality risks. This makes a lower discount rate a necessity to allow the rightful recognition of the severity of these conditions under the current methods guide.

C2. Table 46 (CS Document B, page 177) provides post-treatment monitoring costs for people undergoing treatment with exa-cel. Please can the company confirm the Year 5 should be Year 5+ because it was assumed that 15 years of post-monitoring?

Company response

Vertex confirm that Year 5 should be indicated as Year 5+; the '+' sign was inadvertently omitted.

C3. The company states on page 189, CS Document B that 'Vertex anticipates that, based on expert opinion [ref], a timeline of 3 years' data collection following recommendation…' Please can the company provide details of the expert opinion used to support this statement?

Company response

As part of the advisory board discussion, for which a report was submitted as data on file alongside the CS, the Company received feedback in support of a potential managed-entry consideration (40). Clinical advisers stated that they would expect to see patient follow-up for at least two years to demonstrate that exa-cel is providing a long-term treatment effect. Discussions held as part of a NICE Office for Market Access meeting provide additional support for this time period. Clinical advisers suggested that stable engraftment should be achieved at 1 year, and that this milestone would correlate with long-term outcomes. In summary, clinical expert opinion in the context of C3 relates to both the advisory board submitted as data on file, as well as commercial discussions with NICE and relevant stakeholders via OMA.

C4. Table 61 (CS Document B, page 209) reports the results of the net health benefit (1.5% discount rate). Please can confirm that the estimated total QALY yield is [redacted] for SoC and [redacted] for exa-cel, rather than [redacted] and [redacted], respectively.

Company response

Vertex double-checked the model results, which indicate that Table 61 already reports the correct total QALYs of [redacted] for SoC and [redacted] for exa-cel.

References

1. Vertex Pharmaceuticals Inc. Data on File. Exagamglogene Autotemcel (exa-cel) for the Treatment of Sickle Cell Disease: Indirect treatment comparison. 2023.
2. Frangoul H, Altshuler D, Cappellini MD, Chen Y-S, Domm J, Eustace BK, et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia. New England Journal of Medicine. 2020;384(3):252-60.
3. Frangoul H, Bobruff Y, Cappellini MD, Corbacioglu S, Fernandez CM, de la Fuente J, et al. Safety and Efficacy of CTX001™in Patients With Transfusion-Dependent β-Thalassemia or Sickle Cell Disease: Early Results From the CLIMB THAL-111 and CLIMB SCD-121 Studies of Autologous CRISPR-CAS9-Modified CD34+Hematopoietic Stem and Progenitor Cells 2020 [Available from: https://crisprtx.com/assets/uploads/2020-ASH-Presentation-Frangoul_CTX001-HEME.pdf.
4. Vichinsky E, Neumayr L, Gold JI, Weiner MW, Kasten J, Truran D, et al. A Randomized Trial of the Safety and Benefit of Transfusion Vs. Standard Care In the Prevention of Sickle Cell-Related Complications In Adults: a Preliminary Report From the Phase II NHLBI Comprehensive Sickle Cell Centers (CSCC) Study of Neuropsychological Dysfunction and Neuroimaging Abnormalities In Neurologically Intact Adult Patients with Sickle Cell Disease. Blood. 2010;116(21):3221.
5. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017;376(5):429-39.
6. Niihara Y, Miller ST, Kanter J, Lanzkron S, Smith WR, Hsu LL, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. New England Journal of Medicine. 2018;379(3):226-35.
7. Howard J, Ataga KI, Brown RC, Achebe M, Nduba V, El-Beshlawy A, et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol. 2021;8(5):e323-e33.
8. Kanter J, Walters MC, Krishnamurti L, Mapara MY, Kwiatkowski JL, Rifkin-Zenenberg S, et al. Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease. N Engl J Med. 2022;386(7):617-28.
9. Magrin E, Semeraro, M., Hebert, N., Joseph, L., Magnani, A., et al. Long-term outcomes of lentiviral gene therapy for the β-hemoglobinopathies: the HGB-205 trial. Nature Medicine. 2022;28(1):81-8.
10. Thom H, Jansen J, Shafrin J, Zhao L, Joseph G, Cheng HY, et al. Crizanlizumab and comparators for adults with sickle cell disease: a systematic review and network meta-analysis. BMJ Open. 2020;10(9):e034147.
11. Sridharan K, Sivaramakrishnan G. Efficacy and safety of iron chelators in thalassemia and sickle cell disease: a multiple treatment comparison network meta-analysis and trial sequential analysis. Expert Rev Clin Pharmacol. 2018;11(6):641-50.
12. Dick MH, Abdelgadir A, Kulkarni VV, Akram H, Chatterjee A, Pokhrel S, et al. Comparing the Safety and Efficacy of L-Glutamine, Voxelotor, and Crizanlizumab for Reducing the Frequency of Vaso-Occlusive Crisis in Sickle Cell Disease: A Systematic Review. Cureus. 2022;14(5):e24920.
13. Tucci F, Galimberti S, Naldini L, Valsecchi MG, Aiuti A. A systematic review and meta-analysis of gene therapy with hematopoietic stem and progenitor cells for monogenic disorders. Nat Commun. 2022;13(1):1315.

14. Vertex Pharmaceuticals Inc. Data on File. Exa-cel Efficacy and Safety Update (16 April 2023). 2023.
15. Vertex Pharmaceuticals Inc. Data on file. CLIMB SCD-121 Interim Clinical Study Report. 2022.
16. Barcelos G, Besser M, O'Flaherty E, O'Sullivan S, Bourke S, Oluboyede Y, et al. PCR116 Quality of Life of and Economic Burden on Caregivers of Individuals With Sickle Cell Disease in the UK and France: A Cross-Sectional Survey. Value in Health. 2022;25(12):S1-S546.
17. Digital N. Health Survey for England, 2019: Data tables 2020 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2019/health-survey-for-england-2019-data-tables.
18. Bradt P, Spackman E, Synnott PG, Chapman R, Beinfeld M, Rind DM, et al. Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value. Institute for Clinical and Economic Review, January 23, 2020 2021 [Available from: https://icer.org/wp-content/uploads/2021/02/ICER_SCD_Evidence-Report_031220-FOR-PUBLICATION.pdf.
19. NHS trusts and NHS foundation trusts. National Cost Collection: National schedule of NHS costs. 2021/22.
20. National Health Service. Birmingham Women's Fertility Centre. Treatment charges in 2020. Available at https://bwc.nhs.uk/download.cfm?doc=docm93jijm4n1679 2022 [
21. NHS Blood and Transplant. Blood and Components - Contract Equivalent Cost per Item. 2023/24.
22. National Health Service. Stem cell and bone marrow transplants 2022 [updated 07 September 2022.
23. Young E. Analysis of hospital activity and costs following allogeneic stem cell transplantation in England. 2021.
24. National Institute for Health and Care Excellence. Crizanlizumab for preventing sickle cell crises in sickle cell disease. Committee Papers 2020 [Available from: https://www.nice.org.uk/guidance/ta743/documents/committee-papers.
25. Shah N, Bhor M, Xie L, Halloway R, Arcona S, Paulose J, et al. Evaluation of Vaso-occlusive Crises in United States Sickle Cell Disease Patients: A Retrospective Claims-based Study. J Health Econ Outcomes Res. 2019;6(3):106-17.
26. Badawy SM, Beg U, Liem RI, Chaudhury S, Thompson AA. A systematic review of quality of life in sickle cell disease and thalassemia after stem cell transplant or gene therapy. Blood Adv. 2021;5(2):570-83.
27. St Martin A, Hebert KM, Serret-Larmande A, Jouhet V, Hughes E, Stedman J, et al. Long-term Survival after Hematopoietic Cell Transplant for Sickle Cell Disease Compared to the United States Population. Transplant Cell Ther. 2022;28(6):325 e1-e7.
28. Vertex Pharmaceuticals Inc. Data on file. Sickle Cell Disease with recurrent VOCs and Transfusion-dependent β-thalassaemia: Economic and Clinical Burden of Disease in England. 2023.
29. Robson M, Asaria M, Cookson R, Tsuchiya A, Ali S. Eliciting the Level of Health Inequality Aversion in England. Health Econ. 2017;26(10):1328-34.
30. McNamara S, Holmes J, Stevely AK, Tsuchiya A. How averse are the UK general public to inequalities in health between socioeconomic groups? A systematic review. Eur J Health Econ. 2020;21(2):275-85.

31. Neumann P, Sanders, G., Russell, L., Ganiats, T., Siegel, J. Cost-Effectiveness in Health and Medicine. Oxford: Oxford University Press; 2017. 1-496 p.
32. Drummond M, Sculpher, M., Claxton, K., Stoddardt, G., Torrance, G. Methods for the Economic Evaluation of Health Care Programmes. Oxford; 2015.
33. Love-Koh J, Cookson R, Claxton K, Griffin S. Estimating Social Variation in the Health Effects of Changes in Health Care Expenditure. Med Decis Making. 2020;40(2):170-82.
34. Love-Koh J, Schneider P, McNamara S, Doran T, Gutacker N. Decomposition of Quality-Adjusted Life Expectancy Inequalities by Mortality and Health-Related Quality of Life Dimensions. Pharmacoeconomics. 2023;41(7):831-41.
35. Love-Koh J, Asaria M, Cookson R, Griffin S. The Social Distribution of Health: Estimating Quality-Adjusted Life Expectancy in England. Value Health. 2015;18(5):655-62.
36. Anderson M, Pitchforth, E., Edwards, N., Alderwick, H., McGuire, A., Mossialos, E., Hernandez-Quevedo, C. The United Kingdom: Health System Summary. WHO/ European Observatory on Health Systems and Policies, Brussels; 2022.
37. Moran M. Governing the Healthcare State: A comparative study of the United Kingdom, the United States and Germany. Manchester, United Kingdom: Manchester University Press; 1999.
38. Robson M, O'Donnell, O., Van Ourti, T. Aversion to Health Inequality - Pure, Income-Related and Income-Caused. Tinbergen Institute; 2023.
39. Cookson R, Griffin, S., Norheim, O., Culyer, J. Distributional Cost-Effectiveness Analysis: Quantifying Health Equity Impacts and Trade-Offs. Oxford: Oxford University Press; 2020.
40. Vertex Pharmaceuticals Inc. Data on file. Exa-cel UK HTA Advisory Board. 2022.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Exagamglogene autotemcel for treating severe sickle cell disease [ID4016]

Updated model inputs

[October 2023]

File name	Version	Contains confidential information	Date
ID4016_Exa-cel CEA in SCD_UK CQ [CON REDACTED]	1.0	Yes	13/10/2023

CEA Model input changes after clarification questions

Details of all updated model parameters are provided in the table below.

Parameter	Location in the model	Description of change	Previous value	Updated value	Justification
Weight ratio	"Cohort inputs" sheet, cell E8	Used the distribution of patient weight as per CLIMB SCD-121	1 (assumption)	[redacted]	It was raised in question B2.a

DCEA input changes after clarification questions

We have corrected the eligible treatment population size, although it had a minimal impact on the ICER.

Parameter	Location in the model	Description of change	Previous value	Updated value	Justification
Eligible treatment population size	'DCEA Inputs', cell C4	Changed to correct value to align with patient cascade	[redacted]	[redacted]	Corrected error

Updated base-case results

Table 1: 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				[redacted]		[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

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] **and** [redacted]
2. Name of organisation	Anthony Nolan and The Sickle Cell Society
3. Job title or position	[redacted], [redacted], Anthony Nolan [redacted], [redacted], The Sickle Cell Society
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Anthony Nolan** saves the lives of people with blood cancer and other blood disorders. Founded in 1974 as the world's first stem cell register, we're motivated by a mother's determination to save her son, Anthony. Now saving three lives every day, our charity is a lifesaving legacy. By growing our register of potential stem cell donors, conducting ground-breaking research into improving transplant outcomes, and providing outstanding support and clinical care for patients and their families, Anthony Nolan cures people's blood cancer and blood disorders. **The Sickle Cell Society** is a national Charity registered with the Charity Commission since 1979. Our national reach is through a wide network of well informed, committed and active supporters, members and support groups. We work nationally, regionally, and locally. Because of our unique status we have good international links and are frequently contacted by patients and clinicians globally for access to some of our resources The Society's aim is to empower and assist people living with sickle cell disorder (SCD) to achieve their full economic and social potential. We have a small staff team of 9 WTE, consisting mainly of part time staff. Our operating costs are in the main funded by donations and grants. We have a board of trustees (9) at least 50% of whom live with SCD or cares for someone who lives with the condition.

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.**	Anthony Nolan has not received any funding from Vertex Pharmaceuticals Inc, nor any associated subsidiary entities. The Sickle Cell Society has received the following grant funding and financial support from Vertex Pharmaceuticals Inc, between June 2022 and December 2023:
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?	Information for this appraisal was gathered from a range of sources, including: • In-depth telephone and online video interviews with sickle cell patients. • Clinical specialist haematologists working with red blood cell disorders and stem cell transplantation. • Patient experiences collated for the APPG on Sickle Cell and Thalassemia's report into 'No one's Listening: An inquiry into the avoidable deaths and failures of care for sickle cell patients in Secondary Care'. • Joint survey for sickle cell patients and carers [final results to be included as an addendum to our comments on the technical engagement document]. • The Sickle Cell Society also runs a helpline and information service where we receive lots of diverse information from patients and carers including about clinical trials and the potential for new treatments for SCD.

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	• SCD affects over 15,000 children and adults across the UK.
	• Vertex's CLIMB SCD-121 trial, associated with the population and indication for exagamglogene autotemcel for treating severe sickle cell disease:
	  ○ Defines severe SCD as a "history of >2 VOCs per year in the previous 2 years"
	• The 2019 SWAY global SCD survey assessed the impact of SCD on daily life. Of the global population surveyed:
	  ○ 90% of patients experienced at least 1 VOC in the past 12 months
	  ○ 39% of patients experienced 5 or more VOCs in the past 12 months
	• Within the market authorisation cohort of people with severe SCD, aged 12-35 years old, it can be suggested that a significant proportion of the UK SCD patient community will at some point in their lives become eligible for consideration of exagamglogene autotemcel therapy.
	
	Living with severe Sickle Cell Disease
	Sickle cell disease is an invisible genetic condition that affects no two people in the same way. Some with the disease deal with lifelong pain and complications, others are unaffected. The international Sickle Cell World Assessment Survey (SWAY) aimed to provide insights into patient-reported impact of SCD on QoL, in its 2019 results it found:
	• Chronic pain was present on average 4.0 (Standard Deviation 1.98) days per week.
	• Overall, 36% were on disability financial support, 25% part/full-time employed, 24% unemployed, 12% students, 3% other.
	• Employed patients reported a high impact on work, with 76% reducing hours and 58% been made to stop working.
	• In the 7 days before survey completion, patients missed an average 7.3 (SD 10.56) hours' work.
	
	Of the patients we interviewed, and the experiences collated through other sources, key symptomatic factors and their common themes included:

	Vaso-Occlusive Crisis (VOCS) – This can occur once a year or more depending on the disease severity for patients, when sickled red blood cells block blood flow to the point that tissues become deprived of oxygen. • In being asked to describe what a crisis actually feels like, one man responded with "describing the actual pain I feel is a real challenge – I can say that it feels like being stabbed everywhere repeatedly or having all your bones broken, but the words just don't do the pain justice". • One patient commented that "the pain isn't always the same every time, it can be all over or just in one place, and you can't tell how long you're going to suffer from it" • A young woman described how important it was to figure out the potential triggers of a crisis, whether that is hot – or – cold weather, or overexerting herself. The problem is that "by limiting yourself, you just making your world smaller and smaller". ○ As a child, she explained how " Playing outside and sports day or making snow angels would result in crises so you learn that these are things you shouldn't do or approach with cautious" • The impact of sub-standard healthcare was noted particularly in the APPG's 'No One's Listening' report with one patient commenting that "Being ill with sickle cell vaso-occlusive crisis can feel tantamount to being invisible for the amount you feel heard or respected." The prospect or expectation of poor care at a time of crisis only adds to patient's anxiety, a credible trigger for many to begin a crisis or worsen one. **Chronic fatigue –** People with SCD experience fatigue because of anemia, which makes them feel tired all the time. • A man described how the tiredness is not long other people feel tired, "it's like your bones and mind are just so heavy, you don't have the energy to even think anymore" • A patient also noted that their fatigue is continuous, "it's with me morning, noon and night" and that there isn't any relief, a moment to catch your breath and actually live the life you want to. • Fatigue can understandably have a serious impact on education and work. A young woman remembered how she missed a lot of schooling and exams as a child. She later through a 3-year university degree, but some academic staff were more understanding and supportive than others. • Another patient explained how it was so hard to concentrate in class, along with all the school they missed as well, you had to either try to catch-up or just accept that you were going to fail.

	Acute chest syndrome – a condition caused by sickled cells clumping together in the lungs. It can be life-threatening and can result in lung injury, breathing difficulty, and low oxygen to the rest of the body. • One woman explained that she's always scared of getting another chest infection after needing to be admitted to emergency care and given oxygen to support her breathing. "Not being able to breath, in that moment, its worst thing in the world and you can't do anything about it, you're just paralysed with fear". **Exercising and keeping fit –** not being able to exercise and exert yourself is really limiting and directly impacts patients overall wellbeing. • A patient commented that he loved sports and lots of his family are sporty but it's never been something he can join in too much, "with sickle cell, you have to learn to pace yourself, to take regular breaks. When I was at school, team sports were a no no, it was too fast paced, too much going on and you can't risk keeping up with the others". • A young women described how short occasional walks can help take her mind off pain but she's not able to do 30 minutes exercise a day like the NHS recommends you should do/ **Mental health and wellbeing impact** Having SCD can have an incredibly negative impact on the lives and well-being of patients, and this is only reinforced more so as symptoms become more severe and more numerous. • As a child, having sickle cell means keeping up with friends and activities is more difficult. Being careful with what you do and where you go, it encourages patients to withdraw and socially isolate themselves. • Children can be unthinkingly cruel, and several patients pointed to bullying and exclusion for being different and not being able to join in with everything. "it's like I'm in a bubble and everyone else is doing something exciting except for me". • The impact of SCD naturally feeds into every part of people's lives; will they have their own family due to the potential impact on fertility? Who will be there to look after them when they are older? And the knock-on effects to their careers or ability to work at all.

	Effect on daily life Patients with SCD described how having sickle cell has a direct effect on their day-to-day lives, including their ability to work, have a social life, travel, and live with spontaneity: • The simplest thing such as staying hydrated can become annoying, a man said that its like he's always drinking something and going to the toilet the next. It disrupts his sleep and means knowing where toilets are when going out is always a thought in the back of his mind. • Managing chronic or acute pain and fatigue always place social plans in jeopardy and make studying or working reliably a big problem. A young woman said finding an understanding tutor or manager was key to making working life a possibility. • A patient explained that not getting infections has always been a priority, and the Covid pandemic was such an anxiety-inducing time. **Carers** We haven't interviewed carers directly, but patients did comment about the experiences of their families. • One person's mum was upset that her child could never join in with the other kids, and she had to keep warning them about over-exerting themselves, rather than just being kids. • Attending emergency care with a family member who has SCD is worrying for many. The feeling of not being listened to and not getting access to necessary pain relief has left both patients and family feeling powerless and can itself be a traumatising experience.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Excluding opioid painkillers and blood transfusions there is only a few licensed drugs for sickle cell disorder (SCD); • Hydroxyurea. This is a chemotherapy drug which has proven to be beneficial to some patients living with SCD. • Crizanlizumab was approved by NICE for patients aged over 16 but this only reduces the likelihood of crises, unlike the potential held for exa-cel. • Whilst not a drug itself, Allogeneic Haematopoietic Stem Cell Transplantation (HSCT) for adults with sickle cell disease was approved in 2019. However, this is only for sibling donors and excludes both unrelated and haploidentical donors. o What's more, any allo-transplant comes with significant risks of Graft versus Host Disease and other post-transplant late effects. Even if a patient is eligible for a transplant, both they and their clinical team may conclude that it is not the right option for them. We know, without exception, from our conversations with patients, carers and families that they would like to see more choice of disease modifying SCD treatments that can enable individuals with the condition to have improved quality of life. Despite the clinical knowledge that SCD has existed for over 100 years, as a national Patient Advocacy Organisation we and indeed many of our members believe it is frankly woeful and disturbing that there has been no innovation in SCD treatment options when compared to like genetic blood conditions. This adds to the inequality experienced by many people living with the condition. Data from the 2019 Sickle Cell World Assessment Survey (SWAY) clearly shows that the most common treatment goal of patients is 1) improved quality of life 2) prevent worsening of their condition and 3) reduce the number of VOCs/crises. Whilst Hydroxyurea is the only licensed UK drug, we also know that it is not a treatment for everyone who has the condition. The SWAY data also shows that approximately one third of patients were receiving Hydroxyurea globally. The proportion of patients in the UK who said they were currently using Hydroxyurea at the time of the SWAY survey was 19% (of 299 patients).

8. Is there an unmet need for patients with this condition?	Yes of course there is unmet need, much of which is neither recognised or acknowledged. SCD is the most common genetic blood in the UK, associated with both acute and chronic complications and a reduction in median life expectancy of approximately 20 years. Apart from standard pain killers and regular transfusions, there is only two licensed treatment which can prevent painful episodes in SCD; Hydroxyurea and crizanlizumab (which has a tighter education). As explained under question 7 above Hydroxyurea is not for everyone. In addition, despite the fact that it can be effective for some patients, there are many myths, mistrust and concerns amongst many individual patients and parents about Hydroxyurea. In the main this is because a) it is a chemotherapy drug and b) of the long term side effects. Many treating clinicians in the field of SCD will also know this. We continue to urge NICE to take the experiences and priorities of by patients and parents with high importance and understand that for some these are genuinely strongly held beliefs. In our view it would also be fair to say that even some treating clinicians have differing views about the use of Hydroxyurea, for example for very young children. The SWAY data also shows that healthcare utilisation does not accurately reflect the incidence of VOCs. The data shows that 24% of VOCs were managed at home. This in our view is extremely dangerous. The most common reason for home VOC management was a previous poor experience of accident and emergency department/hospital. It is not uncommon for our organisation to receive complaints about accident and emergency experience, particularly from young black men in relation to allegations of misuse of opioid painkillers or not believing their level of pain on admission. VOCs are the primary cause of up to 98% of hospital admissions for SCD patients. The APPG inquiry has demonstrated the high-level of inadequate investment in sickle cell care, and the impact this has on service-quality and ultimately the outcomes of patients. There is routine failure to comply with national care standards or standards set by NICE itself around pain relief when patients attend A&E. In our resource-strapped NHS, these experiences and the culture-changed needed will not happen overnight.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Trial data from CLIMB SCD-121 suggests that all patients saw an increase in their levels of Hb and HbF. HbF levels were also maintained during the trial period and further data suggests that the vast majority of trial participants gave remained VOC-free up to 36.5 months so far. It has been concluded that for eligible patients, this gene therapy represents a potential functional cure for SCD. As well as primarily improving the quality of lives for patients with severe SCD, this gene therapy offers the prospect of a single-intervention therapeutic with a much-reduced prospect of needing to engage with emergency care teams. This is good for patients and good for NHS service providers.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	What SCD patients have always wanted most is choice and empowerment in managing their condition and resolving the disease's underlying symptoms to a point where it has no significant impact on their day-to-day lives, prospects and opportunities. Gene therapies such as this one may not be the right choice for every patient, but along with greater choice in donor cell-source for HSCT and more disease-management therapies, patients want to be in control of their care. Gene therapies which use autologous transplant still carry a risk of infertility due to the use of conditioning agents, but this can be mitigated.

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.	There is potential for every patient with HbSS or HbSC to benefit, particularly those with frequent episodes of pain. VOCs increase with age and in frequency and severity. Adults aged over 35 years therefore more likely to benefit. Trials are also being conducted for children under 12 years old and this should be kept under active review.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Without exception there are serious inequality issues directly affecting SCD patients, some of which we have alluded to earlier in this submission. SCD in the UK is overwhelmingly confined to black populations or people who have black heritage. The COVID-19 pandemic has in part exposed the scale of health inequalities in the UK. As the APPG report found: “People of every race have a right to equality in health treatment. Yet the experience of people living with sickle cell is that the failings in treatment and the lack of understanding outlined in this report show deep inequality in the healthcare system. This is a serious and longstanding issue which must be addressed.” As two patient organisations invested in support patients to survive and thrive, we work with these issues every day, so this is no surprise to us or many people who live with SCD. After such a long time of there being little to investment into SCD therapies, this gene therapy serves as the first of hopefully more opportunities in righting the wrongs of historical choices which have not been made on the basis of unmet need and patient equity. The choice set before this NICE Committee is to promote a significant improvement in quality of life for many SCD patients and promote equity in healthcare for the whole SCD community across the UK.

Other issues

13. Are there any other issues that you would like the committee to consider?	We urge NICE to carefully consider the question of the lack of treatment innovation and the associated health inequalities experienced by this group of patients by taking a more patient centric approach together with the current NICE methodology. Lastly, we all understand the very challenging circumstances that individuals, families, businesses and the public sector are currently having to deal with the funding and service pressures, but nevertheless this opportunity to provide access to this potential functional cure for SCD is not one to overlooked.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• SCD is most common severe inherited disorder in the UK, and a significant number will be eligible • Only two licensed drugs, and one high-risk therapy available for treatment • Clear health need for potentially curable therapies for SCD with proven efficacy • Serious health inequalities and sub-standard care at play for the SCD community, the vast majority who are BAME • The burden of the condition is all-consuming and its impact on the quality of life is significant

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 or NO

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 sickle cell disease [ID4016]

Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

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

Information on completing this submission

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

About you

1. Your name	[redacted]
2. Name of organisation	British Society for Haematology (BSH)
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
5a. Brief description of the organisation (including who funds it).	BSH is an organisation promotes excellence in the study, research, and practice of haematology for the benefit of professionals and the wider public. The chief ways that BSH acts on its mission are: 1. providing and supporting multi-disciplinary education for students and professionals at all levels; 2. raising standards of clinical care and laboratory practice through guidelines and the provision of expert advice; 3. providing support for research via its publications, programmes, and grants 4. providing networking opportunities that bring haematology professionals together; 5. representing the interests and concerns of haematology professionals at national and international levels
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.)	Exagamglogene autotemcel is a potentially curative treatment for sickle cell disease. The only curative option currently available to patients is an allogeneic stem cell transplant from a matched sibling donor, which is not available for most patients due to the lack of 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.)	The following outcomes would constitute treatment response • changes to haematological parameters (haemoglobin levels) • proportion of subjects not needing any disease modifying treatment, including blood transfusion, hydroxyurea, crizanlizumab and voxelotor following treatment with CTX001 gene therapy • proportion of subjects who have not experienced any sickle vaso-occlusive episodes for at least 12 consecutive months • proportion of subjects who have not had any further stroke or progression of cerebrovascular disease in those with established cerebrovascular disease • proportion of subjects able to wean off long term opioids 12 months following treatment • proportion of subjects who have no progression of organ dysfunction, as measured by echocardiogram, pulmonary function tests, glomerular filtration rate, • time to engraftment • low proportion of subjects with no off-target effects of CTX001 gene therapy, including development of therapy related myelodysplasia or leukaemia • mortality • adverse effects of mobilisation, myeloablation, neutropaenia • health-related quality of life.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are very limited disease modifying therapies for sickle cell patients and more importantly there are no real curative treatments for patients suffering from frequent sickle cell crises apart from allogenic bone marrow transplant which is limit in its availability due to lack of suitable matched siblings. There is a high unmet need for this cohort of patients who live with a disease that can result in unpredictable, severe and often life threatening complications. This should be viewed as a high priority for the NHS as the only currently available novel therapy is Crizanlizumab and that is accessed via a managed access program, unfortunately emerging data would suggest likely low efficacy of this therapy. The other novel therapy Voxeletor while in use in elsewhere in the world isnot currently available in the United Kingdom. Neither of these therapies is curative

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Treatment is supportive for the majority of patients. Current therapy options that are disease modifying (non curative) • Blood transfusion is used for patients with frequent vaso-occlusive crisis or serious complications to reduce end organ damage. However there are complications as a consequence of transfusion such as iron overload which then requires further medical management with chelation therapy. In addition the blood SCD patients receive while matched for the main antigens and any antibodies present does still present some risk due to to ethnic variationin blood groups. So despite providing cross matched units, (even in emergencies ,where possible), patients may still develop antibodies. Additionally patients on the regular programs who start transfusions after later in life, are more likely to develop alloantibodies to transfused red cells as they are more likely to mount an immune response. This has significant impact on their future management as it may introduce delay in acquiring blood for future transfusions and places

	them at risk for transfusion reactions including delayed transfusion reactions which may be life or organ threatening. • Alloimmunisation can also lead to patients, especially when they develop multiple or complex antibody combinations not being able to access blood even in an emergency, as an provision of blood gets increasingly challenging with antibody formation. • Hydroxyurea is the mainstay of management but does not provide effective management for all patients and has side effects that can be intolerable/ unacceptable for some patients • Newer therapies: o the efficacy of Crizanlizumab is currently under review as the preliminary results from the ongoing global phase III study STAND (NCT03814746) showed no statistically significant difference between crizanlizumab (doses of either 5mg/kg or 7.5mg/kg) and placebo in annualized rates of vaso-occlusive crises (pain crises) leading to a healthcare visit over the first-year post randomization. These findings are inconsistent with previous trial results from SUSTAIN (NCT01895361), which demonstrated the superiority of crizanlizumab 5.0mg/ kg compared to placebo. o There is no current access to Voxeletor for patient who either were not part of the clinical trials or did not get on the early access program which ended in October 2022. d The only available curative treatment is allogeneic stem cell transplant that is available for a minority of patients who have 'severe' disease: • History of >= 3 severe pain crises or other acute complications per year despite institution of supportive care measures (optimal treatment with hydroxycarbamide (HC) or transfusion therapy). Other acute complications would include acute hepatopathy or splenic sequestration or acute priapism. (This can be further refined using the CLIMB SCD trial inclusion criteria, namely patients with severe sickle cell disease having at least two vaso-occlusive crisis events per year for two consecutive years and documented severe sickle cell disease genotype) • Recurrence of acute chest syndrome despite optimum treatment with hydroxycarbamide (HC) or transfusion therapy • Clinically significant neurologic vascular event or deficit lasting over 24 hours and confirmed radiologically (i.e. stroke) or progressive cerebral vasculopathy

	• Administration of regular transfusion therapy, either by simple transfusion or exchange transfusion with the aim to prevent severe sickle complications by maintaining a low HbS%. Severe sickle complications include a history of >= 2 chest syndromes, >= 3 painful crises or severe recurrent priapism • Patients assessed as requiring transfusion but with red cell allo- antibodies/very rare blood type, rendering it difficult to continue/commence chronic transfusion • Patients requiring hydroxycarbamide/transfusion for treatment of SCD complications who cannot tolerate either therapy due to significant adverse reactions • Established end organ damage relating to SCD including but not limited to progressive sickle vasculopathy and hepatopathy.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are a variety of national guidelines BSH guidelines: 1. Significant haemoglobinopathies – A guideline for screening and diagnosis April 23 2. Monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias Oct 21 3. Management of sickle cell disease in pregnancy Aug 21 4. Hydroxycarbamide in children and adults with sickle cell disease May 18 5. Red cell Transfusion in SCD Part 1 &II Nov 16 6. Acute chest syndrome SCD March 15 National standards of care: Standards for the clinical care of adults with sickle cell diseaseSickle cell disease in childhoold: standards and recommendations for clinical care
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.)	There are established networks of clinical care in England with care being overseen by Specialist Haemoglobinpathy teams (SHTs) and the Haemoglobinopathy Coordinating Centres (HCCs) to ensure patients have equitable care. Approval for allogeneic stem cell transplant and the use of newer therapies have been developed following guidance developed by the National Haemoglobinopathy Panel. The networks will be peer reviewed in 2024 to assess compliance with national standards.

9c. What impact would the technology have on the current pathway of care?	Exagamglogene autotemcel will be a novel therapy and will offer many patients especially those with more severe disease who do not have an allogeneic donor the chance potentially curative treatment. Potentially Exagamglogene autotemcel will be delivered by a small number of units; HCCs will work with their SHTs to develop pathways for this treatment.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Exagamglogene autotemcel is a novel agent and will be an additional treatment option for patient with significant disease burden/ complications of SCD despite current treatment options (transfusions, hydroxycarbamide, Voxeletor, Crizanlizumab). The main difference is that it is potentially curative,
10a. How does healthcare resource use differ between the technology and current care?	There is a wealth of published literature on the increasing disease burden of sickle cell disease with the accumulation of co-morbidities with increasing age and premature mortality. Individuals with SCD and a history of end-organ damage such as stroke demonstrate higher rates of health care utilization, including more hospital days, emergency department visits, outpatient visits, lab tests, and outpatient pharmacy claims compared to those without end-organ damage. This has been shown by a number of publications using Hospital episode data in the England.Exagamglogene autotemcel will be a single treatment expected to reduce both acute events as well as chronic complications, and by extension reduce health care utilisation.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Exagamglogene autotemcel will be administered in the tertiary care setting by specialist units with experience of delivering cellular therapies and who are JACIE accredited.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There will be a training requirement for the collection, preparation and administration of this product specifically but this is expected to follow principles for other Advanced Therapy Medicinal Products (ATMPs). Units delivering Exagamglogene autotemcel are likely to require an expansion of capacity as this is an additional new treatment.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, we expect successful treatment would lead to 1. Reduction in acute and unpredictable presentations such as with vaso occlusive events, acute chest syndrome and lead to fewer presentations to hospital 2. Stabilisation of complications such as neurological events, cardio-pulmonary complications 3. Reduction in the likelihood of needing blood transfusions

	4. Significant reduction in opiate requirement for patients with chronic pain 5. Overall reduction in health care utilisation 6. Improved quality of life
11a. Do you expect the technology to increase length of life more than current care?	Long term data following gene therapy in SCD is currently not available. Patients with recurrent vaso –occlusive events have a higher mortality than age matched controls; additionally accrual of organ morbidity is associated with mortality. Hnece a therapy thet has potential to impact and reduce both acute events such as VOC and morbidity would be expected to lead to an improvement in mortality.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Patient surveys report significant disease burden. • as much as 50% of patients with SCD report moderate to extreme pain , • Multiple SCD patient reported outcome surveys in the UK, as well as the rest of the world has shown participants with SCD report a reduction in self-reported health , a reduction in physical well-being and a reduction in emotional well-being compared to the general population • Patients reported that their health made it hard to do things A reduction in clinical manifestations is likely to lead to improved physical well-being and an improvement in QOL.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The patients with a similar disease profile to those on the clinical trial and those with a moderate to severe disease phenotype would be expected to have the greatest clinical benefit. The conditioning regime used for the treatment would preclude a subset of patients from receiving this treatment. Although gene therapy is potentially curative the risk of the treatment may outweigh any benefit for patients with a mild disease phenotype.

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	Gene therapy involves various steps from the collection of stem cells, conditioning chemotherapy and then patient follow up post product infusion. This treatment will be delivered only in JACIE accredited units that are familiar with Advanced Therapy Medicinal Products (ATMPs). The pathway would involve selection of appropriate patients,

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.)	referral and joint assessment with the team delivering the gene therapy and follow up thereafter. The majority of clinicians that manage sickle cell disease will not directly be administering this treatment but will work collaboratively with the cellular therapies unit. The possibility of potentially curative therapy should be discussed with patients as part of their annual review. Patients will require exchange transfusions pre procedure – this is an additional step but all haemoglobinopathy units have provision for this.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No, treatment will be delivered within national recommendations.
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 SCD patient reported outcome surveys focusing on quality of life, show the significant impact that the frequent and daily pain associated with SCD has on patients, it also notes the un-predictability of SCD crises impacts on patient ability to attend school or work regularly with 1 study showing 1 lost day per 9 due to Sickle associated complications. This technology based on the early phase trials would be expected to lead to significantly improve this.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on	Exagamglogene autotemcel is innovative in that it is potentially curative. It offers a curative option at the level of the stem cell, but does not require a donor other than the patient, hence will be more accessible for patients who qualify for it. It also has advantage over the allogeneic offer in that it cannot result in graft versus host disease, a

health-related benefits and how might it improve the way that current need is met?	condition which can blight patients lives post allogeneic stem cell transplant, patients will also not need to take immune suppressing medication post gene therapy and have a lower risk of graft rejection due to a mismatch. There is only 1 licensed drug treatment for sickle cell in the UK freely available to patients which is Hydroxycarbamide and as noted above this medication although effective, does not work for all patients,. The novel therapy Crizanlizumab which is currently available via a managed access program has not been found to be as effective in the real world, and emerging trial evidence suggest it may not offer much more than placebo .
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 stem cell transplant and as noted fewer than 18% of patients will have a matched sibling donor available to donate then Exagamglogene autotemcel which uses stem cell from the patients is highly innovative and offers the option of cure to a wider population of patients. The advantage of not relying on a patient having matched sibling, who consents to donate and instead using autologous cells cannot be overstated. Other available therapies for sickle cell disease are disease modifying and are not effective for some patients.
16b. Does the use of the technology address any particular unmet need of the patient population?	We do not have effective treatments in SCD so Exagamglogene autotemcel offers a treatment and potential cure to haemoglobinopathy patients that is is innovative. It will offer a chance at disease free survival, reduced health utilisation, improved or at least stabilised organ function and improved quality of life. The advantage is that using autologous cells are used unlike allogeneic stem cell transplant which is available to only a few patients with a compatible donor. Other available therapies for sickle cell disease are disease modifying and are not effective for some patients.

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 technology itself will require stem cell harvest from patients with GCSF or plerixafor pre treatment, this is expected to be overall well tolerated however some bone pain during the treatment is expected. The admission for stem cell infusion will be associated with chemotherapy treatment called Busulphan. This drug can have adverse impact on the liver hence patient selection will take this into account. The actual admission period is associated with a period of isolation and increased risk of infection, which is likely to offer some mental health challenge similar to that seen in other patients undergoing similar cellular therapies. However once discharged from the acute admission to receive the therapy and once patients achieve white cell and then platelet and red cell engraftment, the expectation is a much improved quality of life with reduced to absent acute pain episodes due to the sickle cell condition and

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Treatment with Hydroxycarbamide is discussed with all adult patients and offered to all paediatric patients. Crizanlizumab is available at present to patients who have had 2 pain episodes in the preceding 12 months. Allogeneic stem cell transplant is available to patients with a matched sibling donor who have had a number of complications as listed in answer 9. So this technology potentially will cover a similar group of patients.
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?	Absence of acute pain episodes (VOC) Reduced admission to hospital with complications of SCD Improved haemoglobin Reduced fatigue in patients Reduced/absent need for transfusion in the regularly transfused sickle patients Reduced use of iron chelating drugs Reduced use of opioid analgesia Most above was measure
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None we are aware of

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None we are aware of, the CRISPR Cas 9 approach to genetherapy in sickle cell is a rapidly growing field with many other groups performing similar so the evidence continues to be accumulated
21. How do data on real-world experience compare with the trial data?	Gene therapy is not presently available in the “real world” for SCD so there is little to compare the trail data to.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No, the group of patients that would benefit are generally of the BAME community, studies have also shown they usually score high on deprivations measures. Hence this technology offers a chance at some equity in health care.
22b. Consider whether these issues are different from issues with current care and why.	

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.	• • • • •

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 or NO

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 sickle cell disease [ID4016]

Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

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

Information on completing this submission

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

About you1. Your name	[redacted]
2. Name of organisation	National Haemoglobinopathy Panel, England www.nationalhaempanel-nhs.net
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).	In October 2019 NHSE announced the outcomes from its service review and designated 23 specialist haemoglobinopathy centres (SHT), ten (10) haemoglobinopathy co-ordinating centres (HCC) for sickle cell disease, four (4) centres for thalassaemia and set up a **National Haemoglobinopathy Panel (NHP).** The National Haemoglobinopathy Panel (NHP) supports the HCCs, providing expert advice on options for individuals with complex needs living with SCD, thalassaemia or rare inherited anaemias. The NHP also supports decision making on novel treatments, improving access to interventions and clinical trials. The NHP is commissioned through the NHS England/Improvement London specialised commissioning regional team. HCCs provide network development, leadership, learning and education across their network area, while SHTs provide clinical services including specialist interventions and work with LHTs to enable equitable access to high standards of care.

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 NHP is funded by NHSE and hosted by King's College Hospital London, it is not funded by Industry
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NONE

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.)	The main aim of treatment is to achieve cure but there is currently no such therapy available and therefore the main therapy is to prevent infection by using penicillin prophylaxis, vitamin supplementation using folic acid and the only disease modifying therapy is hydroxyurea which has been in use for over 35years. This treatment is only palliative but does not eliminate the symptoms and even though it may improve the quality of life not all patients respond to the treatment. While recently in 2017 (L-Glutamine) and 2019 (Crizanlizumab and Voxelotor) three additional medications were FDA approved, both L-Glutamine and Voxelotor have not been supported by NICE and Crizanlizumab only has limited restricted approval.
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.)	A clinically significant response the proportion of patients that are symptom free such as reduced acute pain episodes referred to as vaso-occlusive crises (VOCs), the frequency and the interval between episodes, whether the patients experience improvement in the health-related quality of life less fatigue and in the long time increase survival such as improvement in life span. Recent patient survey data (SWAY and SHAPE) from the UK showed that fatigue, joint pains, poor quality of life are leading issues in over 60% of patients and therefore reduction in these problems especially if it is sustained are a welcome development The ultimate outcome is cure from sickle cell disease and to make sure that this cure is safe and improves patient quality of life.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Sickle cell disease is an inherited red blood cell disorder that places a substantial emotional, physical, and financial burden on patients and their families. Recent service review by NHSE reported over 17,000 individual episodes in the UK and over 250 babies are born with the disorder every year. The majority of those affected are from ethnic minorities especially African as well as Mediterranean, middle east and Indian ancestry and over 80% live in greater London. The challenges affecting these patients was recently captured by the SCTAPPG report 2021 called ‘No one’s listening report’ that highlighted issues of inequity, discrimination and racial bias. Similar issues were identified in US and other EU countries.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Hydroxyurea is the only disease modifying treatment and not all patients respond. Blood transfusion is well known option for treatment The issues with blood transfusion include the development of excess iron and if poorly control this may lead to end organ damage. Blood transfusion is
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are a variety of national, institutional and local trust guidelines e.g. Guidelines - SELSEHCC (ststn.co.uk); PH2-acute-management-of-scd-crisis.pdf (oxford-haematology.org.uk) 1. Significant haemoglobinopathies – A guideline for screening and diagnosis April 23 2. Monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias Oct 21 3. Management of sickle cell disease in pregnancy Aug 21 4. Hydroxycarbamide in children and adults with sickle cell disease May 18 5. Red cell Transfusion in SCD Part 1 &II Nov 16 6. Acute chest syndrome SCD March 15 National standards of care: Standards for the clinical care of adults with sickle cell disease Sickle cell disease in childhood: standards and recommendations for clinical care
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.)	The care of sickle cell disease is well defined and requires considerable resources and man power to implement Patients are selected according to agreed criteria for Indication such as **chronic blood transfusion** for primary and secondary stroke prevention, **bone marrow transplantation** e.g. age, high risk complications such as stroke, unremittent pain that does not respond to hydroxyurea therapy. **Hydroxyurea therapy** is offered to all children with sickle cell anaemia, the most severe form of the disorder and the adults with significant morbidity. While different degree of **pain management in acute and chronic setting** is depending on the patients symptoms which may include standard analgesia like paracetamol, ibuprofen, opiates and other adjuvant therapies.
9c. What impact would the technology have on the current pathway of care?	

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	While the institution of hydroxyurea and blood transfusion has had significant impact, there remains a major gap in curative therapy that would affect the patient's overall quality of life, ability to engage in career development and raise their families
10a. How does healthcare resource use differ between the technology and current care?	Exagamglogene autotemcel will be a single treatment and is expected to reduce both acute events, and prevent progression or development of chronic complications. Treatment with this technology is expected to reduce health care utilisation Studies focussing on hospital episode statistics (HES) indicate high health utilisation by individuals with SCD with most specialist services reporting 15-25 percent of their population on regular blood transfusion programs (either top up transfusions with 2-4 units monthly or 6-10unit exchange transfusions 4-8 weekly). SCD patients are also regularly admitted to hospital with painful vaso-occlusive crisis requiring supportive care. These patients have a high burden of co-morbidity. HES data indicate that SCD patients not on transfusion can have up to four additional comorbidities, resulting in significant healthcare burden.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This would be restricted to highly specialised treatment centres with the level of staffing and technology and accommodation for clinical activity and patient support
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Successful implementation will require high level of isolation from the risk of infection, high technology that is required for bone marrow transplantation will need to be expanded with both human and equipment investments. This would actually support the development highly skilled centres in the UK These would attract greater research funding
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Data from clinical trials have been presented in international conferences. Data presented at the EHA conference in June 2023 reported on results in 31 patients with severe SCD characterized by recurrent vaso-occlusive crises (VOCs) (mean of 3.9 VOCs per year over the prior two years) were free of VOCs after exa-cel infusion through duration of follow-up, with follow-up ranging from 2.0 to 32.3 months. SCD patients had mean HbF (as a proportion of total Hb) of approximately 40% by Month 4 and maintained thereafter. This is an excellent outcome and shows great promise for severely affected SCD patients

11a. Do you expect the technology to increase length of life more than current care?	Exagamglogene autotemcel therapy is expected to improve the overall quality of life, these have been reported by a growing cohort of patients over 3 year period. While the long term outcome remains to be proven it is vital that this promising technology is implemented in the UK. The patients are keen to have access to therapies that are more likely abolish pain and discomfort and with a prospect of cure this is highly valuable.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Data emanating from clinical trials is very promising by the improvement health related quality of life based on validated patient related outcome measures such as SF-36, WHOQOL, Health Related Quality of life Pedsql amongst others.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This needs to be tested over time. Not all patients are expected to receive these interventions hence the role of National Haemoglobinopathy panel (NHP) and the Haemoglobinopathy coordination centres (HCC) MDT that are nie well established to

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.)	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. This will be guided by the established networks, NHP and HCC

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Formal stopping rules will be developed by the NHP bone marrow transplant and gene therapy committee who are working with relevant HCCS and NHP to make sure that patient safety is paramount. The programme is supported by a robust data management and registry (National Haemoglobinopathy Registry). This will allow monitoring pf all those receiving these therapies are adequately monitored, data collection will be supported by NHS Trusts as well.
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?	The information from clinical trials and real world data supports the expectation that wide ranging outcomes will become obvious over time.
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?	Exagamglogene autotemcel therapy is innovative bringing into reality to well accepted theory that fetal haemoglobin will ameliorates the symptoms of sickle cell disease. It is based on the CRISPR-9 technology capable pf meeting the need for patient care. This is one of the few interventions for high risk patients.
16a. Is the technology a 'step-change' in the management of the condition?	Currently there really is only limited curative therapy options which is dependent of the availability of suitable bone marrow donors. Other drawbacks on bone marrow transplants are the complications such as graft versus host disease, infertility.

16b. Does the use of the technology address any particular unmet need of the patient population?	There are considerable unmet needs in sickle cell disease. It is also evident that racial disparity has limited progress in the search for curative therapies. The group of patients that are likely to benefit from this technology and those at risk of inequity in healthcare provision, high risk of communicable and noncommunicable disorders. They are more likely to live-in low-income settings and high deprivation boroughs in England
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?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, patients with severe sickle cell disease all have discussions with their clinical teams and most will be on disease ameliorating treatment in the form of either hydroxycarbamide or transfusion or be referred for an SCT if they have a matched sibling donor unless the patient themselves opt not to.
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?	

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?	Not ware, trials are ongoing
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	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 older than the age group studied for whom the unmet need will remain a significant issue.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	In the United Kingdom, the majority of British SCD patients tend to be of Black African and Caribbean heritage. The index of multiple deprivation data indicate that Black people, are most likely to live in the lowest 10% of the economically deprived neighbourhoods in the UK. Additionally, UK research has demonstrated that SCD patients from the most socioeconomically deprived areas are at highest risk of both hospital re-admissions and in-hospital mortality, suggesting there are significant inequalities in healthcare access and health outcomes amongst people with SCD.
22b. Consider whether these issues are different from issues with current care and why.	No

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• There a high degree of unmet need for treatment option in SCD • The only currently available curative therapy option is available to <15% of patients • The Sickle Cell disease patients are additionally impacted by high levels of deprivation and low patient reported experience • 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 sickle cell disease [ID4016]

Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

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

Information on completing this submission

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

About you

1. Your name	[redacted]
2. Name of organisation	Royal College of Pathologists
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
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Diplomates, Affiliates and trainees, supported by the staff who are based at the College's London offices. The College is a charity with over 11,500 members worldwide, the majority of members are doctors and scientists working in hospitals and universities in the UK. The College oversees the training of pathologists and scientists working in 17 different specialties, which include cellular pathology, haematology, clinical biochemistry and medical microbiology.
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.)	Exagamglogene autotemcel is a potentially curative treatment for sickle cell disease. The only curative option currently available to patients is an allogeneic stem cell transplant from a matched sibling donor, which is not available for most patients due to the lack of 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.)	The following outcomes would constitute treatment response • changes to haematological parameters (haemoglobin levels) • proportion of subjects not needing any disease modifying treatment, including blood transfusion, hydroxyurea, crizanlizumab and voxelotor following treatment with CTX001 gene therapy • proportion of subjects who have not experienced any sickle vaso-occlusive episodes for at least 12 consecutive months • proportion of subjects who have not had any further stroke or progression of cerebrovascular disease in those with established cerebrovascular disease • proportion of subjects able to wean off long term opioids 12 months following treatment • proportion of subjects who have no progression of organ dysfunction, as measured by echocardiogram, pulmonary function tests, glomerular filtration rate, • time to engraftment • low proportion of subjects with no off-target effects of CTX001 gene therapy, including development of therapy related myelodysplasia or leukaemia • mortality • adverse effects of mobilisation, myeloablation, neutropaenia • health-related quality of life.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are very limited disease modifying therapies for sickle cell patients and more importantly there are no real curative treatments for patients suffering from frequent sickle cell crises apart from allogenic bone marrow transplant which is limit in its availability due to lack of suitable matched siblings. There is a high unmet need for this cohort of patients who live with a disease that can result in unpredictable, severe and often life threatening complications. This should be viewed as a high priority for the NHS as the only currently available novel therapy is Crizanlizumab and that is accessed via a managed access program, unfortunately emerging data would suggest likely low efficacy of this therapy. The other novel therapy Voxeletor while in use in elsewhere in the world isnot currently available in the United Kingdom. Neither of these therapies is curative

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Treatment is supportive for the majority of patients. Current therapy options that are disease modifying (non curative) • Blood transfusion is used for patients with frequent vaso-occlusive crisis or serious complications to reduce end organ damage. However there are complications as a consequence of transfusion such as iron overload which then requires further medical management with chelation therapy. In addition the blood SCD patients receive while matched for the main antigens and any antibodies present does still present some risk due to to ethnic variationin blood groups. So despite providing cross matched units, (even in emergencies ,where possible), patients may still develop antibodies. Additionally patients on the regular programs who start transfusions after later in life, are more likely to develop alloantibodies to transfused red cells as they are more likely to mount an immune response. This has significant impact on their future management as it may introduce delay in acquiring blood for future transfusions and places

	them at risk for transfusion reactions including delayed transfusion reactions which may be life or organ threatening. • Alloimmunisation can also lead to patients, especially when they develop multiple or complex antibody combinations not being able to access blood even in an emergency, as an provision of blood gets increasingly challenging with antibody formation. • Hydroxyurea is the mainstay of management but does not provide effective management for all patients and has side effects that can be intolerable/ unacceptable for some patients • Newer therapies: o the efficacy of Crizanlizumab is currently under review as the preliminary results from the ongoing global phase III study STAND (NCT03814746) showed no statistically significant difference between crizanlizumab (doses of either 5mg/kg or 7.5mg/kg) and placebo in annualized rates of vaso-occlusive crises (pain crises) leading to a healthcare visit over the first-year post randomization. These findings are inconsistent with previous trial results from SUSTAIN (NCT01895361), which demonstrated the superiority of crizanlizumab 5.0mg/ kg compared to placebo. o There is no current access to Voxeletor for patient who either were not part of the clinical trials or did not get on the early access program which ended in October 2022. d The only available curative treatment is allogeneic stem cell transplant that is available for a minority of patients who have 'severe' disease: • History of >= 3 severe pain crises or other acute complications per year despite institution of supportive care measures (optimal treatment with hydroxycarbamide (HC) or transfusion therapy). Other acute complications would include acute hepatopathy or splenic sequestration or acute priapism. (This can be further refined using the CLIMB SCD trial inclusion criteria, namely patients with severe sickle cell disease having at least two vaso-occlusive crisis events per year for two consecutive years and documented severe sickle cell disease genotype) • Recurrence of acute chest syndrome despite optimum treatment with hydroxycarbamide (HC) or transfusion therapy • Clinically significant neurologic vascular event or deficit lasting over 24 hours and confirmed radiologically (i.e. stroke) or progressive cerebral vasculopathy

	• Administration of regular transfusion therapy, either by simple transfusion or exchange transfusion with the aim to prevent severe sickle complications by maintaining a low HbS%. Severe sickle complications include a history of >= 2 chest syndromes, >= 3 painful crises or severe recurrent priapism • Patients assessed as requiring transfusion but with red cell allo- antibodies/very rare blood type, rendering it difficult to continue/commence chronic transfusion • Patients requiring hydroxycarbamide/transfusion for treatment of SCD complications who cannot tolerate either therapy due to significant adverse reactions • Established end organ damage relating to SCD including but not limited to progressive sickle vasculopathy and hepatopathy.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are a variety of national guidelines BSH guidelines: 1. Significant haemoglobinopathies – A guideline for screening and diagnosis April 23 2. Monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias Oct 21 3. Management of sickle cell disease in pregnancy Aug 21 4. Hydroxycarbamide in children and adults with sickle cell disease May 18 5. Red cell Transfusion in SCD Part 1 &II Nov 16 6. Acute chest syndrome SCD March 15 National standards of care: Standards for the clinical care of adults with sickle cell diseaseSickle cell disease in childhoold: standards and recommendations for clinical care
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.)	There are established networks of clinical care in England with care being overseen by Specialist Haemoglobinpathy teams (SHTs) and the Haemoglobinopathy Coordinating Centres (HCCs) to ensure patients have equitable care. Approval for allogeneic stem cell transplant and the use of newer therapies have been developed following guidance developed by the National Haemoglobinopathy Panel. The networks will be peer reviewed in 2024 to assess compliance with national standards.

9c. What impact would the technology have on the current pathway of care?	Exagamglogene autotemcel will be a novel therapy and will offer many patients especially those with more severe disease who do not have an allogeneic donor the chance potentially curative treatment. Potentially Exagamglogene autotemcel will be delivered by a small number of units; HCCs will work with their SHTs to develop pathways for this treatment.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Exagamglogene autotemcel is a novel agent and will be an additional treatment option for patient with significant disease burden/ complications of SCD despite current treatment options (transfusions, hydroxycarbamide, Voxeletor, Crizanlizumab). The main difference is that it is potentially curative,
10a. How does healthcare resource use differ between the technology and current care?	There is a wealth of published literature on the increasing disease burden of sickle cell disease with the accumulation of co-morbidities with increasing age and premature mortality. Individuals with SCD and a history of end-organ damage such as stroke demonstrate higher rates of health care utilization, including more hospital days, emergency department visits, outpatient visits, lab tests, and outpatient pharmacy claims compared to those without end-organ damage. This has been shown by a number of publications using Hospital episode data in the England.Exagamglogene autotemcel will be a single treatment expected to reduce both acute events as well as chronic complications, and by extension reduce health care utilisation.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Exagamglogene autotemcel will be administered in the tertiary care setting by specialist units with experience of delivering cellular therapies and who are JACIE accredited.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There will be a training requirement for the collection, preparation and administration of this product specifically but this is expected to follow principles for other Advanced Therapy Medicinal Products (ATMPs). Units delivering Exagamglogene autotemcel are likely to require an expansion of capacity as this is an additional new treatment.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, we expect successful treatment would lead to 1. Reduction in acute and unpredictable presentations such as with vaso occlusive events, acute chest syndrome and lead to fewer presentations to hospital 2. Stabilisation of complications such as neurological events, cardio-pulmonary complications 3. Reduction in the likelihood of needing blood transfusions

	4. Significant reduction in opiate requirement for patients with chronic pain 5. Overall reduction in health care utilisation 6. Improved quality of life
11a. Do you expect the technology to increase length of life more than current care?	Long term data following gene therapy in SCD is currently not available. Patients with recurrent vaso –occlusive events have a higher mortality than age matched controls; additionally accrual of organ morbidity is associated with mortality. Hnece a therapy thet has potential to impact and reduce both acute events such as VOC and morbidity would be expected to lead to an improvement in mortality.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Patient surveys report significant disease burden. • as much as 50% of patients with SCD report moderate to extreme pain , • Multiple SCD patient reported outcome surveys in the UK, as well as the rest of the world has shown participants with SCD report a reduction in self-reported health , a reduction in physical well-being and a reduction in emotional well-being compared to the general population • Patients reported that their health made it hard to do things A reduction in clinical manifestations is likely to lead to improved physical well-being and an improvement in QOL.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The patients with a similar disease profile to those on the clinical trial and those with a moderate to severe disease phenotype would be expected to have the greatest clinical benefit. The conditioning regime used for the treatment would preclude a subset of patients from receiving this treatment. Although gene therapy is potentially curative the risk of the treatment may outweigh any benefit for patients with a mild disease phenotype.

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	Gene therapy involves various steps from the collection of stem cells, conditioning chemotherapy and then patient follow up post product infusion. This treatment will be delivered only in JACIE accredited units that are familiar with Advanced Therapy Medicinal Products (ATMPs). The pathway would involve selection of appropriate patients,

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.)	referral and joint assessment with the team delivering the gene therapy and follow up thereafter. The majority of clinicians that manage sickle cell disease will not directly be administering this treatment but will work collaboratively with the cellular therapies unit. The possibility of potentially curative therapy should be discussed with patients as part of their annual review. Patients will require exchange transfusions pre procedure – this is an additional step but all haemoglobinopathy units have provision for this.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No, treatment will be delivered within national recommendations.
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 SCD patient reported outcome surveys focusing on quality of life, show the significant impact that the frequent and daily pain associated with SCD has on patients, it also notes the un-predictability of SCD crises impacts on patient ability to attend school or work regularly with 1 study showing 1 lost day per 9 due to Sickle associated complications. This technology based on the early phase trials would be expected to lead to significantly improve this.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on	Exagamglogene autotemcel is innovative in that it is potentially curative. It offers a curative option at the level of the stem cell, but does not require a donor other than the patient, hence will be more accessible for patients who qualify for it. It also has advantage over the allogeneic offer in that it cannot result in graft versus host disease, a

health-related benefits and how might it improve the way that current need is met?	condition which can blight patients lives post allogeneic stem cell transplant, patients will also not need to take immune suppressing medication post gene therapy and have a lower risk of graft rejection due to a mismatch. There is only 1 licensed drug treatment for sickle cell in the UK freely available to patients which is Hydroxycarbamide and as noted above this medication although effective, does not work for all patients,. The novel therapy Crizanlizumab which is currently available via a managed access program has not been found to be as effective in the real world, and emerging trial evidence suggest it may not offer much more than placebo .
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 stem cell transplant and as noted fewer than 18% of patients will have a matched sibling donor available to donate then Exagamglogene autotemcel which uses stem cell from the patients is highly innovative and offers the option of cure to a wider population of patients. The advantage of not relying on a patient having matched sibling, who consents to donate and instead using autologous cells cannot be overstated. Other available therapies for sickle cell disease are disease modifying and are not effective for some patients.
16b. Does the use of the technology address any particular unmet need of the patient population?	We do not have effective treatments in SCD so Exagamglogene autotemcel offers a treatment and potential cure to haemoglobinopathy patients that is is innovative. It will offer a chance at disease free survival, reduced health utilisation, improved or at least stabilised organ function and improved quality of life. The advantage is that using autologous cells are used unlike allogeneic stem cell transplant which is available to only a few patients with a compatible donor. Other available therapies for sickle cell disease are disease modifying and are not effective for some patients.

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 technology itself will require stem cell harvest from patients with GCSF or plerixafor pre treatment, this is expected to be overall well tolerated however some bone pain during the treatment is expected. The admission for stem cell infusion will be associated with chemotherapy treatment called Busulphan. This drug can have adverse impact on the liver hence patient selection will take this into account. The actual admission period is associated with a period of isolation and increased risk of infection, which is likely to offer some mental health challenge similar to that seen in other patients undergoing similar cellular therapies. However once discharged from the acute admission to receive the therapy and once patients achieve white cell and then platelet and red cell engraftment, the expectation is a much improved quality of life with reduced to absent acute pain episodes due to the sickle cell condition and

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Treatment with Hydroxycarbamide is discussed with all adult patients and offered to all paediatric patients. Crizanlizumab is available at present to patients who have had 2 pain episodes in the preceding 12 months. Allogeneic stem cell transplant is available to patients with a matched sibling donor who have had a number of complications as listed in answer 9. So this technology potentially will cover a similar group of patients.
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?	Absence of acute pain episodes (VOC) Reduced admission to hospital with complications of SCD Improved haemoglobin Reduced fatigue in patients Reduced/absent need for transfusion in the regularly transfused sickle patients Reduced use of iron chelating drugs Reduced use of opioid analgesia Most above was measure
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None we are aware of

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None we are aware of, the CRISPR Cas 9 approach to genetherapy in sickle cell is a rapidly growing field with many other groups performing similar so the evidence continues to be accumulated
21. How do data on real-world experience compare with the trial data?	Gene therapy is not presently available in the “real world” for SCD so there is little to compare the trail data to.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No, the group of patients that would benefit are generally of the BAME community, studies have also shown they usually score high on deprivations measures. Hence this technology offers a chance at some equity in health care.
22b. Consider whether these issues are different from issues with current care and why.	

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.	• • • • •

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 or NO

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 sickle cell disease [ID4016]

Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

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

Information on completing this submission

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

About you

1. Your name	[redacted]
2. Name of organisation	United Kingdon 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 an unrestricted educational grant 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

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 sickle cell disease, a disorder associated with multiple comorbidities and life expectancy that is shortened by more than twenty years compared age-sex matched general population as has been confirmed by multiple studies. At present the only curative option available to patients with sickle cell is an allogeneic stem cell transplant from a matched sibling donor, due to lack of donor availability this is an option only <15% of eligible patients.
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.)	No hospitalisations for sickle cell related complications within 12 months of completing the treatment No sickle acute vaso-occlusive episodes within 12 months of completing the treatment No need for blood transfusion Improved health-related quality of life No need for any other sickle cell disease modifying treatment including hydroxycarbamide or crizanlizumab Improved haemoglobin level Significant reduction or complete wean off opioid medications Successful wean off or changes to haematological parameters (haemoglobin levels) within 12 months of completing the treatment Low or no patients with no off-target effects of this technology including development of therapy related myelodysplasia or leukaemia No mortality

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	YES. Sickle cell was described in 1910, its genetic basis in 1957 yet in the clinic at present we have only one approved therapy to offer patients for the condition, namely hydroxycarbamide. Blood transfusions are used in supportive care and symptom alleviation. Newer drugs such as crizanlizumab and voxelotor are unlikely to receive approval due to concerns regarding efficacy. Sickle cell is associated with a myriad of complications and devastating morbidity including stroke which can be seen even in toddler age children with the diagnosis. Patients suffer intermittent and unpredictable acute episodes referred to as sickle cell crises which usually present as acute pain but may also present with single organ impairment or failure as is seen in an acute chest syndrome, or may present with multi-organ failure. Although patient survival has improved with improvement in supportive care, many individuals with SCD continue to die in early adulthood from complications of the disease. There is a dire need for curative approaches to treatment of SCD in England to combat the known high 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 sickle cell disease in the NHS in England is supportive. There is one drug therapy hydroxycarbamide licensed for management of pain, and acute chest syndrome. Blood Transfusion has been shown to reduce risk of stroke in randomised controlled trials, and patients recently (2019) gained access to a novel therapy Crizanlizumab via a managed access program. However a pivotal phase 3 study was unable to demonstrate efficacy of crizanlizumab over placebo, and it is therefore unlikely to be approved for use in the NHS. • Hydroxycarbamide is the mainstay of sickle disease management. It is an orally active drug with once daily dosing, originally used in treatment of leukaemia, but subsequently repurposed for sickle cell disease. Although effective in improving several clinical outcomes, its adverse effects on fertility and cytopaenia make it intolerable or unacceptable for a proportion of patients. It is also not effective in all patients. • Blood transfusion is used manage the most severe complications of the sickle condition such as acute presentations with stroke across the life span, it is also used as primary prevention for children and adults at risk of stroke. Additionally, blood transfusion is also used to treat a number of other sickle complications including acute chest syndrome, acute liver failure, pulmonary hypertension and sequestration crises although the evidence base for most of this care strategy is based on small case

	series, based on expert opinion and experience. Transfusion is also the current treatment offered to patients with severe sickle cell who fail or are unable to tolerate Hydroxycarbamide. However, treatment with blood transfusion is not without complications. One third of sickle cell patients develop antibodies to transfused red cells, which can make it more difficult to find compatible blood units for them, and a small cohort have multiple and complex combinations of antibodies, that they are rendered effectively "un-transfusable". For a condition that may need to be rescued in extremis by transfusion, this presents a significant impact on mortality. 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: o Crizanlizumab is the only novel therapy available to patients with sickle cell in England and that is via a managed access program. Unfortunately, emerging data from the ongoing global phase III study STAND (NCT03814746) showed no statistically significant difference between crizanlizumab (doses of either 5mg/kg or 7.5mg/kg) and placebo in annualised rates of vaso-occlusive crises (pain crises) leading to a healthcare visit over the first-year post randomisation. This has led to the European Medicines Agency to recommend revocation of its authorisation and suggest a likely bleak future for this therapy. o Voxelotor which is the second agent shown in clinical trials to impact the sickle conditions with improvement in haemoglobin levels is not currently available in England. Patients currently on the medicine in England at present, are those who took part in the clinical trials or accessed it via the named or early access programs which ceased in October 2022. • The only currently available curative treatment is allogeneic stem cell transplant t 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 15% of patients are likely to have suitable bone marrow donors thus severely restricting this curative option for patients
9a. Are any clinical guidelines used in the	There are a variety of national guidelines BSH guidelines: 1. Significant haemoglobinopathies – A guideline for screening and diagnosis April 23

treatment of the condition, and if so, which?	2. Monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias Oct 21 3. Management of sickle cell disease in pregnancy Aug 21 4. Hydroxycarbamide in children and adults with sickle cell disease May 18 5. Red cell Transfusion in SCD Part 1 &II Nov 16 6. Acute chest syndrome SCD March 15 National standards of care: Standards for the clinical care of adults with sickle cell disease Sickle cell disease in childhood: standards and recommendations for clinical care
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 sickle cell disease was divided into 10 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 in 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 complex patient management.
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 severe sickle cell who would otherwise qualify as it overcomes the main hurdle inhibiting many patients from progressing, the lack of 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 reduce acute events, and prevent progression or development of chronic complications. Treatment with this technology is expected to reduce health care utilisation The only other available curative intent is matched sibling donor stem cell transplant (SCT). The criteria for this treatment although broadly overlapping with this technology, has some differences in the age range of patients treated, and additionally stroke and being at risk of stroke are indications for SCT but not covered by this technology at present.

10a. How does healthcare resource use differ between the technology and current care?	Exagamglogene autotemcel will be a single treatment and is expected to reduce both acute events, and prevent progression or development of chronic complications. Treatment with this technology is expected to reduce health care utilisation Studies focussing on hospital episode statistics (HES) indicate high health utilisation by individuals with SCD with most specialist services reporting 15-25 percent of their population on regular blood transfusion programs (either top up transfusions with 2-4 units monthly or 6-10unit exchange transfusions 4-8 weekly). SCD patients are also regularly admitted to hospital with painful vaso-occlusive crisis requiring supportive care. These patients have a high burden of co-morbidity. HES data indicate that SCD patients not on transfusion can have up to four additional comorbidities, resulting in significant healthcare burden.
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. Significant reduction or absence of hospitalisation with sickle vaso-occlusive crises 2. Significant reduction or absence of any sickle vaso-occlusive crises presentations such as with vaso occlusive events, acute chest syndrome and lead to fewer presentations to hospital 3. Significant reduction or absence of a transfusion requirement 4. Significant reduction or absence of a requirement to manage pain with opioid medication.
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. Patients with SCD currently have mortality rates that are substantially higher than age and sex matched members of the general population in England by some 20 plus years.

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 show a reduction in wellbeing in SCD, with high amounts of daily pain, multiple missed days of school or work due to impact of health, a reduction in physical and emotional well-being. A reduction in disease associated morbidity is likely to lead to improved physical well-being and an improvement in QOL.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Sickle patients with mild disease and absence of vaso-occlusive episodes are less likely to derive benefit. In this cohort the treatment risks may outweigh any potential benefit. The patient group to whom the treatment will be effective in the clinic is likely to reflect the exact group who received it in the clinical trials. There is likely to be some restriction due to organ related co-morbidities and perhaps age, only because sickle cell patients accrue organ damage with age, which may make the technology less suitable for them. Busulphan chemotherapy conditioning is relatively intensive treatment, hence a good performance status score is generally required. Busulphan containing conditioning regimes are avoided in adults undergoing matched sibling donor SCT, where a much less intense conditioning protocol is used.

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	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 and parents, will cover the risk of infertility from the conditioning regimen, especially when the patient is too young to undergo fertility preserving treatments, will include likely impact on

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	fertility. We have emerging studies now reporting that although important, the risk of infertility has not been found to be a barrier to patients 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. There is no ongoing treatment that will need to be stopped.
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 SCD patient reported experience surveys focusing on quality of life, have consistently shown the significant impact that the frequent and daily pain associated with SCD has on SCD patients. These studies also note the un-predictability of SCD crises impacts patient's ability to attend school or work regularly. This technology based on the early phase trials results would be expected to lead to significant improvements.
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 allogeneic donors. This promises to increase the option of cure to many more individuals. Currently only 15% patients are eligible to receive sibling stem cell transplants. 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 15% of 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 patients severe sickle disease their only treatment option if they do not have a matched sibling donor is to remain on a lifelong transfusion program and if unfortunately a patient with severe sickle cell is "un-transfuse-able" either due to a combination of antibodies or previous severe transfusion reactions. They have extremely poor prognosis indeed. This technology offers patient with severe sickle cell a chance at disease free survival, improved quality of life, reduced health utilisation and hope of stabilised organ function.
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 plerixafor 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. None of these however are permanent effects and once the admission for treatment is completed would not be expected to remain an issue. Instead once their blood counts recover post the treatment based on early trial data

	this will be within a few months of receiving it, the expectation is a steady improvement in overall health and well being with an absence of sickle vaso-occlusive episodes.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes patients with severe sickle cell disease all have discussions with their clinical teams and most will be on disease ameliorating treatment in the form of either hydroxycarbamide or transfusion or be referred for an SCT if they have a matched sibling donor unless the patient themselves opt not to.
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 sickle pain or vaso-occlusion episodes Reduced or absent hospitalisations due to sickle cell complications Improved fatigue Improved haemoglobin levels Absence of progressive organ damage due to SCD Reduced or absent need for any sickle cell disease ameliorating therapies Reduced or absent need for chelation therapy

	Reduction in stroke risk secondary to SCD All the listed outcomes were measured other than stroke risk
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 older than the age group studied for whom the unmet need will remain a significant issue.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	YES. In the United Kingdom, the majority of British SCD patients tend to be of Black African and Caribbean heritage. The index of multiple deprivation data indicate that Black people, are most likely to live in the lowest 10% of the economically deprived neighbourhoods in the UK. Additionally, UK research has demonstrated that SCD patients from the most socioeconomically deprived areas are at highest risk of both hospital re-admissions and in-hospital mortality, suggesting there are significant inequalities in healthcare access and health outcomes amongst people with SCD.
22b. Consider whether these issues are different from issues with current care and why.	NO

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• There a high degree of unmet need for treatment option in SCD • The only currently available curative therapy option is available to <15% of patients • The Sickle Cell disease patients are additionally impacted by high levels of deprivation and low patient reported experience • 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 sickle cell disease [ID4016]

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.

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

Information on completing this submission

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

About you

1. Your name	[redacted]
2. Name of organisation	Clinical Reference Group, Haemoglobinopathy
3. Job title or position	[redacted]

	[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)? No Other (please specify):
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?	There are a variety of national guidelines: BSH guidelines: 1. Significant haemoglobinopathies – A guideline for screening and diagnosis April 23 2. Monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias Oct 21 3. Management of sickle cell disease in pregnancy Aug 21 4. Hydroxycarbamide in children and adults with sickle cell disease May 18 5. Red cell Transfusion in SCD Part 1 &II Nov 16 6. Acute chest syndrome SCD March 15 National standards of care: Standards for the clinical care of adults with sickle cell disease Sickle cell disease in childhood: standards and recommendations for clinical care
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.)	Since 2019, care for patients with SCD is provided through managed clinical networks via a hub and spoke system of working via NHSE Specialised Commissioning. Ten haemoglobinopathy coordinating centres (HCC) provide administrative oversight to SCD patients in England. Clinical care is managed via several specialist haemoglobinopathy teams (SHT) per HCC. Local haemoglobinopathy teams provide responsive care that is funded through CCG contracts. The National haemoglobinopathy panel provides MDT support to all 10 HCCs for complex clinical cases, and for approval of new drugs and therapeutics.
8. What impact would the technology have on the current pathway of care?	Exagamglogene autotemcel (exa-cel) would be transformative for patients with severe SCD who have no access to an allogeneic transplant, the currently available curative treatment for sickle cell disease, due to lack of suitable donors. Due to the autologous nature of the procedure, no graft rejection or graft versus host disease is expected

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 specific treatment is not in use in the context of sickle cell disease at present
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. Exa-cel will be used in severely affected SCD patients who do not have a suitable allogeneic donor for stem cell transplant. At present, these patients will receive hydroxycarbamide or red cell transfusions. Pathways are present to provide stem cell transplant in patients. Exa-cel will use the same pathways as an autologous transplant is needed for this procedure. Additionally, plerixafor will be needed to mobilise the stem cells of the patient. This is currently not commissioned by the NHS.
10a. How does healthcare resource use differ between the technology and current care?	Studies focussing on hospital episode statistics (HES) indicate high health utilisation by individuals with SCD with most specialist services reporting 15-25 percent of their population on regular blood transfusion programs (either top up transfusions with 2-4 units monthly or 6-10unit exchange transfusions 4-8 weekly). SCD patients are also regularly admitted to hospital with painful vaso-occlusive crisis requiring supportive care. These patients have a high burden of co-morbidity. HES data indicate that SCD patients not on transfusion can have up to four additional comorbidities, resulting in significant healthcare burden. Treatment with exa-cel will increase hospital visits in the first few months of treatment but it is expected that hospital episode will dramatically reduce after that, as patients will no longer need supportive management for sickle cell complications.
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	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

example, for facilities, equipment, or training.)

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. Plerixafor mobilisation will be needed and training for this will need to be provided.

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.

Year	Predicted patient numbers	Service costs using CAR-T tariff
2024	0	£0
2025	8	£628,135
2026	21	£1,590,932
2027	33	£2,394,124
2028	21	£1,590,923
2029	6	£401,596
2030	2	£133,865
Total	91	£6,739,583

10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?

This is a one-off treatment for which patients will need to fulfil criteria as set and agreed. They will need to be consented and receive treatment. There is no ongoing treatment that will need to be stopped.

11. What is the outcome of any evaluations or audits of the use of the technology?

Data from clinical trials have been presented in international conferences. Data presented at the EHA conference in June 2023 reported on results in 31 patients with severe SCD characterized by recurrent vaso-occlusive crises (VOCs) (mean of 3.9 VOCs per year over the prior two years) were free of VOCs after exa-cel infusion through duration of follow-up, with follow-up ranging from 2.0 to 32.3 months. SCD patients had mean HbF (as a

	proportion of total Hb) of approximately 40% by Month 4 and maintained thereafter. This is an excellent outcome and shows great promise for severely affected SCD patients

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	**SCD is the most common clinically significant genetic disease in the world**. Despite this, there is little global awareness or understanding of the condition, or of other related red blood cell disorders. Whilst we have understood the function of genes involved in the disease for many years, little has been done to develop effective treatments and cures. The evidence suggests that racial bias and condition-related stigma have contributed to a lack of investment in SCD and continue to negatively impact the care patients receive around the world**.** When compared to funding for other genetic conditions that generate more mainstream exposure, it is evident that SCD has been unfairly neglected. For example, cystic fibrosis affects one third fewer Americans than SCD but receives 7 to 11 times the research funding per patient. Consequently, very little in the way of drug and therapeutics development has happened in SCD globally, resulting in only a handful of approved drugs for clinical mitigation. Structural and interpersonal racism or bias may play a role in the quality of care patients receive. A US study showed that SCD patients attending A&E – many in excruciating pain - waited significantly longer for care than other groups, and that race was a contributing factor. In the UK, repeated cycles of peer reviews in haemoglobin disorders have demonstrated persistent inability to provide timely and effective pain relief during acute painful episodes, despite having a NICE guideline recommending a 30-minute time limit to receive analgesia. Although it is not sure whether racism is directly responsible for this, patients have repeatedly reported discriminatory behaviour in UK A&E departments. Majority of British SCD patients tend to be of Black African and Caribbean heritage. The index of multiple deprivation data indicate that Black people, are most likely to live in the lowest 10% of the economically deprived neighbourhoods in the UK. Additionally, UK research has demonstrated that SCD patients from the most socioeconomically deprived areas are at highest risk of both hospital re-admissions and in-hospital mortality, suggesting there are significant inequalities in healthcare access and health outcomes amongst people with SCD.
12b. Consider whether these issues are different from issues with current care and why.	Similar equality issues affect current clinical practice. Hence there has been so little progress in treatment of this condition so far. This treatment will go a long way in bridging some of the historical equality gaps in investment in technology and research.

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 or NO

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

Title: Exagamglogene autotemcel for treating sickle cell disease

Produced by Warwick Evidence

Authors

Jo Parsons, Assistant Professor[1]
Emanuela Castelnuovo, Senior Health Economist[1]
Naila Dracup, Information Specialist[1]
Martin Connock, Honorary Senior Research Fellow[1]
Xavier Armoiry, Honorary Senior Research Fellow and Professor of Pharmacy[1,2,3]
Amy Grove, Professor of Health Technology Assessment and Implementation Science[1]
Peter Auguste, Assistant Professor in Health Economics & Decision Modelling[1]

[1]Warwick Evidence, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, CV4 7AL
[2]Claude Bernard University Lyon, Villeurbanne 69100, France
[3]Lyon University Hospitals- Hôpital Edouard Herriot Pharmacy department, 69003 Lyon, France

Correspondence to

Mr Peter Auguste
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry, CV4 7AL.

Date completed 28/11/2023

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/60/84.

Declared competing interests of the authors

Description of any pecuniary relationship with sponsors, both personal and of the TAR Centre. If there are none, please state 'none'.

Acknowledgements

We would like to thank Professor Baba PD Inusa, consultant paediatric haematologist, King's College, London and Dr Elizabeth Rhodes, consultant haematologist, St. George's University Hospitals NHS Foundation Trust who provided clinical support. Emeritus Professor Aileen Clarke, Professor of Public Health, and Health Services research, University of Warwick who quality assessed the EAG report.

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.

This report should be referenced as follows:

Parsons J, Castelnuovo E, Dracup N, Connock M, Armoiry X, Auguste P. Exagamglogene autotemcel for treating sickle cell disease, Warwick Evidence, 2023: A Single Technology Appraisal.

Contributions of authors

Jo Parsons (Assistant Professor), Martin Connock (Honorary Senior Research Fellow), Xavier Armoiry (Honorary Senior Research Fellow and Professor) and Amy Grove (Professor) reviewed and critiqued the clinical effectiveness evidence. Martin Connock reviewed and critiqued the statistics and undertook any additional statistical analyses. Xavier Armoiry reviewed and critiqued the mixed treatment comparisons. Naila Dracup (Information Specialist) critiqued the company's searches and undertook additional searches. Emanuela Castelnuovo reviewed and critiqued the cost-effectiveness evidence and undertook additional economic analyses. Baba Inusa (Paediatric Haematologist) and Elizabeth Rhodes

provided expert clinical advice. Peter Auguste (Assistant Professor) reviewed the cost-effectiveness evidence and co-ordinated the project and the report.

Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

Table of Contents

Table of Tables

Table of Issues

Table of Figures

Definition of Terms and List of Abbreviations

ACS	Acute chest syndrome
AE	Adverse events
BMTS	Bone Marrow Transplantation Subscale
BSH	British Society for Haematology
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CS	Company submission
DCEA	Distributional cost-effectiveness analysis
EAG	Evidence assessment group
EMA	European Medical Agency
Exa-cel	Exagamglogene autotemcel
FACT-BMT	Functional Assessment of Cancer Therapy-Bone Marrow Transplant
FAS	Full Analysist Set
HLA	Human leukocyte antigen
HR	Hazard ratio
HRGs	Healthcare Resource Groups
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient-level data
KM	Kaplan-Meier
LYG	Life years gained
MAIC	Matching adjusted indirect comparison
MHRA	Medications and Healthcare products Regulatory Agency
NHR	National Haemoglobinopathy Register
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPR	Numeric pain rating
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
OS	Overall survival
PES	Primary efficacy set
PSA	Probabilistic sensitivity analysis
PICO	Population, intervention, comparator and outcomes
PICOTS	Population, Interventions, Comparators, Outcomes, Timing and Study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PSSRU	Personal social services research unit
QALY	Quality adjusted life year
RBC	Red blood cells
SAE	Serious adverse event
SCD	Sickle cell disease
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review

SMR	Standardised mortality ratio
SoC	Standard of care
STA	Single technology appraisal
VOC	Vaso-occlusive crises
WTP	Willingness-to-pay

Executive Summary

This summary provides a brief overview of the key issues identified by the external Evidence 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 presents a summary of the key issues identified in this appraisal of the clinical and cost-effectiveness of exagamglogene autotemcel (exa-cel) within its marketing authorisation for treating people aged 12 to 35 years with sickle cell disease (SCD) who do not have an available human leukocyte antigen (HLA)-matched related haematopoietic stem cell donor compared to established clinical management without exa-cel including hydroxycarbamide, blood transfusion and best supportive care.

Table 1: Summary of key issues

ID4016	Summary of issue	Report sections
Issue 1	Single-arm trial with short-term follow-up	Section 2.2.1
Issue 2	Generalisability of trial outcomes to NHS practice	Section 1.3.4
Issue 3	Trial sample size	Section 2.2.1
Issue 4	Short-term follow-up of participants	Section 2.2.1
Issue 5	Lack of control/comparator arm	Sections 1.3.3 and 2.2.1
Issue 6	The model does not have the requisites for a Markov structure	Section 3.2.2
Issue 7	Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	Section 5.1.2.6
Issue 8	VOC rates as a predictor in a risk equation for acute and chronic complications	Section 5.1.2.3
Issue 9	Modelling of adverse events is partial to exa-cel short list and selected events.	Section 3.2.7
Issue 10	Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using distribution of patients' weight.	Sections 3.2.10 and 5.1.2.9
Issue 11	The cost of supportive blood transfusions alongside implantations of exa-cel is not included in model costs.	Section 5.1.2.10
Issue 12	Range of acute and chronic complications included in the model is large, but risk reduction is based on assumptions	Section 3.2.6.2
Issue 13	Underestimation of uncertainty in modelling of overall survival in exa-cel and SoC. Distributions not appropriately parameterised and some key inputs excluded from the PSA.	Sections 3.2.9
Issue 14	Inclusion of severity modifier and implementation of 1.5% discount rate	Sections 1.3.7 and 3.2.11
Issue 15	Non-reference case distributional cost-effectiveness analysis	Section 1.3.8
NHS, National Health Service; PSA, probabilistic sensitivity analysis		

Table 2 presents the key differences between the company's preferred assumptions and the EAG's preferred assumptions. Due to the EAG's concerns about the company model, we have not undertaken analyses to estimate the impact to the company's base-case ICER, by using the EAG's preferred assumptions.

Table 2: Key differences between company and EAG's preferred assumptions

Company assumption	EAG assumption
The model does not use the NHS-PSS perspective	The proportion of people who fail apheresis should be assigned the cost of apheresis only;

Company assumption	EAG assumption
	the proportion who fails to receive exa-cel should be assigned the cost of apheresis, the cost of the drug, but not the cost of conditioning
Model structure - The model does not follow a Markov structure	The model structure should be redesigned as a proper Markov structure, with mutually exclusive and exhaustive mortality rates.
Modelling of acute events based on the number of VOCs - entirely speculative	VOC rates should not be used as in independent variable in a risk equation but as risk modifier
Modelling of adverse events is partial to exa-cel – very short list and selected events	All AEs from the CLIMB SCD-121 study should be used in the model, particularly when details on resource use are also available VOC data from CLIMB SCD-121 should be used and if excluded, justified.
The total cost of apheresis is inappropriately calculated	The methods used to incorporate the cost of apheresis and conditioning should be adjusted to incorporate appropriate rates and costs of dropouts; the cost of drugs (plerixafor, iron chelators and hydroxyurea) should be computed using the distribution of patient weight, the model should be able to take alternative total costs for apheresis and drug costs used in the longer term
The model does not correctly account for the cost of supportive blood transfusions given before and alongside exa-cel	A clarification is required regarding whether supportive transfusions will be part of the therapeutic protocol for exa-cel implantation; such costs should be included in the model fully
Cost of adverse events not considered appropriately	AEs related with exa-cel from CLIMB SCD-121 should be appropriately costed and incorporated in the model
Underestimation of uncertainty in modelling overall survival in exa-cel and SoC	Distributions should be included in the PSA for all death rates used in the model
Base-case ICER is deterministic	Base-case ICER estimates should be probabilistic, i.e., the ratio of mean costs and mean QALYs from the PSA
Severity modifier of 1.7x, 1.5% discount rate per annum and DCEA	Base-case ICER estimates using an appropriate severity modifier which is based on 3.5% discount rate.
AE, Adverse event; ICER, Incremental cost-effectiveness ratio; PSA, Probabilistic sensitivity analysis; QALY, Quality adjusted life-year; SCD, Sickle cell disease; VOC, Vaso-occlusive crisis	

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.

1.2.1 Discount rate of 1.5%

Overall, the technology is modelled to affect QALYs by:

- The incremental Life Years Gain (LYG) is [redacted].
- The expected total QALYs with SoC is [redacted].
- The expected total QALYs with exa-cel is [redacted].
- The incremental QALYs without a severity modifier is [redacted].
- The incremental QALYs with a severity modifier of 1.7 is [redacted].
- The incremental QALYs with a severity modifier of 1.7 and DCEA is [redacted].

Overall, the technology is modelled to affect costs by:

- The total cost of the SoC is [redacted].
- The total cost of the exa-cel is [redacted].
- The incremental cost of exa-cel versus SoC is [redacted].

1.2.2 Discount rate of 3.5%

Overall, the technology is modelled to affect QALYs by:

- The incremental Life Years Gain (LYG) is [redacted].
- The expected total QALYs with SoC is [redacted].
- The expected total QALYs with exa-cel is [redacted].
- The incremental QALYs without a severity modifier is [redacted].
- The incremental QALYs with a severity modifier of 1.7 is [redacted].
- The incremental QALYs with a severity modifier of 1.7 and DCEA is [redacted].

Overall, the technology is modelled to affect costs by:

- The total cost of the SoC is [redacted].
- The total cost of the exa-cel is [redacted].

- The incremental cost of exa-cel versus SoC is [redacted].

1.3 *The decision problem: summary of the EAG's key issues*

The EAG's key issues related to the decision problem are listed in Issue 1 Table.

Issue 1: Single-arm trial with a short-term follow-up

Report section	Section 2.2.1
Description of issue and why the EAG has identified it as important	Clinical effectiveness evidence is based on a small study with short term follow-up and no comparator (CLIMB SCD-121)
What alternative approach has the EAG suggested?	There seems no feasible alternative approach that can resolve the issues associated with this study design.
What is the expected effect on the cost-effectiveness estimates?	The cost-effectiveness model appears largely unrelated to the clinical effectiveness findings. The impact of any alternative approach is indeterminate.
What additional evidence or analyses might help to resolve this key issue?	More patients followed-up for longer in CLIMB SCD-121 would help but cannot resolve the fundamental issues.
EAG, evidence assessment group; SCD, sickle cell disease	

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

The EAG's key issues related to the clinical effectiveness evidence are reported in Table Issue 2 to Table Issue 5.

Issue 2: Generalisability of trial outcomes to NHS practice

Report section	Section 1.3.4
Description of issue and why the EAG has identified it as important	The CLIMB SCD-121 study uses data collected across 16 study centres across the US (9 sites), Canada (1 site), UK (1 site), France (1 site), Belgium (1 site), Germany (2 sites) and Italy (1 site). During clarification the company confirmed that [redacted] patients enrolled into the CLIMB SCD-121 at D120 were from the UK (with [redacted] patients from the UK included in the PES). The EAG has concerns over the difficulty to determine if the evidence reflects characteristics of patient population, and characteristics of standard of care and treatment received (before and during the trial period) in England and Wales, based on the small sample from the UK.
What alternative approach has the EAG suggested?	No feasible alternative seems available given that the data presented is based on so few UK SCD patients.
What is the expected effect on the cost-effectiveness estimates?	Most outcomes from CLIMB SCD-121 are unused in the economic model submitted by the company.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that additional evidence is required because the number of patients providing clinical evidence is small and their duration of follow-up is short; this is particularly the case from a UK perspective because of the extreme sparsity of UK participants.
EAG, evidence assessment group; NHS, National Health Service; PES, primary efficacy set; SCD, sickle cell disease	

Issue 3: Trial sample size

Report section	Section 2.2.1
Description of issue and why the EAG has identified it as important	The EAG has concerns around the small sample size in the CLIMB SCD-121 study (Primary and key secondary endpoints are based on 29 patients). Analyses beyond about 12 months were based on severely diminishing numbers of patients. The FAS supplies data for more patients (N= 42) and longer maximum follow-up, but numbers followed up diminish rapidly beyond about a year, and the evidence is inadequate for robust decision making. This small sample size in the trial informing efficacy evidence results in uncertainty about the efficacy of exa-cel and limits the scope of robust inferences that can be drawn from the evidence.
What alternative approach has the EAG suggested?	Given the noted shortcomings in the available evidence the EAG cannot suggest an alternative approach that would not suffer from similar fundamental deficiencies.
What is the expected effect on the cost-effectiveness estimates?	Direct evidence from CLIMB SCD-121 appears to have little or no identifiable input to the economic model.
What additional evidence or analyses might help to resolve this key issue?	While evidence suggests strong effectiveness of exa-cel for a limited number of patients in the short term the demonstration of prolonged effectiveness requires more patients to be followed up for a longer period. CLIMB SCD-121 cannot provide evidence for a comparator so this issue can only be satisfactorily resolved in a study with more patients, longer follow up, and an appropriate comparator arm to exa-cel.
EAG, evidence assessment group; FAS, final analysis set	

Issue 4: Short follow-up of trial

Report section	Section 2.2.1
Description of issue and why the EAG has identified it as important	As the study is still ongoing there is a lack of long-term follow up data available. Currently, the efficacy and safety findings are based on follow-up of between 1.3 to a maximum of 43.6 months for a couple patients (N=2). The company suggest that exa-cel is likely to restore patients with severe SCD to full or near-full health, but as no long-term follow-up data is yet available; it is impossible to assess the efficacy of exa-cel beyond the short term.
What alternative approach has the EAG suggested?	The only feasible alternative appears to be to await longer term evidence from CLIMB trials and to then assess effectiveness.
What is the expected effect on the cost-effectiveness estimates?	A rate (e.g., annualised) for severe VOC in CLIMB SCD-121 was not reported other than for the first 12 months; this is surprising since VOC rates drive the economic model. Currently, the cost-effectiveness model inputs appear to be largely independent of CLIMB SCD-121 outcome measures. The alternative approach (longer follow-up and more patients) might allow VOC rate measures in CLIMB SCD-121 to be input for the exa-cel arm. However, the problem of modelling a comparator arm would remain unresolved.
What additional evidence or analyses might help to resolve this key issue?	The EAG acknowledges that patients participating in CLIMB-131 will be monitored for up to 15 years following exa-cel infusion, but these longer-term data are not available. Currently, CLIMB-131 is hardly relevant for the decision problem.
EAG, evidence assessment group; SCD, sickle cell disease; VOC, vaso-occlusive crisis	

Issue 5: Lack of control/comparator arm

Report section	Section 1.3.3
Description of issue and why the EAG has identified it as important	CLIMB SCD-121 is a Phase 1/2/3 single-arm, open-label, multi-site, single-dose study. The EAG notes that as a single-arm study, there are no randomised comparators or control groups in the CLIMB SCD-121 trial. Without a control group the EAG was unable to determine, with a reasonable degree of certainty the true impact of exa-cel.
What alternative approach has the EAG suggested?	None seem feasible given the nature of CLIMB SCD-121.
What is the expected effect on the cost-effectiveness estimates?	Indeterminate.
What additional evidence or analyses might help to resolve this key issue?	The EAG note that this issue cannot be resolved given the study design of CLIMB SCD-121.
EAG, evidence assessment group; SCD, sickle cell disease	

1.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

In this section we highlight key issues with the company's cost-effectiveness evidence submitted.

- The model does not follow a Markov structure.
- The economic analyses do not account for costs and outcomes of treatment failures between apheresis and myeloablation.
- The model assigns a rate of VOCs for one year after receipt of exa-cel in the exa-cel arm, and a lifetime risk of VOCs in the SOC arm. This approach does not reflect evidence from CLIMB SCD-121. The model does not include VOC relapse at later times, also not reflecting evidence from CLIMB SCD-121
- Modelling of acute events based on the number of VOCs is not appropriate.
- For some computations, the number of VOCs is handled like a probability, i.e., the number (or proportion) of people that experience VOCs, whilst the number is a rate, i.e., mean number of VOCs for people alive in the model.

- Modelling of adverse events is partial to exa-cel- short list and selected events.
- Rates of chronic complications may be biased because of the computation methods.
- Mortality rates may be biased due to computation methods.
- Underestimation of uncertainty in modelling of overall survival in exa-cel and SoC. Distributions not appropriately parameterised and some key parameters excluded from the PSA.
- The cost of apheresis (plerixafor) is calculated for the average patient not for patient distribution of weight; the company's computation does not include wastage.
- The total cost of apheresis in inappropriately calculated.
- The economic analysis does not correctly account for the cost of supportive blood transfusions given before and alongside exa-cel.
- Inclusion of non-reference case DCEA, 1.5% discount rate and severity modifier may result in double counting. The EAG has concerns about the methods in which the DCEA, severity modifier and 1.5% discount rate have been calculated and applied in the model.

Issue 6: The model does not follow a Markov structure

Report section	Section 3.2.2
Description of issue and why the EAG has identified it as important	The model structure is not organised as a Markov structure, i.e., a model where state occupancy is calculated based on vectors of transition probabilities that are mutually exclusive (at each cycle, a person can transition to another state only) and exhaustive (total of probabilities = 1). It is plausible that people alive may experience more than one acute event; however, this logic cannot be transferred to deaths (see Section 3.2.9 on mortality extrapolation). Deaths are calculated by applying each acute complication a death rate specific to the event, corrected by the proportion of alive population. This approach implies that deaths are counted for each event independently from other events. Although the (incremental) death rates are applied to the "alive" population, the "alive" population is determined in a circular manner, subtracting the number of total deaths in the model from 1. This circularity provides no guarantee that the sum of deaths is less or equal to the total number of people in the cohort. The overall effect is that some people may "die twice" at each cycle in the model, i.e., people in the model are "double counted". Because of the lack of face validity, rates of chronic complications and mortality calculated in the model may be biased; the results of the model are affected by structural biases of uncertain entity and direction.
What alternative approach has the EAG suggested?	Model rebuild using standard practices for Markov state-transition models.
What is the expected effect on the cost-effectiveness estimates?	Uncertain. There are concerns about the model structure used to undertake the cost-effectiveness analysis. Hence, in the opinion of the EAG, this is likely to invalidate the company's cost-effectiveness analyses and results.
What additional evidence or analyses might help to resolve this key issue?	N/R

1.6 *Other key issues: summary of the EAG's view*

Issue 7:The economic analyses do not account for costs and outcomes of treatment failures between apheresis and myeloablation

Report section	Section 5.1.2.6
Description of issue and why the EAG has identified it as important	The exa-cel cohort showed that approximately 20% of people eligible for exa-cel in fact do not receive it. Some of the dropouts are due failure of apheresis (the process used to harvest cells from the patient) whilst others fail to obtain enough exa-cel for reimplantation (i.e., exa-cel yield falls below the lower bound for therapeutic efficacy). The latter group undergoes apheresis, accrues the cost of manufacturing exa-cel but drops out of the process just before myeloablation. After dropping out of the process, these patients continue to receive SoC.
What alternative approach has the EAG suggested?	Apheresis and myeloablation are not part of SoC, therefore they are only necessary if people are meant to receive exa-cel. As such, costs and outcomes for these people must be included in the model as part of the NHS perspective.
What is the expected effect on the cost-effectiveness estimates?	The model accounted for the cost of apheresis for these groups, but not for the cost of manufacturing exa-cel in the second group (which is a liability for the NHS). For both groups, the model failed to incorporate outcomes.
What additional evidence or analyses might help to resolve this key issue?	A small decision tree to calculate the probability of dropout after apheresis and of dropout after manufacturing of exa-cel but before myeloablation should be added. Once dropouts are accounted for, costs and longer-term outcomes for these people should be included in the exa-cel arm.

Issue 8:The incorporation of VOC rates (i.e., the primary endpoint in CLIMB SCD-121) as if they were a predictor in a risk equation for acute and chronic long-term complications of SCD is inappropriate

Report section	Section 3.2.6.1
Description of issue and why the EAG has identified it as important	The model extrapolates all longer-term events from hazard ratios of each event, multiplied by the rate of VOCs at each cycle. The rate of VOC is applied in the model as mean number of events per month; for each complication, this rate is multiplied by a hazard ratio, as if the number of VOCs were a term in a risk equation. Yet the original study with all likelihood did not use VOCs in this way; in any case, the original risk equations are not published. In addition, the original study did not show that the risk of complications is zero when patients report no VOCs, but only that the risk is reduced. Therefore, applying the "number of VOCs" as a significant independent variable, associated with a specific coefficient for the risk of acute and chronic complications in the manner of the model originates from a misinterpretation of the analysis in the original study (Shah et al 2019). Therefore, the number of VOCs per cycle (the intermediate outcome) cannot be used as an intermediate (surrogate) outcome in the model.
What alternative approach has the EAG suggested?	VOCs should be used to stratify risk, i.e., it should be used to identify two groups with different risks of certain events. VOCs, per se, should be used as one of the modelling relevant outcomes.
What is the expected effect on the cost-effectiveness estimates?	Because VOCs are used as multipliers, the correction of this approach is expected to increase the ICER
What additional evidence or analyses might help to resolve this key issue?	Methods used to incorporate VOCs should be modified.

Issue 9: Modelling of adverse events is partial to exa-cel- short list and selected events

Report section	Section 3.2.7
Description of issue and why the EAG has identified it as important	Adverse events with exa-cel are available from the CSR of CLIMB SCD-121. The company's model does not include these events on grounds that the HRG cost for myeloablation (obtained from standard NHS costs sources) already incorporates the adverse events of busulfan (the drug used during myeloablation) and other AEs. Whilst this is true, NHS costs cannot include adverse events for products not yet used in clinical practice.
What alternative approach has the EAG suggested?	AEs for exa-cel should be incorporated.
What is the expected effect on the cost-effectiveness estimates?	This addition is likely to increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	Rates of adverse events from CLIMB SCD-121 should be incorporated in the model.

Issue 10: The cost of drugs used during apheresis (plerixafor), during iron chelating regimens alongside blood transfusions and for hydroxyurea should be modelled using the distribution of patients' weight (rather than the average weight) to account for wastage

Report section	Sections 3.2.10 and 5.1.2.9
Description of issue and why the EAG has identified it as important	The costs of prescriptions that are patient-weight dependent should be calculated for all possible weights of the patient population (weight distribution). This is a well-established practice in cost-effectiveness modelling. The model does not allow for an easy incorporation of patient weight distribution because the formulae for calculating these costs are keyed into model traces, and across model cohorts and arms, all based on the average patient weight.
What alternative approach has the EAG suggested?	Costs for those drugs and relative procedures should be recalculated; the model should be modified to include an input for total costs of therapies by cycle.
What is the expected effect on the cost-effectiveness estimates?	The cost of drugs may differ from the average cost in either direction, it is not possible to predict the impact of this change.
What additional evidence or analyses might help to resolve this key issue?	N/R

Issue 11: The cost of supportive blood transfusions alongside implantation of exa-cel is not included in model costs

Report section	Section 5.1.2.10
Description of issue and why the EAG has identified it as important	The costs of supportive blood transfusions alongside exa-cel have been included but limited to resource use well below the trial protocol. It is not known whether the use of supportive transfusions may become part of clinical protocols for the use of exa-cel. Whilst normally trial-driven costs should not be included in the model, the use of supportive transfusions may become a feature of the use of exa-cel in real practice.
What alternative approach has the EAG suggested?	Costs for supportive transfusions with exa-cel should be included in the model
What is the expected effect on the cost-effectiveness estimates?	The cost of supportive transfusions will increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	N/R

Issue 12: The range of acute and chronic complications included in the model is large, but clinical parameters, particularly efficacy (risk reduction) is overwhelmingly based on assumptions

Report section	Section 3.2.6.2
Description of issue and why the EAG has identified it as important	It is accepted practice that modelling of cost-effectiveness can rely on assumptions around certain parameters when evidence is missing. Nonetheless, the credibility of a model conceptualisation is a qualitative evaluation based both on the amount of evidence incorporated in the model as well as the plausibility of clinical relationships hypothesised in the model structure. For example, parameters and efficacy of exa-cel with regards to bone problems, neurocognitive problems, liver disease and sickle cell retinopathy are assumed based on parameters for pulmonary hypertension, in their turn based on assumptions. The extent of parameters and structural uncertainty in a cost-effectiveness model should not be overwhelming, to ensure that both the logic and the outputs of the model are plausible.
What alternative approach has the EAG suggested?	The gaps in the evidence should be recognised; the model should be grounded in evidence, most clinical events parameters should be derived from data, sparingly complemented by assumptions that can be logically defended. When certain clinical endpoints have no evidence base, they should be excluded from the model.
What is the expected effect on the cost-effectiveness estimates?	The effect of these changes is unpredictable.
What additional evidence or analyses might help to resolve this key issue?	Either searching or developing more evidence for the major SCD endpoints could be helpful.

Issue 13: Underestimation of uncertainty in modelling of overall survival in exa-cel and SoC. Distributions not appropriately parameterised and some key parameters excluded from the PSA

Report section	Sections 3.2.9
Description of issue and why the EAG has identified it as important	The model PSA excludes stratified mortality rates and national statistics for background mortality. The use of these data in the model, including stratifications and data organised by age bands, is extensive; hence the exclusion from PSA drastically reduces the possibility of correctly accounting for uncertainty in the model.
What alternative approach has the EAG suggested?	Include all mortality data in the PSA.
What is the expected effect on the cost-effectiveness estimates?	The effect of these changes will increase uncertainty in the model.
What additional evidence or analyses might help to resolve this key issue?	N/R

Issue 14: Inclusion of severity modifier and implementation of 1.5% discount rate

Report section	Sections 1.3.7 and 3.2.11
Description of issue and why the EAG has identified it as important	The calculation of the severity modifier is likely associated with extensive uncertainty that is difficult to quantify and may be underestimated in the base-case cost-effectiveness analysis, and the application of this modifier in addition to implementation of 1.5% discounting is likely to result in double counting and bias.
What alternative approach has the EAG suggested?	NICE stipulates that applying absolute and proportional shortfall calculations should include discounting at the reference-case rate of 3.5% per annum.
What is the expected effect on the cost-effectiveness estimates?	The effect of these changes would likely increase the cost-effectiveness results.
What additional evidence or analyses might help to resolve this key issue?	Model rebuild using standard practices for Markov state-transition models, which encompasses addressing the concerns raised and using a 3.5% discount rate.

Issue 15: Inclusion of non-reference case distributional cost-effectiveness analysis

Report section	Section 1.3.8
Description of issue and why the EAG has identified it as important	The inclusion of non-reference case distributional cost-effectiveness analysis. The underlying aversion to inequality appears to be based on opinion of a single expert and that a proxy for health deprivation has been employed.
What alternative approach has the EAG suggested?	Exclude DCEA from the base-case to be more in-line with NICE reference case.
What is the expected effect on the cost-effectiveness estimates?	The expected effect of these changes would likely increase the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	N/R

1.7 *Summary of EAG's preferred assumptions*

The EAG's preferred assumptions are outlined in Table 2, with further details in Table 26, Section 5.3.

External Assessment Group Report

1 INTRODUCTION AND BACKGROUND

1.1 *Introduction*

This single technology appraisal (STA) was conducted to appraise the clinical and cost-effectiveness of exagamglogene autotemcel (exa-cel) versus standard of care for patients with severe sickle cell disease (SCD), namely those 12 years of age and older with recurrent vaso-occlusive crises (VOCs) who have **β^S/β^S, β^S/β^0 or β^S/β^+**, for whom a human leukocyte antigen (HLA)-matched related haematopoietic stem cell (HSC) donor is not available. A regulatory submission was made to the MHRA on 29 December 2022. Regulatory approval is anticipated by the company in October 2023.

Formal guidelines for management of SCD in the UK come from the British Society for Haematology (BSH) guidelines,[1] and NICE provide guidance on management of acute painful sickle cell episodes in hospital (NICE CG143, published in June 2012 and updated in October 2022).[2] BSH guidelines suggest the use of hydroxycarbamide or red blood cell (RBC) transfusions for management of SCD but there are currently no formal NICE guidelines on the treatment for patients with SCD.[1]

1.1.1 Disease overview (obtained from company submission)

SCD is a life-long disease characterised by unpredictable episodes of severe pain, chronic haemolytic anaemia, widespread organ damage and shortened life expectancy.

SCD is an umbrella term describing a group of inherited diseases characterised by a mutation in the HBB gene encoding β-globin, resulting in the expression of abnormal, sickle haemoglobin (HbS).[3, 4] The polymerisation of deoxygenated HbS causes red blood cells to become rigid, fragile, and misshapen, resembling a characteristic sickle shape. This results in a range of acute and chronic complications.[3, 5]

SCD affects multiple organs leading to acute and chronic complications such as acute chest syndrome (ACS), stroke, priapism, splenic sequestration, osteonecrosis,

renal failure, pulmonary hypertension, liver disease, bone damage, limited growth, increased susceptibility to infections, fatigue, and progressive cognitive decline.[6, 7]The mean age of death in the UK amongst patients with severe SCD is 40.2 years.[7, 8]

SCD is characterised by acute pain events, which can be triggered by illness, dehydration, stress, or wind speed, or pain itself, however, they can also occur unpredictably and without warning.[9-11] The frequency of acute pain events or VOCs varies between patients.[11]

1.2 *Background*

1.2.1 Prevalence of SCD (obtained from the company submission)

It is estimated that there are 14,200 patients with SCD in the UK, of which approximately 11,580 are 12 years of age or above.[12] This equates to less than 2 in 10,000 people. Chronic organ complications are the main cause of morbidity and mortality in SCD patients from around the third decade of life.[5] Higher rates of acute pain events (which results in higher rate of hospitalisation and ACS) are linked with increased mortality risk.[13] Patients with an average of three or more acute pain events per year across their lifetime have been shown to have worse survival outcomes compared to those with less than three per year.[14]

SCD prevalence is high in regions where malaria is endemic, including sub-Saharan Africa, the Mediterranean, the Middle East, and India.[15-17] Globally, the number of people living with SCD increased by 41.4% from 5.46 million to 7.74 million in 2021.[18] Data from the National Haemoglobinopathy Register (NHR) indicates that in England SCD disproportionately affects individuals of African or Caribbean ethnicity.[19]

1.2.2 Treatment options (obtained from the company submission)

Treatment options for SCD are limited to either established therapies, such as hydroxycarbamide and RBC transfusions, or the potentially curative allo-SCT.[20, 21] There are several risks associated with allo-SCT including those associated with bone marrow ablation, infections, GvHD, graft rejection and increased mortality, and

these risks plus the lack of HLA-matched donors partially explain the relatively low usage in SCD patients.[22, 23]

Only approximately 10% of SCD patients are receiving hydroxycarbamide in England according to the NHR, with most patients in receipt of this likely to be those experiencing frequent acute pain events.[24] Limited use can partially be explained by poor adherence, the need for frequent monitoring, and potential safety and tolerability issues. There are also concerns about fertility risks linked with the use of hydroxycarbamide.[25-28] Established therapies, like hydroxycarbamide and RBC transfusions, address some of the disease symptoms but do not offer a cure for SCD.

Recent crizanlizumab Phase 3 trial results did not meet the primary endpoint[29] and subsequent EMA decision to revoke conditional marketing authorisation has reduced available treatment options for addressing acute pain events in SCD patients further.

1.2.3 Technology positioning

Exa-cel is positioned for the treatment of SCD in patients 12 years of age and older with recurrent VOCs who have **β^S/β^S, β^S/β^0 or β^S/β^+**, for whom an HLA-matched related HSC donor is not available. See Figure 1 for proposed positioning of exa-cel in treatment pathway of SCD.

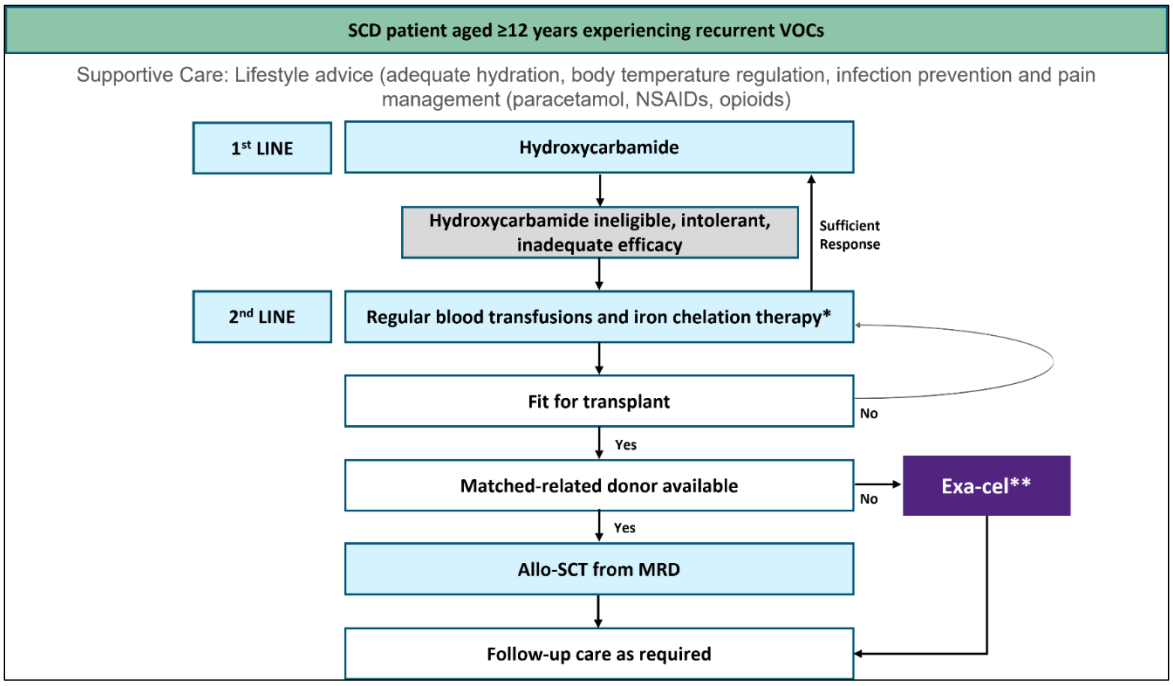


Figure 1: Proposed positioning of exa-cel in the treatment pathway (copied from CS Document B, Section B.1.3.4 page 55).

1.3 *Critique of company's definition of decision problem*

The company's description of the decision problem (summarised in CS Table 1) defines the relevant population, intervention, comparator, and outcomes as follows:

Population: Individuals with sickle cell disease (SCD) where there is no human leukocyte antigen (HLA)-matched related donor; **Intervention**: *Exagamglogene autotemcel (exa-cel)*; **Comparator**: *Established clinical management without exa-cel including: hydroxycarbamide, blood transfusions (exchange and top-ups) and best supportive care*; **Outcomes**: *Changes to haematological parameters (haemoglobin levels), proportion of patients who have not experienced any severe sickle cell crisis for at least 12 consecutive months, complications arising from sickle cell disease, proportion with and time to engraftment, mortality, adverse effects of treatment and health-related quality of life*.

Section B.1 of the Company Submission Document B discusses the company's view of the decision problem and CS Document B Table 1 summarises this view and how it may or may not differ from that in the NICE final scope. There are no subgroups specified in the NICE scope or in the company decision problem, and there are

special considerations. The EAG's critique the company's conception of the decision problem is outlined in sections 1.3.1 through to 1.3.5.

1.3.1 Population

In CS Document B Table 1 (*"The Decision Problem"*) the NICE scope defines the population as individuals with SCD, where there is no HLA-matched related donor. The company is more specific and states the population as SCD patients of 12 years of age or older for whom no HLA-matched related donor is available, and further states that this population aligns with the proposed Medications and Healthcare products Regulatory Agency (MHRA) marketing authorisation.

At the time of writing Marketing authorisation has yet to be granted and it is not known if the proposed MHRA authorisation will be adopted. Irrespective of the defined population, alignment with marketing authorisation is not yet established.The CS population itemised in Table 1 differs from that analysed in the Full Analysis Set (FAS) that was aged 12 to 35 years with genotypes specified as: **β^S/β^S, β^S/β^0 or β^S/β^+**. The company categorises the population addressed as having "*severe SCD*" defined on the basis that these patients experience recurrent vaso-occlusive crises. In the FAS evidence base the population was described as follows: *"Severe SCD was defined by the occurrence of at least 2 VOCs (any of: acute pain crisis, acute chest syndrome, priapism, splenic sequestration) per year in the two years prior to enrolment."* Given that VOC definitions vary, as do concepts of SCD severity, multiple selections of patients might satisfy such criteria. Results emanating from several data sets are presented in the submission. The company consider the FAS encompassing 43 individuals is adequate for decision making. The EAG notes the small sample size and short follow-up of FAS but recognise the lack of a superior available alternative from the company's trial evidence.

In line with the NICE scope a key inclusion criterion for CLIMB SCD-121 was the lack of *"an available 10/10 human leukocyte antigen (HLA)-matched related donor"* for allo-SCT. The evidence submitted does not detail the process by which it is established that patients in the FAS lacked such a donor. CS states *"In the UK only 24 SCD patients, the majority likely paediatric, have received allo-SCT"* implying indeed that very few UK adult severe SCD patients would have a matched donor.

The company suggest (CS Document B pg. 53 Figure 10 *"Epidemiological cascade for SCD in the UK")* that 1750 ([redacted]%) of 2,150 UK severe SCD patients fit for exa-cel treatment would lack a matched HLA donor, which is based on published data from Gragert et al.[30] In view of the low number of UK allo-SCT interventions performed and the NHS perspective of the analyses, in EAG opinion 18.6% is likely a considerable overestimate. In considering market uptake (CS Table 56) estimates that after five years the accumulated number of UK patients that will have received exa-cel treatment will be [redacted]. This seems a very small number relative to the 1,750 itemised in the epidemiological cascade burden-of-illness (BoI) study in CS Figure 10, and in the context of the company's equity concerns and DCEA approach appears disappointingly low.

1.3.2 Intervention

CS Section B.1.2 of defines exa-cel as follows: "Exagamglogene autotemcel (exa-cel), ..., is a cellular product consisting of autologous CD34+ human haematopoietic stem and progenitor cells (hHSPCs) modified by ..., ex-vivo CRISPR/Cas9-mediated gene editing...". So, the intervention is a cell preparation that is infused into patients.

The EAG notes that infusion of the *"ex-vivo modified CD34+ cells"* requires additional interventions of recipients and of candidates who may subsequently fail to become recipients; these interventions include stimulation and collection of autologous stem cells, bone marrow ablation and subsequent patient maintenance during the time between ablation and infusion and immediately post infusion during attainment of *"engraftment"* of exa-cel. The EAG considers that the whole *"treatment pathway"* as depicted in CS Figure 3 represents a superior description of the intervention to that provided in CS (i.e., a cell preparation) and conclude that the CS appears to consider that "treatment" and "intervention" are different entities. According to the Dictionary for Clinical Trials[31] intervention is defined as follows: *"The action that is taken when one intervenes. In clinical trials the most common type of intervention is to give treatment"* The CS definitions of treatment and intervention are somewhat confusing and what constitutes the start of "treatment" is difficult to determine. Figure 2 depicts the exa-cel treatment process schematic. The intervention is used at the end of stage 3.

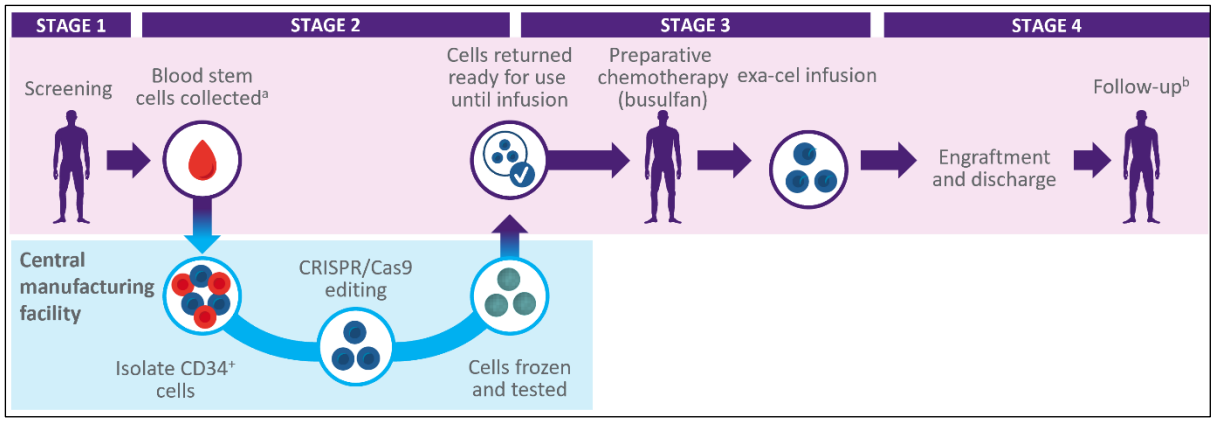


Figure 2: Exa-cel treatment process schematic (obtained from CS Document B, Figure 3)

1.3.3 Comparators

The wording of comparators in the NICE scope differs somewhat from that addressed in the company submission. In Table 1 of CS Document B, the company lists two comparators: best supportive care (SoC) and hydroxycarbamide. The EAG notes that the CLIMB SCD-121 evidence base lacks a randomised comparator. An attempt to remedy this deficiency is presented in the form of an unanchored matching adjusted indirect comparison (MAIC) comparing exa-cel versus SoC. The only outcome considered in the MAIC was based on VOC (either measured as patients free of VOC for 12 months, or as the annualised rate of VOC).

1.3.4 Outcomes

The outcome measures identified in the NICE scope[32] and listed by the company in CS Document B Table 1 are identical and constitute the following: changes in haematological parameters (haemoglobin levels); proportion of patients who have not experienced any severe sickle cell crisis for at least twelve consecutive months; complications arising from SCD; proportion with and time to engraftment; mortality; adverse effects of treatment; health-related quality of life.

The EAG notes in CS Table 1 that mortality and adverse events are listed as separate outcomes while in CS clinical effectiveness / safety sections they are not individually reported but instead mortality, death(s) after treatment, is subsumed within the adverse events outcome now entitled *"Adverse reactions"* (CS Document

B Section B2.10). This seems somewhat contrary to usual practice where all-cause mortality is usually a separate and important outcome; this would seem doubly so in the case of a novel intervention such as exa-cel.

CS Section B2.4.3.4 *"Safety analysis"* lists *"Mortality, including all-cause mortality and transplant-related mortality"* as *"endpoints"*. Results for these outcomes seem absent from the submission, except those for transplant-related mortality.

The Summary of safety (CS Doc B section B.2.10.2) mentions that *"One patient had a fatal AE, however it was not related to exa-cel. The patient died at Day 130 following Exa-cel infusion due to respiratory failure after COVID-19 infection, [redacted]".* Another patient experienced a serious adverse event: [redacted]. Indication that the treatment pathway (as depicted in CS Figure 3) might predispose severe SCD patients to virus infection(s) or other life-threatening events that might impact on mortality appears not to have been adequately considered or discussed in the CS; in the opinion of the EAG such predisposition cannot be discounted and, in view of the small sample size and short duration of CLIMB SCD-121 data sets, these two events observed do not seem particularly rare. Larger samples and longer follow-up are required.

In summary, the EAG found the CS handling of mortality outcome somewhat confusing and inadequate.

Section B3 (Cost Effectiveness) also deals with Mortality. Section B.3.3.4 describes the CS generation of survival curves as follows: *"Patients are at risk of death throughout the modelled lifetime horizon… risk of death is dependent on the patients' VOC status, frequency of VOCs and occurrence of complications and other transplant-related events."* In the opinion of the EAG these risks of death assertions are assumptions that are difficult to quantify since there is sparse evidence about survival of severe SCD patients who have undergone the treatment pathway depicted in CS Figure 3. Many *"complications"* were included in mortality modelling leading to a complex procedure to reach mortality estimates. The EAG notes that the CS did not present mortality curves, they were only retrievable from CS Appendix and from within the economic model.

A pre-requisite for inclusion in CLIMB SCD-121 was the occurrence of at least two VOC events per year during the two-year period before screening whilst receiving appropriate supportive care. The EAG notes that the primary/key efficacy outcome or endpoint in CLIMB SCD-121 was the proportion of patients that achieved VF12, defined as freedom from VOCs for twelve months after the last RBC transfusion support. It seems preferable that the post-treatment VOC period would be two years to align with the pre-treatment requirement.

In the context of varying definitions of VOC, the small number of patients in CLIMB SCD-121, and the short follow-up time applied for the key outcomes the EAG doubt that the clinical evidence is sufficiently robust for decision making.

1.3.5 Economic analysis

In CS Table 1, the NICE scope states: "*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 an NHS and Personal Social Services perspective."* Although discount rate is not mentioned in the NICE scope it is usual that a 3.5% annual discount is applied to both costs and benefits of treatments.

The CS states that in accordance with NICE methods guide 1.5% rather than 3.5% discounting may be used when treatment satisfies three preconditions:

1. Restores people to full or near-full health when they would otherwise die or have severely impaired lives
2. Is likely to restore them to full or near full health
3. Benefits are likely to be sustained over a very long period

Regarding 1), direct evidence comes from a small single-arm trial (CLIMB SCD-121) of limited use for robust estimates of survival and necessitating the development of company's "Markov" modelling of mortality using data from many sources. The resulting model suggests undiscounted life-years gained by exa-cel, SoC, and matched general population patients were 49.9 years, 23.15 years, and 60.7 years,

respectively. According to this analysis patients without exa-cel treatment have a life span reduced by approximately 36 years, while restoration to near-full health is approached with a short fall from full health life span of about eleven years. These values do not provide consideration of the likely substantial uncertainties associated with estimation and should be viewed with caution.

Regarding 2), the comments regarding 1) also apply to condition 2)

Regarding 3), CS Document B pg. 153 states *"Long-term efficacy following exa-cel is also the most plausible outcome based on the published literature on SCD patients treated with allo-SCT".* The conclusion of an advisory board convened by Vertex[7] was stated in CS (Table 1 pg. 20) as *"the consensus opinion 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 (12))"*. The EAG notes that the key outcome in CLIMB SCD-121 was VOC freedom for only 12 months rather than 24 months. Because of the relatively short duration of follow-up and the single-arm nature of the CLIMB SCD-121 study in the EAG's opinion it is not possible to establish with certainty that benefits are likely to be sustained for a very long period. The CS asserts that benefit will be sustained in the long term because there is no known mechanism by which the editing of the BCL 11a enhancer can be reversed, because in the single-arm trial VOC incidence greatly diminishes after exa-cel infusion relative to the pre-exa-cel period, and because SCD recipients of allo-SCT, who do not experience graft rejection or GVH disease, have prolonged survival. The CS fails to present detailed supporting evidence. Since CS Section 3.5 states *"The cost-effectiveness analysis was conducted from the UK NHS… perspective,"* survival of UK SCD allo-SCT recipients will provide the most relevant evidence about the claimed prolonged survival after allo-SCT. The CS does not supply this data however CS pg. 52 *states "The total number of patients with all haemoglobinopathies to undergo allo-SCT in the UK in 2021 was just 36, including 24 SCD patients, the majority of which are likely to have been paediatric (134)."* Since the relevant UK SCD population is aged 12 to 35 years and most of the few UK allo-SCT recipients were paediatric there appears to be an absence of relevant evidence to support the assertion of no waning of effect.

1.3.6 Special consideration including issues related to equity or equality

Relative to a standard cost-effectiveness analysis encountered in Single Technology Appraisals (STAs) and in most Highly Specialised Technology (HST) assessments, the SCD submission introduces two further adjustments additional to 1.5% discounting. In total three adjustments have been made, 1.5% rather than 3.5% discounting, use of a distributional cost-effectiveness analysis (DCEA) approach, and application of a severity modifier. These adjustments profoundly influence the base-case ICER.

In CS Document B Table 1 *"The decision problem"* the company explained that *"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."* Therefore, as part of this submission, the company conducted a DCEA as a framework for incorporating health inequality concerns into the economic evaluation of exa-cel.

In the following, the EAG critiques two adjustments: a) the use of a severity modifier, b) employment of a DCEA economic model.

1.3.7 Severity modifier

According to CS pg.149 the company's description of severity modifier and of the conditions required to justify 1.5% discounting are as follows, *"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."* The EAG's opinion is that this considerably overlaps the conditions that need to be fulfilled for use of 1.5% discounting, stated as: *"Restores people to full or near-full health when they would otherwise die or have severely impaired lives"* since patients who *"would otherwise die"* are those that receive SoC rather than exa-cel. This overlap will lead to double counting in the cost-effectiveness analysis that will bias in favour of exa-cel.

Although based on QALY shortfall (CS pg.149) the calculation of a severity modifier requires a model of survival for the SCD population receiving SoC together with that for a matched UK general population to which utility values are then applied. The EAG notes firstly that the matching applied to the general population only encompassed age and gender and may have missed other attributes that would

influence survival and secondly that multiple inputs were required to deliver the "Markov" SoC survival model, each of these associated with uncertainty. In the opinion of the EAG, comparison between SoC and general population models required for estimation of the severity modifier will be associated with a very high degree of uncertainty that does not appear to be fully considered in the CS.

The EAG found the "Markov" SoC model difficult to validate as described in Section 3.2.9, the EAG found that the SMR (SoC versus general population) falls outside the range that the CS judged to be reasonable.

In the opinion of the EAG the calculation of the severity modifier is likely associated with extensive uncertainty that is difficult to quantify and may be underestimated in the base-case cost-effectiveness analysis, and the application of this modifier in addition to implementation of 1.5% discounting is likely to result in double counting and bias. The application of this modifier does not seem sufficiently robust for decision making.

1.3.8 Distributional cost-effectiveness analysis

The NICE HST programme only considers drugs for rare conditions (i.e., drugs for Orphan diseases). CS Doc B pg. 27 states that the prevalence of the relevant UK SCD population equates to less than 2 in 10,000 people, and therefore satisfies the MHRA's designation of an orphan condition (CS Document B REF (1)). More than 6,000 hereditary monogenetic orphan conditions such as SCD have been identified.

CS Section B.1.4 itemises "Equality considerations" deemed important by the company and points to a patient-perceived lack of understanding of the disease amongst medical professionals. The EAG agrees that this is likely but that the same could be said of most orphan conditions because of their great number, their individuality, and their rarity.

DCEA *"reweights cost-effectiveness results based on a decision-makers aversion to inequality"*. The re-weighting is calculated using cost and benefit estimates within each of the five quintiles of the Index of Multiple Deprivation (IMD) according to the proportion of the relevant UK SCD population within each deprivation quintile. The assertion that the *"DCEA shortfall value, therefore, does not represent a disease-specific modifier"* appears somewhat mystifying to the EAG since the disposition of patients between quintiles will depend on the orphan disease considered.

The CS states that overwhelming majority (91.6%) of UK SCD patients are of African or Caribbean ethnicity. The majority (72.4%) of UK SCD patients between 12-35 years of age and with recurrent VOCs (i.e., those resembling the patients in the single arm CLIMB SCD-121 trial) were found to be disposed in the two most deprived quintiles of the IMD. The disposition of these patients between quintiles is presented in Table 3 (data also presented in Figure 44 of Appendix L to CS Document B) compared to the corresponding distribution for the general population (based on Figure 45 from Appendix L to CS document B).

Table 3: Socio-economic status of SCD patients identified in Vertex's BoI study versus general population

Socio-economic status (IMD), N (%)*	SCD with recurrent VOCs (N=1,117)	General population
Q1 (least deprived)	38 (3.4%)	[redacted]
Q2	81 (7.25%)	
Q3	190 (17%)	
Q4	395 (35.4%)	
Q5 (Most deprived)	413 (37%)	
BoI, burden-of-illness; IMD, index of multiple deprivation; SCD, sickle cell disease; Q, quintile; VOC, vaso-occlusive crisis		

Key: BoI: burden of illness; 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**:** Table 6, Vertex BoI study.[33]

The two most deprived quintiles (IMD 4 and 5) only contain 35.9% of the general population compared with 72.4% for the UK SCD population. The CS states that IMD deprivation "*was a sufficient proxy for representing health inequalities across the treatment and general populations since CPRD-HES ethnicity data were inadequate for analysis in the SCD population"*. Thus, these dispositions are relevant to the application of a DCEA undertaken by the company to obtain a base-case ICER. CS Document B pg.195 implies that the aversion to inequality value of 11 used by the company was based on the recommendation of a single external expert (CS Document B pg.196: "*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"*), although informed by a systematic review[7] that provided values ranging from "*5.76 to 28.9*"). The company acknowledge that another analysis listed as an open-source discussion paper from the Tinbergen Institute also authored by Robson M., 2023[34] offers a different value of 3.5; the company doubt this a valid value on statistical grounds.

The EAG notes that the underlying aversion to inequality appears to be based on opinion of a single expert and that a proxy for health deprivation has been employed. The various aversion values considered in the CS appear to come from the same research group and are noticeably various.

In the context of HST assessments it is relevant to examine whether a DCEA approach has been used previously and if DCEA would have been justified. The literature testifies that inequity of health provision is common for rare orphan diseases; it seems that a DCEA approach might be equally justifiable for these. Since DCEA represents a new approach, its introduction only for this assessment might result in undesirable inequity relative to previous HST assessments.

2 CLINICAL EFFECTIVENESS

2.1 *Critique of the methods of review(s)*

The company conducted a systematic literature review (SLR) to identify clinical trial evidence to summarise the efficacy and safety of exa-cel in patients with severe SCD.

Eligible comparators (CS Appendix D, Table 70) were lovotibeglogene autotemcel, (lovo-cel), crizanlizumab, voxelotor, L-glutamine (not approved in EU), hydroxycarbamide, allogeneic stem cell transplantation, red blood cell transfusions and other types of transfusions (simple/exchange), iron chelation therapy, placebo, or best medical care. A detailed description of the methods and the findings of the SLR were reported in Appendix D of the CS. The SLR was conducted in May 2022, and was subsequently updated in July 2023. The SLR included randomised controlled trials (RCTs) and single-arm trials.

2.1.1 Searches

Literature searches were carried out and reported to inform the SLR in CS Document B, Section B.2.1 and CS Appendix Document D1.1. An appropriate range of databases, conference proceedings and HTA (Health Technology Assessment) databases were searched (CS Appendix D.1.1, Table 69). The EAG considers an appropriate range of natural language and database-specific thesaurus search terms were used to search for the disease and all relevant comparators, as identified by the Clinical SLR PICO Criteria (CS appendix D, Table 70) and decision problem (CS B 1.1) and were combined using relevant syntax. No age or date limits were applied, and date limits were applied to the clinical SLR update search, to restrict the searches from the date of the original clinical SLR search. The searches were restricted to studies published in English language, which has the potential to introduce a language bias. The search is limited to RCTs, which could miss systematic reviews and meta-analyses, which can be a source of primary studies. A search filter was applied to identify randomised controlled and single arm trials in accordance with the inclusion criteria (CS Appendix D.1 Table 70: Clinical SLR PICO Criteria).

It is noted that the interface used for the Embase search for the initial and the updated search were different due to changes in database subscription from Ovid SP to Elsevier (CS Appendix D1.1). The searches were translated sufficiently to be compatible with Elsevier from Ovid by incorporating the appropriate syntax (CS Appendix D.1, Search terms: Updated July 2023 clinical SLR (ran on 01/07/2023)). The EAG considers the impact of the change of database subscription for Embase to be minimal.

The company reported that searches of HTA databases including *'NICE, HAS, and G-BA were reviewed for published, ongoing, or suspended treatments of SCD. However, 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 search terms and numbers of results for these searches are not provided (CS Appendix D.1, Search strategy).

The process of searching for conference abstracts is not described clearly. The search terms and numbers of results from searching conference abstracts are provided for the updated search, whereas only the names of the conferences are reported for the original clinical SLR search (CS Appendix D, table 69). The EAG requested the search terms for the original SLR conference abstract search, which were provided in the company response. However, the EAG note that the search terms differ from the updated SLR conference abstracts search terms. The company does not report to have searched clinical registers in addition to the Cochrane Central Register of RCTs, search engines or drug manufacturers websites. The company reported that *'one poster and three oral presentations were retrieved from the CRISPR Therapeutics website which were not identified in the clinical SLR searches'*; however, this is not listed as a source and the search terms are not provided in the search methods. The clarification response states that *'a review of publications listed on ClinicalTrials.gov'* was carried out. One additional record was retrieved from this review'; The details of this search are not reported in the search methods; therefore, this aspect of the search is not transparent or reproducible.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow-diagram (CS Appendix D, Figure 36) for the original clinical SLR reflects the numbers retrieved from the database searches. However, the section *'Search strategies for hand-searching of relevant congresses'* reports seven results from

searches carried out for three conferences and the PRISMA flow-diagram reports *'conference searches (n=14)'.* The PRISMA flow-chart of the original clinical SLR (CS Appendix D, Figure 36) states that bibliographies of 24 reviews were assessed for additional studies. The review titles and the methods used to identify them are not provided. The review titles were requested in the clarification questions and the company confirmed that four review articles were reviewed (Clarification Response Table 3) which is significantly less than was reported in the PRISMA flow diagram (CS Appendix, section D1, Figure 36).

The PRISMA flow-diagram for the update search (CS Appendix D, Figure 37) accurately reports the number of results identified in the database searched. However, the number of results that were assessed for inclusion from the conference searches is not clear. The search terms and numbers of results of congress proceedings searched are provided but it is also not clear which results from these searches were included in the review, as the overall reported search result figures for the update congress searches are 1189. The update search PRISMA flow diagram (CS Appendix D, Figure 37) also reports that n=3 *'records were identified by hand search'* but the source and search results are not reported.

2.1.2 Inclusion criteria

The inclusion and exclusion criteria for studies were pre-specified based on the PICOTS (Population, Interventions, Comparators, Outcomes, Timing and Study design) framework. No variations to the inclusion criteria are reported for the updated search. The methods of the reviews are described in detail in the CS, Appendix D and are critiqued in Sections 2.1. The EAG considers the inclusion criteria (CS Appendix D, Table 70) suitable for the SLR.

2.1.3 Study selection

Search and selection were undertaken in two phases: (a) title and abstract screening and (b) full text screening. In both phases, two investigators working independently screened all citations identified in the literature search, then independently reviewed the full texts. Any discrepancies were resolved by a third investigator.

The section 'Identifying search results' states that 3775 results were identified from database searching; however, this does not take into consideration the search

results from the update search which identified a further 296 results. It states that 61 studies were included and five were prioritised for the ITC assessment.

The company reports (CS Appendix D1.1) that the searches resulted in 100 results included in the SLR, and an additional 12 eligible conference abstracts. A total of 112 publications reporting 52 studies were included. Of these, five were prioritised for ITC. The PRISMA flowchart that the company submitted (Appendix D Figure 37) suggests that an additional 19 publications reporting 9 additional studies were identified in the updated SLR, bringing the total included studies to 61. Discussion of the included studies (Appendix D page 63) refers to the 52 included studies rather than the 61.

The summary of reference checking of included studies is only reported in the PRISMA flowchart (Appendix D, Figure 36) (Review of bibliographies from review articles (n=24)). It is not reported which reviews are checked but the details were provided in the company clarification response.

The company present evidence for the intervention of interest. The original SLR identified three publications that reported on CLIMB SCD-121.[35-37] The updated SLR identified one further publication which reported the efficacy and safety data from the first 31 SCD patients dosed with exa-cel in the CLIMB SCD-121 trial.[38] One poster and three oral presentations were retrieved from the CRISPR Therapeutics website which were not identified in the clinical SLR searches (CS Appendix D, Figures 36 and 37).

The company described the five studies that were prioritised for ITC.[39-43] Additionally, eight studies are used to describe the clinical efficacy of CLIMB SCD-121.[35, 37, 38, 44-47] The company has identified and selected the clinical evidence relevant to the technology being evaluated, but there is no discussion of the other included studies in the review.

2.1.4 Critique of data extraction

The company stated that two investigators independently completed data extraction of included studies, but the data extraction table was not provided, and only minimal information was provided on what data were extracted to summarise the evidence for the SLR.

2.1.5 Assessment of methodological quality

The company performed quality assessment on the included study for the CLIMB SCD-121 study using the 'Downs and Black checklist'.[48]

EAG comment: In summary, the SLR is of good quality, however, there were errors in the numbers of included studies presented, using figures from the initial search and not the updated search, and there were areas where more information is needed (process of searching bibliographies, hand searching strategies and what information was extracted from included studies).

2.2 *Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)*

The clinical evidence presented in the CS for the efficacy and safety of exa-cel was obtained from two sources, the CLIMB SCD-121 study and CLIMB-131 study. CLIMB SCD-121 is an ongoing Phase 1/2/3 single-arm, open-label, multi-site, single-dose study. CLIMB-131 is a multi-site, open-label, Phase 3 rollover study. A detailed summary of CLIMB SCD-121 was presented in the CS Document B section B.2.2 Table 11. The EAG critiques the CLIMB SCD-121 study in section 2.2.1.

2.2.1 CLIMB SCD-121

CLIMB SCD-121 (also known as CTX001-121; NCT03745287) 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 severe SCD. The EAG notes that there is no direct comparator or control arm in the study. CLIMB SCD-121 and the description of the study in the CS reflects the methodology detailed in the protocol provided by the company.

The company report that the minimum cell dose for CLIMB SCD-121 is 3.0 x 10^6 CD34+ cells/kg and the maximum cell dose is 20 x 10^6 CD34+. The target CD34+ cell collection is ≥15 x 10^6 CD34+ cells/kg to allow for exa-cel manufacture. The company reported that an additional 2 x 10^6 CD34+ cells/kg will be collected from patients as backup for rescue therapy.

The company defined severe SCD as the occurrence of at least two of the following events each year during the 2-year period prior to screening, whilst receiving appropriate supportive care (i.e., pain management plan or hydroxycarbamide if indicated),[7] acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or IV non-steroidal anti-inflammatory drugs (NSAIDs) or RBC transfusions), ACS, priapism lasting more than 2 hours and requiring a visit to a medical facility or Splenic sequestration.

The company reported that at the D120 database lock point (April 2023), 63 patients were enrolled and 58 of these started the conditioning regimen. Of these, 43 received exa-cel infusion and were the full analysis set (FAS), and 29 were eligible for inclusion in the primary efficacy set (PES). The primary efficacy endpoint of the proportion of patients achieving an absence of any severe vaso-occlusive crisis (VOC) for at least 12 months after exa-cel infusion (VF12) and key secondary endpoint of proportion of patients free from inpatient hospitalisation for severe VOCs (HF12) were measured with the PES, and all other efficacy endpoints were measured with the FAS. The company clarified that 5 patients discontinued before mobilisation, and 11 patients discontinued after mobilisation. The EAG notes that partly due to discontinuation, the sample size is relatively small, and therefore presents some uncertainty in drawing conclusions about the efficacy of exa-cel.

CLIMB SCD-121 is being conducted at 16 study centres across the US (9 sites), Canada (1 site), UK (1 site), France (1 site), Belgium (1 site), Germany (2 sites) and Italy (1 site). During clarification the company confirmed that [redacted] enrolled into the CLIMB SCD-121 at D120 were from the UK (with [redacted] from the UK included in the PES). Based on such a small sample from the UK the EAG is concerned that the evidence presented does not reflect the characteristics of the UK SCD patient population, or the SoC treatment received in England and Wales (both before and during the trial period).

The CS states: Patients will be followed-up within the CLIMB SCD-121 study for approximately two years after exa-cel infusion. All patients that complete or discontinue from CLIMB SCD-121 will be asked to participate in a multi-site, open-label, Phase 3 rollover study, CLIMB-131. CLIMB-131 is described in CS Section B.2.3 and is designed to evaluate the long-term efficacy and safety of exa-cel in

patients who received exa-cel for a total follow-up of 15 years after infusion. Currently, the efficacy and safety findings are based on follow-up between 1.3 to a maximum of 43.6 months. The company reported in the CS that exa-cel is likely to restore patients with severe SCD to full or near-full health, but because of diminishing patient numbers beyond about one year of follow-up, so it is difficult to assess the true efficacy of exa-cel.[49]

As there was no control group in the CLIMB SCD-121 study, the company prioritised five studies from the SLR for inclusion in the ITC. Discussion and critique of the ITC can be found in Section 2.3.

Risk of bias of CLIMB SCD-121

The company submitted a complete quality appraisal of CLIMB SCD-121 in CS Appendix D section D1.3 Table 78 using the Downs and Black checklist.[48] The EAG independently assessed CLIMB SCD-121 using the Downs and Black checklist. Table 4 shows company and EAG quality assessment ratings for the CLIMB SCD-121 study using the Downs and Black checklist, with comments on any differences in rating.

The company has not provided an overall score of study quality. The EAG have independently assessed the CLIMB SCD-121 study for quality and have rated it an overall score of 'fair.'[50] There was minimal deviation for the company quality assessment, which if an overall score was calculated in the same way would also be rated as 'fair.'

Table 4: Quality assessment for CLIMB SCD-121 using Downs and Black (differences between company and EAG ratings in bold).

Description of criteria	Company response	EAG response
Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes
Are the characteristics of the patients included in the study clearly described?	Yes	Yes
Are the interventions of interest clearly described?	Yes	Yes

Description of criteria	Company response	EAG response
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N/A	N/A
Are the main findings of the study clearly described?	Yes	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Yes
Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes
Have the characteristics of patients lost to follow-up been described?	Yes	Yes
Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability is less than 0.001?	Yes	Yes
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes	**UTD**- Cannot find information on study site or recruitment of patients at site- how they were identified or recruited so unable to determine if those recruited were representative of the source population.
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	UTD	UTD
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	UTD	UTD
Was an attempt made to blind study subjects to the intervention they have received?	No	No
Was an attempt made to blind those measuring the main outcomes of the intervention?	No	No
If any of the results of the study were based on "data dredging", was this made clear?	UTD	UTD
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and	Yes	Yes

Description of criteria	Company response	EAG response
controls?		
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes
Was compliance with the intervention/s reliable?	Yes	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A	N/A
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?	N/A	N/A
Were study subjects randomised to intervention groups?	N/A	N/A
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A	**No** Guidance states all non-randomised studies rated as no.
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	No	No
Were losses of patients to follow-up taken into account?	Yes	Yes
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance?	Yes	Yes
EAG, evidence assessment group; UTD, unable to determine		

Outcomes of CLIMB SCD-121

The primary aim of the CLIMB SCD-121 study was to examine the efficacy and safety of exa-cel for patients with severe SCD. The primary efficacy endpoint was the proportion of patients achieving an absence of any severe VOC for at least 12 months after the last transfusion support (VF12).

Secondary outcomes of CLIMB SCD-121 include the proportion of patients free from inpatient hospitalisation for severe VOCs (HF12) sustained for at least 12 months after the last transfusion support, severe VOC free duration for patients who

achieved VF12, relative reduction in annualised rate of severe VOCs in patients who did not achieve VF12, proportion of patients with sustained foetal haemoglobin (HbF), total Hb and HbF concentration, change in proportion of F-cells, proportion of alleles with intended genetic modification, change from baseline in reticulocyte count, indirect bilirubin, haptoglobin and lactose dehydrogenase, relative reduction in number of RBC units transfused for SCD-related indications and patient reported outcomes.

Safety was evaluated using adverse events, the presence of successful engraftment, time to engraftment, incidence of transplant-related mortality and all-cause mortality.'

The outcomes listed by the company are largely in line with the final NICE scope and are appropriate, however mortality is listed as a separate outcome on the scope and the company decision problem but reported only as part of the adverse events section (CS Document B section B.2.10).

The EAG notes again that as a single-arm study, there are no randomised comparators or control groups in the CLIMB SCD-121 trial, all patients in the FAS received exa-cel infusion and therefore only the outcomes under the intervention treatment can be observed. Without a control group the EAG were unable to determine the true impact of exa-cel.

EAG comment: As the study is still ongoing there is a lack of long-term follow-up data available. The EAG have concerns around the small sample size (Primary and key secondary endpoints are based on 29 patients), lack of a control arm, and the small UK sample size ([redacted] were from the UK were enrolled at D120, but [redacted] from the UK were included in the PES analysis. These concerns lead to uncertainty in determining the efficacy of exa-cel, based on the data presented.

2.2.2 Critique of efficacy results for CLIMB SCD-121

In the CS Document B section B.2.6.1 and B.2.6.2, the company presented the clinical effectiveness results of exa-cel from the CLIMB SCD-121 study.

2.2.2.1 VF12 and HF12

Following infusion with exa-cel, the CS reports that at the D120 data cut, 28 of 29 (96.6%) patients in the PES achieved VF12 (95% CI: 82.2%, 99.9%; p<0.0001 versus an assumption of 50%), and 29 of 29 (100%) patients in the PES achieved HF12 (95% CI: 88.1%, 100.0%; p<0.0001).

The company designates VF12 the primary efficacy endpoint and HF12 a key secondary efficacy endpoint; both were estimated using the primary efficacy dataset (PES) encompassing 29 individuals. VF12 and HF12 definitions presented in footnotes to CS Tables 12 and 16 were worded: *"…defined as free from* (severe VOC or inpatient hospitalisation) *sustained for at least 12 months after exa-cel infusion"*. However, CS pg .81 explains that *"The duration of HF12 starts 60 days after last RBC transfusion for post-transplant support or SCD management".* Because the 12-month freedom from VOC and from inpatient hospitalisation does not start from the time of exa-cel infusion as inferred in the footnote definitions the EAG find these misleading and unhelpful. Figure 3 summarises the EAG's understanding of these efficacy end points.

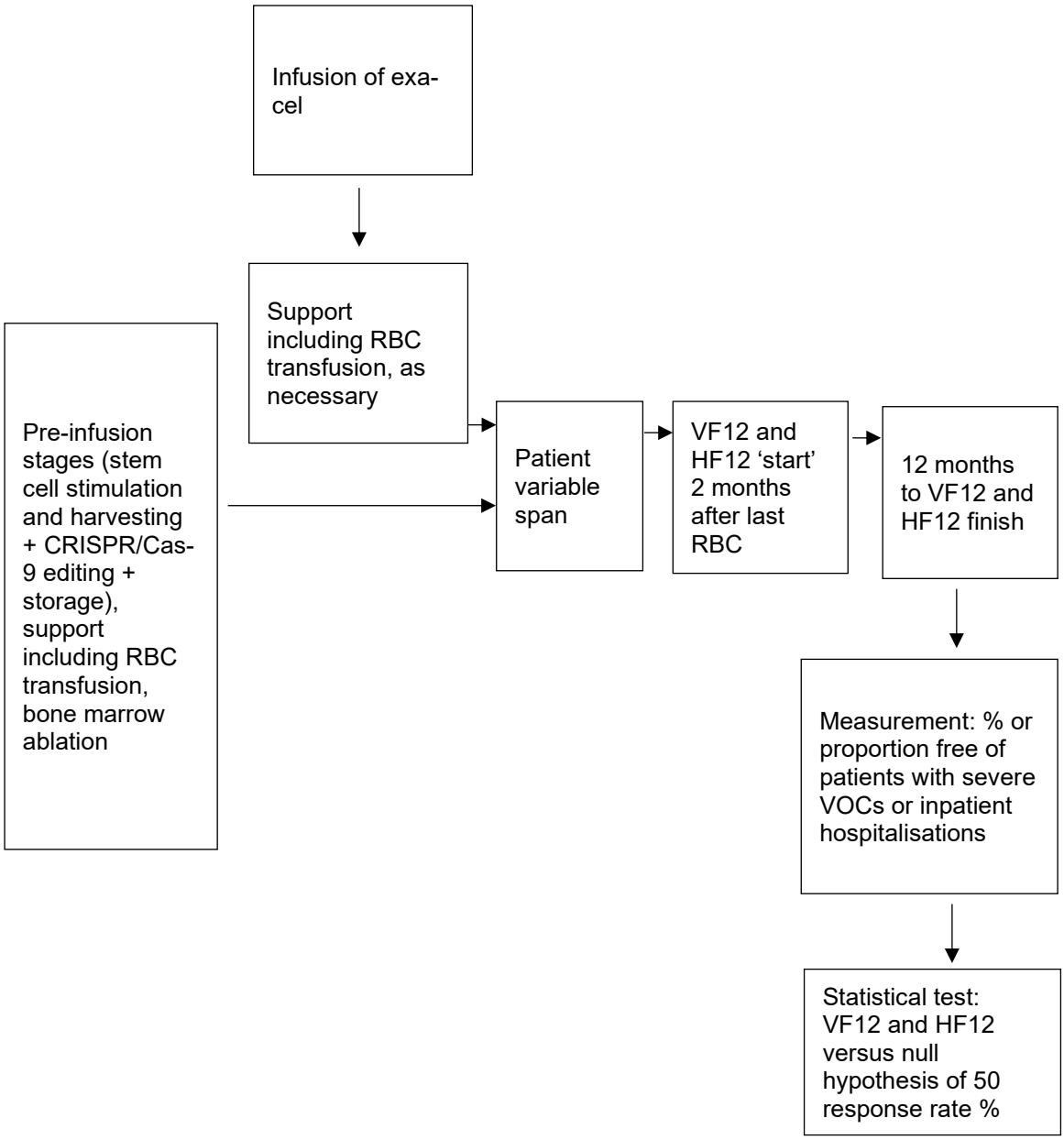


Figure 3: Summary of the EAG understanding of VF12 and HF12 efficacy endpoints

The EAG note that both VF12 and HF12 endpoints essentially depend on the same measure, namely severe VOCs (defined by the company in CS Document B section B.1.1 as comprising any of the following: acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] nonsteroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions, acute chest syndrome, Priapism lasting > 2 hours and requiring a visit to a medical facility or Splenic sequestration), and may not be independent entities; There were [redacted] UK patients included in PES. The EAG note that most of these events in the PES will

occur in other European countries as well as the US where practice for VOC identification and inpatient hospitalisation may not accurately reflect that in the UK.

VF12

Twenty-eight of twenty-nine PES patients achieved VF12 resulting in high statistical significance versus the null hypothesis that takes the value of 50%. The EAG note that the proportion of patients receiving standard care that achieve VF12 is not reported.

Of 43 FAS patients 13 had insufficient follow up to achieve VF12, two of these 13 experienced a VOC and if followed for 12 months would classify as a VF12 failures. Of the remaining 29 PES patients: one failed VF12, one died before 12 months, 28 achieved VF12 one of whom experienced a VOC during post 12-month follow-up. The EAG concludes that VF12 success reported for the PES is a relatively poor indicator of VOC avoidance. EAG note that VF12 appears to be irrelevant to the company's economic model in which annualised VOC rates are used not VF12.

Two patients in the FAS experienced severe virus infection. The EAG considers that the full treatment pathway (as depicted in CS Figure 3) might lead to increased susceptibility to virus infection.

HF12

All PES patients are reported to have achieved HF12. Of 43 FAS patients 13 live patients had insufficient follow to achieve HF12 and one patient died before 12 months follow up was completed. Of the remaining 29 FAS patients all achieved HF12, but one of these experienced inpatient hospitalisation post 12-months.

As far as the EAG can ascertain HF12 values are not relevant to the economic model.

2.2.2.2 Duration of severe VOC and of hospitalisation freedom

VOC freedom

The results for the FAS are presented in CS Figure 15. A total of [redacted] VOC events were recorded amongst [redacted] patients; one patient died without a recorded VOC event. A time to event plot was not presented. No comparative data was available

because CLIMB SCD-121 was a single arm study. In the CS the EAG failed to find a report of an annualised rate that was based on the complete PES or FAS populations.
In the EAG's opinion the small number of patients and limited follow-up preclude meaningful inference.

The company's economic model estimated a [redacted] annualised rate of VOCs (CS Appendix J Table 94) for the SoC arm (93.9 total VOCs over lifetime of 22.37 years). A US study reported a 1.52 mean annual rate of severe VOCs resulting in hospitalisation (these approximate to severe VOCs because of the requirement for ED or inpatient hospitalisation).[51] The median annual rate of SCPC (pain crises, VOC-related outcome) for the SoC arm in the SUSTAIN (crizanlizumab) RCT was 2.98.[40] That in the HOPE (voxelotor) RCT was 3.19. In the Appendix to Document B (pg.141) the life-time total VOC events output from the economic model in the SoC arm as 93.9; given a mean SoC survival output from the economic model of 22.36 years this provides an annualised rate of approximately [redacted].[52] From the perspective of these other data the model output for the SoC may be inflated.

Freedom from inpatient hospitalisation for severe VOCs
No comparative data was available because CLIMB SCD-121 was a single arm study. In the EAG's opinion the small number of patients and limited follow-up preclude meaningful inference about duration of freedom from hospitalisation.

2.2.2.3 Total Hb and HbF concentration over time

In the FAS, mean (SD) total Hb concentration increased from [redacted] ([redacted]) g/dL at baseline to [redacted] ([redacted]) g/dL at month 36 when [redacted] patients only were available for analysis. Total Hb level after exa-cel infusion was [redacted] ([redacted]) g/dL at Month 3 ([redacted] patients analysed) and remained between [redacted] g/dL and [redacted] g/dL up to Month 24 ([redacted] patients analysed), at 30 months [redacted] patients were analysed. Interpretation of results beyond Month 24 is severely limited by small sample size.

CS Figures 18 shows HbF data for [redacted] individual FAS patients at various months of follow up but presents the data as a percentage of total Hb, which is minimally

informative in the absence of Hb in the same graph. CS Figure 19 presents percentages of Hb types (HbF, HbA, HbS, HbA2 and “other”) at various monthly intervals for [redacted] FAS patients.

CS Figure 20 (see Figure 4) presents the mean g/dL of HbF and of total Hb at various months for [redacted] FAS patients extending to a maximum of [redacted] months together with numbers of patients “*available for analysis*” at the designated time points.

Figure 4: Summary of total Hb (g/dL) and HbF (g/dL) over time in D120 (CLIMB SCD-121 and CLIMB-131, FAS) (CS Document B Figure 20 pg. 95)

The EAG were uncertain of the position of “baseline” in the patients’ treatment pathway (depicted in CS Figure 3), and whether “patients available for analysis” represents numbers remaining at risk.

By month four HbF peaks at a mean of about [redacted]. Thereafter to month thirty (when [redacted] patients were available) mean HbF is above [redacted] Months 33 and 36 (two patients available) have a mean HbF approximately 10% lower than the peak at month 4. The remaining patient at month [redacted] has a mean near that of the peak value

The EAG consider these results insufficiently robust to inform about long term maintenance of HbF at around [redacted] to [redacted] g/dL. In the opinion of the EAG longer follow up of a larger number of patients is required. More robust evidence is needed to support the CS statement (CS pg.17) that the "*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).*"

2.2.2.4 Proportion of patients with sustained HbF ≥20%

In the PES, [redacted] ([redacted]%) patients had sustained HbF ≥20% for at least 12 consecutive months.

Proportion of patients with sustained foetal haemoglobin (HbF) was a secondary endpoint, measured using the FAS sample (n=[redacted]) of the CLIMB SCD-121 study.

The first description of this is in CS Table 12 and is defined as *'Proportion of patients with sustained fetal haemoglobin (HbF).'* CS Document B Table 14 provides a more in-depth description of this stating *'Proportion of patients with sustained HbF ≥20% for at least 3 months, 6 months or 12 months, starting 60 days after last RBC transfusion for post-transplant support or SCD management.'*

The company report that 'in the PES, [redacted] ([redacted]%) patients had sustained HbF ≥20% for at least 12 consecutive months.' No reports of 3 or 6 months are presented.

The decision problem (CS Document B Table 1) states that a HbF concentration of ≥30% will restore patients to near full health, yet CS section B 2.6.2.4. states that *'patients who co-inherit SCD and HPFH who have HbF levels >20% have few, if any, disease complications.'* It is unclear which figure is more appropriate yet given the short follow-up length it is difficult to conclude if patients receiving exa-cel are returned to near full health or have few or no disease complications. The EAG notes again that the lack of a control or comparator arm also makes it difficult to define the true effect of the treatment.

2.2.2.5 Proportion of alleles with intended genetic modification (CD34+ cells in bone marrow and in peripheral blood)

The mean (SD) proportion of CD34+ cells of the bone marrow with intended genetic modification was reported for patient visits at 6, 12, and 24 months. The mean value at 6 months was [redacted]% ([redacted]%) with [redacted] of [redacted] FAS patients monitored. The mean remained virtually the same at 12 and 24 months with [redacted] and [redacted] patients monitored respectively. No value was available at 36 months.

The mean (SD) proportion of alleles with the intended genetic modification in peripheral blood was [redacted]% ([redacted]) at month three in [redacted] monitored patients. At month six [redacted] patients were monitored with a mean of [redacted]%. Means remained high at one year ([redacted] patients) and two years ([redacted] monitored). At three years the [redacted] patients monitored had a lower mean of [redacted]%.

Proportion of alleles with intended genetic modification was designated a secondary endpoint of the CLIMB SCD-121 study.

Different time points of outcomes are confusing and hard to examine alongside other outcomes reported. The company asserts that durable engraftment (assessed by a high, stable proportion of alleles with the intended genetic modification being observed in both the CD34+ cells of the bone marrow and peripheral blood), indicates the permanent nature of the intended edit. The EAG question this assertion of permanence because of diminishing number of patients monitored beyond one year. Concerns again about the lack of control/comparator arm are noted by the EAG.

2.2.2.6 Changes in haemolysis biomarkers

The CS looked at change over time post-baseline in reticulocyte count, indirect bilirubin, lactate dehydrogenase (LDH), and haptoglobin for patients in the PES. These represent standard workup tests for haemolysis.

CS Figure 23 indicated a mean LDH at baseline of [redacted] U/L, above normal range of 103 to 223 U/L.[53] At 3 months post-baseline LDH was close to the upper limit of normality as also at month [redacted] after which number of patients monitored diminished considerably.

Post-baseline mean haptoglobin was close to the lower limit of normality (a more stringent hurdle than for LDH) at month [redacted] and month [redacted], after which mean values were above lower limit of normality, and after month [redacted] the number of patients monitored diminished considerably.

Reticulocytes expressed as number of units (1 unit = 10^9 reticulocytes/L) were reported at yearly intervals, with no intermediate time points, and without accompanying total RBC counts. At one-year post-baseline mean units reduced from [redacted] to [redacted]. At two years only [redacted] patients could be analysed.

Mean values for Indirect Bilirubin were reported at yearly intervals (with no intermediate times reported); baseline of [redacted] µmol/L (N=[redacted]) reduced to [redacted] and to [redacted] at 12 months and 24 months respectively; only [redacted] patients could be analysed at two years. Normal range has been reported as 0 to 34 µmol/L.[53]

In the EAG opinion an assertion that haemolysis markers were normalised and maintained normal through time is poorly supported by the evidence presented because only small numbers were followed for short duration. Because of large gaps between time points the reporting of reticulocytes and bilirubin results seems incomplete.

2.2.2.7 Reduction in transfusions

Following exa-cel infusion, [redacted] in the PES had received RBC transfusions for SCD-related indications at the D120 data cut. Prior to exa-cel infusion, patients in the PES had a mean (SD) of [redacted] ([redacted]) annualised units of RBCs for SCD-related indications per year at baseline, with [redacted] of [redacted] patients receiving RBC transfusions in the two years prior to screening.

2.2.2.8 F-cells over time

The mean (SD) percentage of F-cells was [redacted]% (SD:14.0%) at month [redacted] ([redacted] patients analysed) and was >[redacted]% at other follow-up times monitored. The number of patients analysed diminished steadily by month: at six months ([redacted] patients), month12 ([redacted] patients), month 18 ([redacted] patients), month 24 ([redacted] patients), and at month 36 ([redacted] patients).

2.2.2.9 Patient reported outcomes

EQ-5D-5L

The CS doc B states that: "EQ-5D-5L utility scores showed clinically meaningful improvements in overall health status from Month 6 onwards, with a mean (SD) change from baseline at Month 24 of [redacted] (SD: [redacted]) points for the UK index score. For patients ≥18 and ≤35 years of age, EQ VAS scores demonstrated substantial improvement at Month 6 which was sustained at Month 24, with mean (SD) change from baseline at Month 24 of [redacted] (SD: [redacted]) points".

In the "Vertex Data on file" document values were reported for subjects ≥18 and ≤35 years of age in the PES. The change (mean (SD)) at one year for the 23 patients in PES of this age group was [redacted] ([redacted]) for EQ VAS and [redacted] (SD:[redacted]) for UK Health Utility score. At month 18 the mean (SD) change for [redacted] monitored patients was [redacted] ([redacted]) for EQ VAS and [redacted] ([redacted]) for UK Health Utility score. At two year [redacted] patients were analysed, the change for EQ VAS was [redacted] ([redacted]) and change for the UK Health Utility score was [redacted] ([redacted]).[54]

The EAG note the diminishing number of patients analysed with increasing follow up.

Numeric Pain Rating Scale

The CS Document B states: Numeric Pain Rating scores (NRS) were consistently below baseline from Month 6 to Month 24 and showed a clinically meaningful improvement with a ≥1-point reduction from baseline by Month 24. The EAG note that [redacted] patients provide data at baseline and [redacted] patients at 24 months.

FACT-BMT

The company report improvement in the mean Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) (improvement from Month 6, with a mean (SD) change from baseline at Month 18 of [redacted] (SD: [redacted]) points), the Functional Assessment of Cancer Therapy-General (FACT-G) (with a mean (SD) change from baseline of [redacted] (SD: [redacted]) points at Month 24) and Bone Marrow Transplantation Subscale (BMTS) with a mean (SD) change from baseline of [redacted] (SD: [redacted]) points for BMTS at Month 24). The EAG note that the number of patients

providing data at time points was variable and diminished after year one: at baseline [redacted], at 6 months [redacted], at one year [redacted], at 18 months [redacted], at 2 years [redacted].

ASCQ-Me

Mean (SD) change from baseline in standardised ASCQ-Me scores at Month 24 showed an improvement for the domains of emotional impact ([redacted] ([SD: [redacted]] points), social impact ([redacted] [SD: [redacted]] points), stiffness ([redacted] [SD: [redacted]] points) and sleep impact ([redacted] [SD: [redacted]] points). The EAG notes that only [redacted] of the [redacted] patients provide data at 24 months.

In summary in the EAG's opinion the strength of evidence for improvement in patient reported outcomes is weakened by the reduced numbers of patients that were monitored at longer follow-up times. Additionally, due to the open label nature of the trial, patient reported outcomes are subject to performance bias.

2.2.3 Safety results of CLIMB SCD-121

Engraftment

Safety analyses were based on the safety analysis set (SAS), comprised of the [redacted] patients that started mobilisation. The company reported that all patients with at least 43 days of follow-up after exa-cel infusion achieved neutrophil (n=[redacted]) and platelet (n=[redacted]) engraftment. The median (range) time to neutrophil engraftment was 27.0 (15.0 to 40.0) days, and the median (range) time to platelet engraftment was 35.0 (23.0 to 126.0) days. The company report that no back-up cells were required for any participant of CLIMB SCD-121.

Adverse events

CS states Adverse reactions (Section B.2.10) refer to the SAS, defined as all patients that started mobilisation. The company states that discussion of AEs focuses on the period from exa-cel infusion to Month 24 (unless otherwise stated). This suggests pre-infusion adverse events are ignored "unless otherwise stated". The EAG found this model of presentation confusing.

From exa-cel infusion, [redacted] patients ([redacted]%) had at least one AE and [redacted] patients ([redacted]%) had at least one serious adverse event (SAE). [redacted] patients ([redacted]%) had AEs considered related or possibly related to exa-cel (i.e., related to exa-cel only or

exa-cel and busulfan). [redacted] patients had an SAE that was considered possibly related or related to exa-cel. Moreover, a total of [redacted] of [redacted] patients ([redacted]%) experienced Grade 3 or 4 AEs. One patient had a fatal AE; however, it was not related to exa-cel.

As previously mentioned, mortality is not reported as a distinct outcome (as represented in company's conception of the decision problem) but is reported as part of the adverse events section.

2.3 *Critique of the indirect comparison and/or multiple treatment comparison*

2.3.1 Critique of the method

In its final scope, NICE has listed hydroxycarbamide and best supportive care (which included blood transfusions) as relevant comparators to exa-cel. In the absence of head-to-head clinical trials against these strategies, the company had to consider the use of indirect treatment comparison (ITC) methods. For the listed comparators, the source of clinical effectiveness source was based on aggregate data whilst individual-patient data (IPD) were available for exa-cel trials. According to the Decision Support Unit Technical Support Document 18 (DSU TSD18),[55] two main options are available to undertake ITC, namely the use of Matching-Adjusted Indirect Comparison (MAIC) or Simulated Treatment Comparison (STC). As the main exa-cel trial was a single-arm study, there was no common comparator arm to allow anchored indirect comparison which means only unanchored MAIC or STC could be considered.

The company choose to use unanchored MAIC and not STC. While this method is in line with proposed options for ITC[55] in such situations (IPD for one comparator vs aggregate data for the others) and is increasingly used in technology appraisals over the last years, the company could have justified their preference for MAIC over STC. It is therefore unclear if the use of STC may have provided different results. However, unanchored MAIC and STC present common limitations due to the major assumption made that all possible effect modifiers and prognostic factors are accounted for.[55]

The EAG has examined whether other ITC approaches may have been considered in other appraisals relevant to exa-cel and has identified the evidence report

published by the ICER group.[56] However, the document was not informative as it reviewed the comparative clinical effectiveness between exa-cel and another gene therapy named lovo-cel but not that between exa-cel versus SoC.

2.3.2 Critique of the source of data used in the MAIC

To undertake the MAIC, the company had to match IPD from the main exa-cel trial (CLIMB SCD-121) with aggregate data relevant to the exa-cel comparators, as listed above. To this end, they undertook a SLR to identify primary studies to be considered in the ITC based on the following criteria: 1)- Patients with ages overlapping with CLIMB SCD-121 efficacy data; 2)- Report of a VOC-related outcome; 3)- Administered an FDA-approved dose; 4)- Include five or more treated patients.

The EAG considers criteria 2 and 3 to be unclear and/or questionable. Indeed, the criterion 2 can be seen as vague since VOC-related outcome can be either expressed a proportion of patients free of VOC, or a rate of VOC per year. Similarly, different definitions of VOC could be used across studies. With regards to criterion 3, it doesn't indicate as to whether it applies to active comparators not retained in the NICE final scope like voxelotor, crizanlizumab, or L-glutamine, or to hydroxycarbamide/SoC. Should this criterion be relevant to the latter, it is questionable since hydroxycarbamide has been used off-label for decades when it was only available under the HYDREA brand name.[57]

The company indicated that, of a total of 51 studies identified from the SLR, only five were deemed relevant based on the above-listed criteria.

In Table 74 of the CS Appendix D, the summary of studies not included for the ITC assessment was reported. The EAG has noted that for five studies, no reason for exclusion was provided by the company. Hence, the EAG has reviewed these five studies against eligibility criteria. It is unclear why the study by Charache et al.[58] was not included. Although the study population didn't include patients aged between 12 to 18 years old, it may have been considered for the ITC. The same comment applies for the study by Voskaridou et al.,[59] although due to vagueness of the criterion *"VOC-related outcome",* it is unclear if that study met the eligibility criteria.

Overall, due to the uncertainty around the eligibility criteria, the EAG considered that the SLR conducted by the company may not be reproducible.

Of the five studies selected from the search, only three were finally retained for the ITC, the HOPE trial (comparing voxelotor to SoC), the SUSTAIN trial (comparing crizanlizumab to SoC), and the NCT01179217 trial (comparing L-glutamine to SoC), which were presented with full detail in the ITC report, including the definition of VOC in each trial.[40-42, 52] Two were excluded due to insufficient information pertaining to either the population or the outcome of interest.

2.3.3 Critique of the MAIC methodology as presented by the company

The three studies retained from MAIC were all RCTs comparing active therapies to placebo in a double-blind manner, but the arms of interest to the ITC were only those pertaining to placebo, equivalent to SoC.

Consistent with the methodology described by Signorovitch et al., (2010),[60] each IPD from the exa-cel pivotal trial (CLIMB SCD-121) were weighted so that overall trial data matched with aggregated data from the previously mentioned trials, under the principle that CLIMB SCD-121 patients resembling the most to those from the average in the other trials were given higher weights while those resembling the least were given lower weights.

Prior to that, the company selected five baseline covariates as matching variables, based on their importance as effect modifiers and/or prognostic factors. These included (by ranking of importance): 1)- Genotype (β^S/β^S vs non- β^S/β^S genotype); 2)- Baseline annualized number of VOCs; 3)- Age; 4)- Gender; 5)- Race/ethnicity. The EAG considers the choice of the matching variables to be relevant.

Of the 43 patients who received exa-cel infusion, only the PES of data was usable for the purpose of the ITC. Although on page 78 of the CS, the PES is described as a population of 29 patients, the company has indicated within the ITC section that the PES was only based on 17 patients. The company didn't explain the discrepancy between the two sample sizes.

Due to the small sample size of the CLIMB SCD-121 PES, the company finally matched the corresponding dataset to aggregate data from each trial that included

SoC arms only based on a maximum of three variables chosen by ranking of importance. For each comparison (three in total, one per trial), the three variables based on which the matching was undertaken have been reported.

The EAG considers this approach reasonable, but it is unclear why not all the patients from the PES were accounted for. Possibly, this is related to the timing at which ITC analyses were undertaken. The conduct of ITC based on the PES comprising of 29 patients may have enabled a more accurate procedure of matching.

2.3.1 Critique of the outcomes evaluated through ITC

The company undertook an indirect treatment comparison (ITC) using an unanchored MAIC. The only outcome that was considered by the company was the incidence of VOC and this was one of the criteria for selection of studies in the SLR.

It is important to note that there were differences in terms of VOC definition across studies compared to that in the CLIMB SCD-121 trial. For example, this pertained to the inclusion or not of events such priapism, splenic sequestration, or hepatic sequestration.

Although these differences were described and acknowledged by the company, it further limits the interpretation of ITC results.

Other effectiveness endpoints, which were evaluated in the exa-cel trials, such as biomarkers, were not included, and the company did not explain this.

It is likely that other outcomes evaluated in the exa-cel trials have not been measured in other trials used in the MAIC.

The EAG also noted that safety endpoints were not included in the MAIC analyses, and again no rationale was provided by the company. However, this approach seems reasonable since the profile of AEs observed with exa-cel is very specific to the therapy itself, which includes the conditioning regimen prior gene therapy infusion (in particular AE related to the administration of busulfan). Comparing the rate of serious AEs/grade 3-4 AEs may have then been difficult. Similarly, comparing AEs between drugs can be challenging if the duration of exposure differs between drugs.

Ideally, drugs should have been compared based the rate of AEs leading to discontinuation but there is no possible discontinuation for exa-cel once the therapy is infused.

2.3.2 Critique of the results from the MAIC

From pages 120 to 122 of the CS Document B, the results of the MAIC have been summarised, while the full details of results have been presented in the ITC report.

We have indicated that the matching of patients from the CLIMB SCD-121 trial relied on the PES that only comprised of 17 patients at the time of the ITC. The implication is that from a sample size of 17 patients before matching, after matching the effective sample size (ESS) dropped to 12 in the exa-cel versus SoC comparison from the SUSTAIN trial, 13 on that relying on the NCT01179217 trial, and only 4 on the comparison based on the HOPE trial.[40-42, 52]

After matching, depending on the trial considered for the SoC arm, the proportions of patients who remained VOC-free for 12 months were between 92.7% and 100% in the exa-cel reweighted population while these proportions varied between 16.9% and 30.8% in SoC patients.

Although the company mentioned it as a study being retained for the ITC, no results were reported in the main submission for the comparison of between exa-cel and SoC based on the NCT01179217 trial.[41] The company stated that there was no data from that trial on the proportion of patients who remained VOC-free. In the full ITC report, a comparison between exa-cel and SoC based in NCT01179217 trial[41] was presented evaluating the mean rate of VOCs through week 48 and did suggest a dramatic reduction (nearly by 95%) in the exa-cel reweighted arm compared to SoC.

Other results from the MAIC were also presented in the full ITC report and did suggest a considerable benefit of exa-cel compared to SoC accounting for the annualized rate of VOCs (median of 2.98 vs 0.00 for SoC and exa-cel respectively for the comparison based on the SUSTAIN trial; mean of 2.8 vs 0.06 for SoC and exa-cel respectively for the comparison based on the HOPE trial).[42, 52]

2.4 *Conclusions of the clinical effectiveness section*

The CS description of the decision problem had confusing aspects. The summary Table of the decision problem sometimes did not match well with the separately presented descriptive text. The terms intervention and treatment appeared to be used interchangeably even though the intervention was defined as “cell preparation” to be infused into patients whereas the treatment pathway included many preparatory steps prior to infusion. The population was defined loosely in the CS summary Table but much more precisely in the accompanying text. There was some lack of precision in wording used to describe comparators and outcomes (for example mortality was listed as an independent outcome from safety, but consideration of mortality was relegated or subsumed within a heading called “adverse reactions”). Much of the CS summary Table of the decision problem was devoted to Special Considerations covering the use of 1.5% discounting, a DCEA approach and a severity modifier. The justifications for these adjustments seemed to involve some double counting plus output from the economic model resulting in some circularity in the CS justification thesis.

The company’s clinical effectiveness section includes clinical effectiveness from CLIMB SCD-121, SLR of clinical effectiveness undertaken by the company and ITC. Details of the CLIMB SCD-121 and its critique can be found in sections 2.2.1 and 2.2.2

- Briefly, CLIMB SCD-121 (also known as CTX001-121; NCT03745287) 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 severe SCD.
- The EAG’s assessment of the CLIMB SCD-121 study for quality is ‘fair’. There was minimal deviation for the company quality assessment, which if an overall score was calculated in the same way would also be rated as ‘fair.’
- There was no comparator data available. The evidence for VOC outcomes indicates good efficacy of exa-cel in the short term when post-exa-cel infusion results are compared with pre-treatment VOC rates. Pre-treatment levels of other outcomes were unavailable.

- Robust evidence for favourable clinical effectiveness in the longer term is lacking because the CLIMB SCD-121 trial encompassed insufficient numbers of patients and because the number of patients available for analysis diminishes rapidly after short-term follow-up.
- The EAG found that CS Document B tended to present inference from observed data rather than the data itself, and that further details (e.g., number of patients providing data) had to be resourced from other documents such as the Vertex data on file, Appendices to Document B, or required comparison with information within the economic model.
- As far as the EAG could ascertain no clinical evidence from the CLIMB SCD-121 study is used for the company's cost-effectiveness model.
- In the opinion of the EAG there is a lack of robust evidence to support the notion that exa-cel delivers an extended disease-free state for SCD.

As the study is still ongoing there is a lack of long-term follow-up data available. The EAG have concerns around the small sample size (Primary and key secondary endpoints are based on 29 patients), lack of a control arm, and the small UK sample size ([redacted] patients were from the UK were enrolled at D120, but [redacted] patients from the UK were included in the PES analysis. These concerns lead to uncertainty in determining the efficacy of exa-cel, based on the data presented.

The EAG considered the systematic literature review of the clinical effectiveness literature to be of good quality.

- The EAG did not identify any major concerns about the conduct of the systematic review, which might have impacted on the results.
- However, there were errors in the numbers of included studies presented, using figures from the initial search and not the updated search, and there were areas where more information could have been provided (process of searching bibliographies, hand searching strategies and the information extracted from included studies).

In the absence of a head-to-head comparison of exa-cel to SoC, the company considered ITC methods.

- In both the CS and the full ITC report, the company highlighted the main limitations of indirect comparisons between exa-cel and SoC. These pertained to the very limited sample size of the CLIMB SCD-121 PES that was used in the ITC (n= 17), which reduced the number of variables (maximum of 3 per ITC) to match exa-cel IPD with aggregate data from the selected trials. Furthermore, after matching, the ESS of exa-cel reweighted population was extremely small.
- Although the EAG acknowledges that ITCs suggest a benefit of exa-cel relative to SoC, either in terms of proportion of patients free of VOC at 12 months or annualised rate of VOC, the EAG disagrees with the statement made by the company that *"Exa-Cel demonstrated superior efficacy relative to all comparators"*. Indeed, owing to the usual limitations of unanchored MAIC together with the major ones associated with ITCs reported here, the EAG considers that the level of evidence supporting the superiority of exa-cel relative to SoC is low.

The EAG concludes that there is evidence that exa-cel infusion is effective in the short term for the relatively small number of patients trialled but that persuasive evidence that exa-cel represents a life-time cure for UK SCD patients is lacking, for this more patients (particularly from the UK) and longer follow-up are required.

3 COST-EFFECTIVENESS

This section focuses on the economic analysis submitted by Vertex Pharmaceuticals, and additional information received from the company in response to the EAG's clarification questions. The EAG critically appraised the evidence submitted as well as examined the company's electronic model. This section starts with a critique of the company's review of the cost-effectiveness literature, then compares the company's economic analysis to the NICE reference case.

Given the limitations of the economic model, which are outlined in Sections 3.2 through to 3.2.11, the EAG has not undertaken scenario analyses.

The submission received by the EAG includes:

- A systematic review of the economic evidence for the management of people living with sickle cell disease.
- Methods used to undertake the economic analysis, and the company's base-case, sensitivity analysis, probabilistic sensitivity analysis and scenario analyses.
- Electronic version of a model built in Microsoft Excel.
- Budget impact analysis (not included in the EAG's critique)

3.1 *EAG comment on company's review of cost-effectiveness evidence*

The company undertook a systematic review of the economic literature to identify published cost-effectiveness studies of potentially curative stem-cell therapies for the treatment of sickle cell disease, with the purpose of developing an economic model.

3.1.1 Searches

The CS and Appendix G reports that database searches of MEDLINE, Embase, the Cochrane library, conference proceedings and previous HTA submissions were carried out to inform a systematic literature review (SLR) of all relevant treatments of published cost, cost-effectiveness, healthcare resource utilisation (HCRU), economic evaluations, and cost burden evidence related to *'potentially curative stem-cell therapies (i.e., exa-cel) for the treatment of sickle cell disease (SCD)'* (CS Document B.3.1 Published cost-effectiveness studies). The date that the searches were

undertaken was not reported; however, the EAG assumes that this was 10 July 2023, as it is reported that the searches were conducted *'from the inception of the databases to 10 July 2023'* (CS Appendix, Appendix G: Published cost-effectiveness studies).

A comprehensive range of databases were searched (Medline, Embase, Cochrane Library, HTA databases and conference abstracts). The EAG has some concerns with the Medline and Cochrane library search that was run concurrently (CS Appendix G). The search strategy section reports that the Medline and Cochrane library searches were undertaken via the Ovid platform and Embase was searched on Embase via Elsevier. The EAG identified that the syntax utilised for the Medline and Cochrane Library search is incompatible with the Ovid platform, resulting in an un-reproducible search. In clarification, the EAG raised concerns about which database platform was used to search Medline and the Cochrane Library. The company confirmed that the issue *'relates to the erroneous use of a colon ':ab,ti' where '.ab,ti' should have been used.'* The company provided an amended search strategy, with the full-stop and semi-colon syntax amended and noted *'that the difference in hits was minimal'* as the search only yielded one additional result. However, the EAG uphold that the issues with this search remain, as the amended search appears to be retrieving significantly lower results than the other searches run by the company for the clinical SLR on Medline and the Cochrane Library, and the translated searches for Embase via Elsevier and the EAG was not able to re-run this search as reported due to the remaining syntax error, which appear to be due to the erroneous use of brackets being used outside of full stops. The ERG tested this search by searching for the first indexing term from search line 1 on Medline via Ovid: 'exp hemoglobin S/' limited to the date limit dt=19460101-20230710, which retrieved 3384 results for the EAG, compared to 2775 from the updated search (CS Data in File SCD_ Economic HRQOL Searches), a difference of 609 results. The EAG notes that the overall number of results for this search seems very low (n=328) compared to the translated Embase search (n=6800) and the clinical SLR search for Medline and the Cochrane Library (n=1192), which incorporated the same terms for the population section of the search. Two spelling errors were identified in line 3 of the Medline and Cochrane Library and Embase searches: *'drag'* instead of *'drug'* and *'utiliation'* which was used twice in the same search line. Line 3 of the Medline and

Cochrane Library search also includes two invalid indexing terms: "markov decision process"/ and “Markov decision process”/ that retrieve zero results. The nearest indexing term is “Markov chains”/ which was not included in the search strategy. The reported search for Embase search via Elsevier did not have the same syntax issues and retrieved significantly more results (n=6800). It is the view of the EAG that the issues with the Medline and Cochrane Library search may be alleviated by the Embase search, as it contains the same titles as MEDLINE.[61]

Appropriate free text and databases-specific indexing terms were used to identify studies relating to SCD and costs, cost effectiveness and HCRU studies as per the inclusion/ exclusion criteria (Appendix G, Table 86: Inclusion and exclusion criteria for the cost-effectiveness studies). No date or language restrictions were applied to the Medline and Cochrane Library search and the Embase search was restricted to English language studies. The Medline and Embase searches were restricted to human studies using the database limits for Human studies. The EAG recommends using the search filter exp animals/ not humans/ to avoid missing studies that may have been missed by the indexers. Specific publication types were excluded: 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.

The search terms and numbers of results are provided for the conference abstract searches and HTA databases. The company reports to have searched ‘previous HTA submissions’; however, the search terms or numbers of results are not provided (Appendix G: Published cost-effectiveness studies, search strategy). The EAG also recommends a web search engine such as Google to ensure comprehensiveness.

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analysis) flow chart section reports that 7205 studies were retrieved, including ‘77 hits from manual search’. This figure is reporting the results of the database searches for Medline, the Cochrane Library, Embase, and the HTA Databases are reported as the results from ‘manual search’. This figure does not take into consideration the conference abstract searches that are reported. The company report that one study was included from ‘bibliography screening’, which is included in the PRISMA flow diagram, but the company does not report the criteria used to select which studies would have backwards citation searching applied, for example systematic reviews.

Health related quality of life (HRQoL)

Searches were reported to identify HRQoL data for all relevant treatments for SCD and HRQoL studies for Medline, the Cochrane Library, Embase and conference abstracts. The EAG noted that the same syntax errors that impacted the Medline and Cochrane Library cost-effectiveness search impacted the HRQoL search carried out on Medline and the Cochrane Library due to the erroneous use of semi-colons, full stops and brackets that are not compatible with Ovid. The EAG queried this in the clarification questions; however, the company did not address this search in their response. This search retrieved only 24 results, compared to the translated Embase search which retrieved 2024 results. The EAG tested this search by searching for the first indexing term 'exp hemoglobin S/' limited to dt=19460101-20230710 which retrieved 3384 results for the EAG but the HRQoL search line 1 only retrieves 2000 results, highlighting a major issue with the search. The translated search on Embase may alleviate this issue, as it contains the same titles as MEDLINE.[61]

These Medline and Embase searches were limited to human only using the Human filter using the database limits. The EAG would recommend using the filter 'Not (exp animals/ not humans.sh.)' to avoid potentially missing studies that may have been incorrectly indexed. Specific study types were excluded: 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. The Embase search was limited to the English language and the Medline and Cochrane Library searches are not reported to have been. Appropriate HRQoL database-specific indexing and free-text search terms were used.

The search strategy section and the PRISMA-flow diagram reported that *'a systematic database search performed until 6 June 2023, identified 2,024 potential articles.'* This does not incorporate the results that were obtained via the conference abstract searches, which are reported in Appendix G.

3.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

In this section, the EAG report an assessment of the company's economic evaluation against the NICE reference case for technology assessment.[62] The EAG provide a summary of the company's illustrative model structure, as well as the economic evidence used to parameterise the health economic model.

3.2.1 NICE reference case checklist

The EAG has undertaken an evaluation of the CS in relation to the NICE reference case, where the findings are reported in Table 5.

Table 5: 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	All relevant health effects that occur after exa-cel has been given are included. Health effects that occur during the workup necessary to receive exa-cel (apheresis, busulfan conditioning etc.), including failure to receive exa-cel, have not been considered (see NHS perspective, section 3.2.5.1).
Perspective on costs	NHS and PSS	The model did not consider an NHS and PSS perspective, since the costs supported by the NHS during the apheresis and conditioning phase are included only for patients who finally receive a per protocol dose of exa-cel. This approach excludes costs and outcomes for patients who undergo apheresis and conditioning but fail to receive exa-cel (see Section 3.2.10). Because apheresis and conditioning are not normally given in the current standard of care, these procedures are an essential part of the intervention from the NHS perspective (both for costs and outcomes)
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes

Element of health technology assessment	Reference case	EAG comment on company's submission
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Appropriate for that part after the infusion with exa-cel.
Synthesis of evidence on health effects	Based on systematic review	No
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.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	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	Inadequate. Resource use for failures during apheresis and up to the time of exa-cel infusion have not been included leading to underestimated NHS costs. There are also errors in the calculation of unit costs of some therapies.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Non-reference case annual discount rate used.

DCEA, distributional cost-effectiveness analysis; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.

3.2.2 Model structure

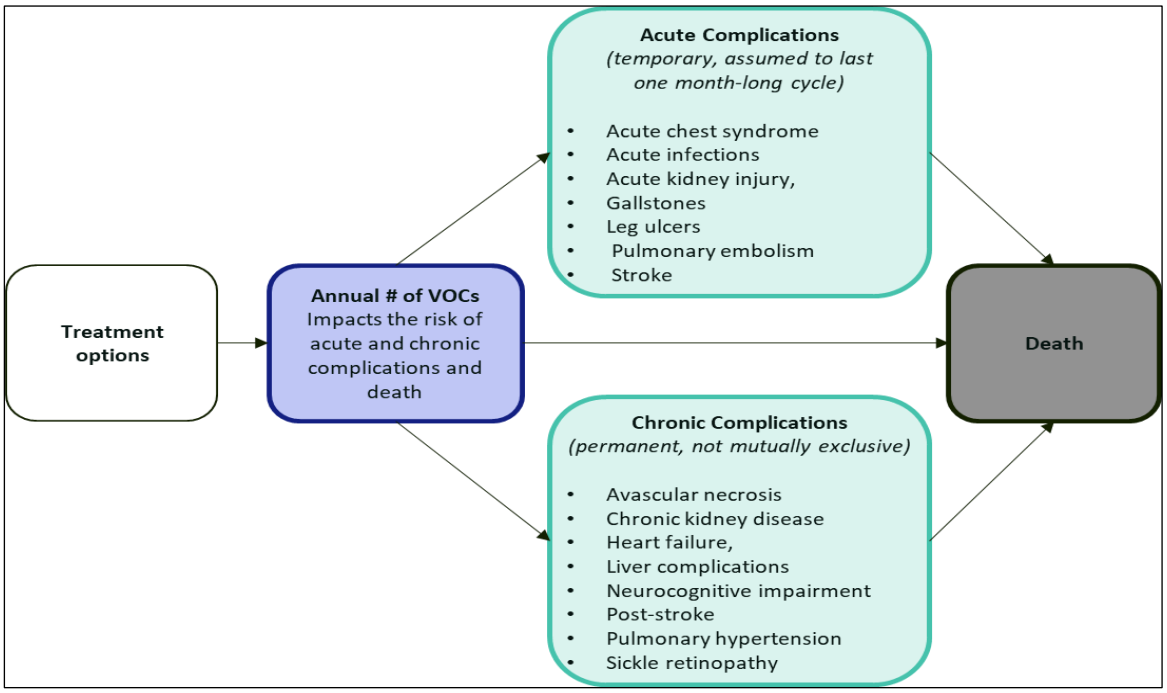


Figure 5: Illustrative model structure (obtained from CS Document B, Figure 26, page, 140)

Five cohorts are modelled:

1. Exa-cel: Cured population, no waning
2. Exa-cel, Cured population, treatment waning
3. Exa-cel: Improved disease population
4. Exa-cel: withdraw from initial and retreatment (no benefit)
5. SoC

For each cohort, the model (*see* Figure 5) calculates proportion of people alive and proportion of people dead. The proportion of people alive are then assigned a (mean) number of VOCs per cycle. The model then calculated the mean number of acute complications based on the mean number of VOCs observed for that cycle and a risk for each complication. Acute complications included in the model are:

- Stroke
- Acute chest syndrome
- Acute infections
- Acute kidney injury (AKI)
- Gallstones

- Pulmonary embolism (PE)
- Leg ulcers

Once the model rate of VOC at each cycle is calculated, acute complication rates are calculated based on number of people alive proportionally to the rate of VOCs, effectively incorporated as an independent determinant of risk of acute complications.

State occupancy for people with chronic events is also calculated for the following chronic complications:

- Chronic kidney disease
- Pulmonary hypertension
- Avascular necrosis
- Heart failure
- Neurocognitive impairment
- Stroke
- Sickle retinopathy
- Liver complications

Rates of each type of acute events are then used to calculate the number of deaths as “incident events”, at each cycle; the model terms these deaths as “incremental”. Finally, the number of incremental deaths is added to the number of general population deaths (adjusted for a risk with SCD) and subtracted from 1 to obtain the number of people alive at next time period.

The model does not follow a Markov structure

The model structure is not organised as a Markov structure, i.e., a model where state occupancy is calculated based on vectors of transition probabilities that are mutually exclusive (at each cycle, a person can transition to another state only) and exhaustive (total of probabilities = 1). The substance of this comment is not that there should be a transition matrix, but that the transitions between one cycle and another should maintain state occupancy below or equal to 1 for all states and that when states are summed, the model cohort should remain of fixed size over time. The model assessed here is implemented as a basic alive/dead model, with rates of complications calculated independently from each other and proportionally to the monthly rate of VOCs (multiplicatively).

Whilst from the viewpoint of model event rates it is plausible that there would be people alive and at the same time with more than one acute event, this logic cannot be transferred to death rates applied to events, which must remain mutually exclusive (also see Section 3.2.9 on mortality extrapolation). In the company's model instead, deaths are calculated applying each acute complication a death rate (specific to the event), corrected by the proportion of "alive" population. This approach implies that deaths are counted for each event independently from other events. Although the (incremental) death rates are applied to the "alive" population, the "alive" population is determined in a circular manner, subtracting the number of total deaths in the model from 1. This circularity provides no guarantee that the sum of deaths is less or equal to the total number of people in the cohort.

The overall effect is that some people may "die twice" at each cycle in the model, i.e., people in the model are "double counted".

The second issue, the rate of each complication at each cycle is calculated using the number of people alive overall, by the event rate. This number does not account for deaths specific to each complication at previous cycles, but only for the total number of deaths, i.e., averaged across all complications. The failure to account for event-specific deaths in the calculation of state occupancy rates at the following cycles results in incorrect rates of acute complications at each cycle and overall. In other words, people can be counted as "alive" with an acute event" and "dead" for another event in the same cycle.

The error is not apparent because a function in the count of total deaths has been added to keep the cumulative percentage of deaths equal to or lower than 100%; at the same time, the number of people alive is calculated by subtraction. For these reasons, the sum of dead and alive will always return 100%. When such a function is removed, the cumulative rate of deaths for acute events over the model horizon is over 500%. Even though constraints in the formulae are fixed such that the population is kept at 100%, the mechanics of the model structure are flawed, resulting in uncontrollable structural error.

3.2.3 Population

The population modelled are people with SCD 12 years of age and older with recurrent VOCs who have the βS/βS, βS/β+ or βS/β0 genotype, for whom an HLA-

matched related HSC donor was not available. The population modelled is similar to participants included in CLIMB SCD-121, having ≥ two VOCs per year in the two years prior to enrolment. Details of the patient characteristics in CLIMB SCD-121 are presented in Section 1.3.1. Patients in the modelled cohort had a starting age of 21.2 and were assumed to experience an average of 4.2 VOCs per year. The company stated that information about chronic complications were obtained from participants in CLIMB SCD-121, of which [redacted]% experienced retinopathy and [redacted]% neurocognitive impairment. Other chronic complication had a [redacted]% at baseline.

3.2.4 Interventions and comparators

The model does not account for costs and outcomes of treatment failures between apheresis and myeloablation.

The model structure should aim to replicate the therapeutic process involved in the administration of exa-cel and comparators.

In the exa-cel model arm, 100% of patients receive exa-cel at cycle 0 after which they incur costs and accrue benefits associated with exa-cel. To account for the cost of apheresis and myeloablation, a one-off total cost is added to account for pre-transplant cost for people who undergo apheresis but do not receive exa-cel (19.0%). The cost so calculated is £65,685, including pre-transplant costs per patient who received exa-cel, £55,214, and an additional £10,471 cost for dropouts.

This approach is incorrect for two reasons:

- Outcomes for the proportion of people who receive apheresis but do not proceed to exa-cel (for any reason) must be modelled, as these people are part of the intervention cohort.
- The NHS perspective must include all costs of the intervention to which the NHS is committed at the time of engaging patients into the process. Specifically, at the completion of Stage 2 (*see* Figure 2) some patients may not proceed to [redacted]. In this case, exa-cel is ordered and manufactured nevertheless, therefore the NHS accrues the relevant cost.

Specifically, the company stated that in 58 patients who started mobilisation, 11 have subsequently been discontinued from trial and have not been dosed with exa-cel. Of these, 5 patients did not proceed to mobilisation because they withdrew consent/non-compliance/were no longer eligible, whilst 6 patients did not proceed to conditioning as they did not achieve the minimum dose due to inability to manufacture drug product (low manufacturing yield or drug product did not meet release testing specifications).

Patients who do not receive exa-cel therefore accrue the cost of apheresis, the costs of blood transfusion in preparation for transplant, and limited to a proportion of these patients, the cost of exa-cel, as well as costs of adverse events associated with apheresis; all accrue outcomes and utilities. The EAG assumed that utilities and outcomes are those of SoC, in addition to outcomes of adverse events with apheresis.

Page 211 of 3664

Vertex Pharmaceuticals Incorporated
Protocol CTX001-121/131 IA2

Table 14.1.9.1b
Summary of CTX001 Dose for Subjects from Study 121
SCD-Full Analysis Set and SCD-Primary Efficacy Set

	SCD-Full Analysis Set N = 35	SCD-Primary Efficacy Set N = 17
CTX001 Dose (10^6 CD34+ cells/kg)		
n	35	17
Mean (SD)	4.7 (2.63)	3.7 (0.79)
Median	4.0	3.5
Q1, Q3	3.2, 4.9	3.1, 4.0
Min, max	2.9, 14.4	2.9, 5.3

Figure 6: Mean CTX001 dose (10^6 CD34+ cells/kg), Table 14.1.9.1b, CTX001-131 CSR, page 211

In addition, a model should not plainly replicate clinical trial data as these are subject to randomness. When modelling the probability that patients may not achieve a sufficient product dose to proceed to conditioning, the most robust approach involves calculating the probability that the yield would be lower than the minimum dose necessary. This can be done in distribution based on data obtained from the CLIMB-131 study.

Using the log-normal distribution, the probability that a subject may receive less than the minimum therapeutic dose (3 10^6 CD34+ cells/kg) is 8.54%. This value is slightly lower the crude rate calculated on actual trial event counts for this parameter.

The calculation of the total cost of apheresis, £65,685, is also incorrect; the correction is presented in Section 3.2.10, Costs of apheresis.

The model does not account for failures during follow-up and does not consider exa-cel failure rates.

The company's model carries the major assumption that a patient will be "cured" for life once s/he receives exa-cel. The primary endpoint of the trial is the rate of VOCs in the 12 months after the patient has stopped receiving supportive blood transfusions alongside transplant with exa-cel. This definition excludes the peri-transplant period, during which one patient reported a VOC, and the follow-up period after 12 months, during which two patients report VOCs (one VOC and three VOCs respectively). In the spirit of the endpoint definition, no patient relapses; however, the theoretical possibility that relapses occur outside the period of relevance for the primary endpoint is corroborated by the CLIMB SCD-121 data. In addition, VOCs in CLIMB SCD-121 are adjudicated, to control for the fact that the study is open-label.

The EAG has calculated the relapse rate in CLIMB SCD-121 from the CSR. Over a total follow-up period of [redacted] months, there are [redacted] cases of relapse, amounting to an incidence of [redacted]%. Whilst the rate is small, such event must be added to the model structure.

3.2.5 Perspective, time horizon and discounting

3.2.5.1 Perspective

As explained in Section 3.2.4, the exa-cel arm considers only the costs and outcomes of patients who receive exa-cel as per protocol. Nonetheless, the NHS perspective must include all costs and outcomes in relation to the intervention being offered to a patient. At the moment of offer, the NHS becomes liable for the costs of apheresis, all the adverse events that may follow, and for the cost of manufacturing exa-cel, for which the NHS becomes liable at the time of ordering the product, for all

patients who successfully undergo apheresis. At the time of clarification questions, the company stated that three patients received a dose slightly lower than the the lower bound of the dose range for exa-cel (2.9×10^6 CD34+ cells/kg) and that a patient would not undergo conditioning if exa-cel manufacturing returns a dose lower to the minimum range of 3.0×10^6 $CD34^+$ cells/kg.

As per Figure 2, some patients will fail to receive exa-cel before conditioning due to inadequate yield or other technical reasons; yet the cost must be accrued in the intervention arm. The cost of exa-cel manufacturing for these patients must be included in the model, whilst, consistently with company's advice, the cost of conditioning should not be accrued in the model for those patients.

3.2.5.2 Time horizon

The model assumed a life-time horizon of 79 years, which is long enough to capture the long-term costs and benefits of the strategies being compared. The EAG considers this plausible to capture meaningful differences between exa-cel and SoC over a long period of time.

3.2.5.3 Discounting

Non-reference case discount rate of 1.5%

The company presents a co-base case comprising economic analyses applying 1.5% and 3.5% discount rates. The company stated that exa-cel meets the criteria of 1.5% discount rate due to:

- *'The technology is for people who would otherwise die or have a very severely impaired life*
- *Exa-cel is likely to restore these patients to full or near-full health*
- *The benefits are likely to be sustained over a very long period'* (CS Document B, Table 33, pages 141-144)

Based on the critique presented in Section 1.3.5, in the EAG's opinion, it is not possible to establish with certainty that benefits are likely to be sustained for a very long period due to the relatively short duration of follow-up. The CS asserts that benefit will be sustained in the long term because there is no known mechanism by which the editing of the BCL 11a enhancer can be reversed, because in the single-

arm trial VOC incidence greatly diminishes after exa-cel infusion relative to the pre-exa-cel period, and because SCD recipients of allo-SCT, who do not experience graft rejection or GVH disease, have prolonged survival. Yet, the CLIMB SCD-121 shows that, despite the theoretical biological plausibility of “cure”, the possibility of VOCs relapse remains a relevant clinical question. Whilst the trial CSR seems to suggest that these VOCs may have been of low severity based on “narrative”, the trial follow-up is insufficient to provide any evidence in support of the assumptions regarding total cure, eradication of VOCs and any relevant longer term hard outcomes.

3.2.6 Treatment effectiveness and extrapolation

3.2.6.1 Risk of VOCs and calculation of events based on VOCs

The model assigns a rate of VOCs for one year after receipt of exa-cel in the exa-cel arm, and a lifetime risk of VOCs in the SOC arm. This approach does not reflect evidence from CLIMB SCD-121. The model does not include VOC relapse at later times, also not reflecting evidence from CLIMB SCD-121

The model assumes that the baseline rate of VOC continues for one year after receipt of exa-cel; this is unnecessary and does not make the model more conservative. On the other hand, the CLIMB SCD-121 trial also showed that [redacted] of [redacted] participants, VF-12 was not achieved.

In the 120D data cut, [redacted] patients in [redacted] had at least 60 days follow-up after the last supportive transfusion; two patients in this group had events adjudicated as VOCs: [redacted].

The model does not contemplate a relapse rate for VOCs, and this is contrary to the evidence from CLIMB SCD-121 and the follow-up study 131. Based on follow-up (in months, available for each patient from Figure 11-11 of the CLIMB-131 study; total of 520.2 patient-months) (*see* Figure 7), the VOC incidence rate is [redacted]% per month ([redacted]) whilst the prevalence is [redacted]% per month. Whilst small and subject to high uncertainty, these rates are based on trial data and show a positive probability of relapse therefore they must be incorporated into the model structure.

Of these [redacted] VOCs, [redacted] associated with a hospitalisation at month [redacted] (Figure 11-12 CLIMB-131 CSR, page 76, not shown).

Figure 7: [redacted]

Modelling of acute events based on the number of VOCs is not appropriate

The model uses the number of VOCs from the baseline of trial CLIMB SCD-121 as the number of VOCs for patients who do not receive exa-cel ([redacted]% in the exa-cel arm) and for people who are in the comparator arm. The rate of VOCs applied in the model is [redacted] average per patient per year, or [redacted] per cycle.

The model extrapolates all longer-term events from hazard ratios of each event, multiplied by the rate of VOCs at each cycle. The rate of VOC is applied in the model as mean number of events per month. The number of complications is then

calculated, for each complication, multiplying the mean VOC rate per cycle by the hazard of each complication. In other words, the number of VOCs is used as the term for the hazard in a risk equation (from Shah et al. (2019)[63] and other literature), for acute and chronic events following exa-cel, or the risk of the same range of events in the comparator arm.

The use of VOCs as a multiplier for hazard for those events is not grounded in evidence.

It is accepted that VOCs are a precursor to SCD complications and mortality and a primary risk factor for cardio-vascular complications in the SCD population. However close inspection of the study by Shah et al.[63] suggests that the use of VOCs as a multiplier may not be appropriate.

Shah et al.[63] is a a retrospective observational study of US Medicaid medical claims. The authors researched the correlation between VOC rates and risk of acute events used records for SCD patients (identified with a diagnosis of SCD (index date), with at least six months data before the index date and with at least one year follow-up data after the index date), with follow-up until disenrollment from medical insurance plan, death or end of study period (31 December 2013).[63] Vaso-occlusive events were defined as inpatient stay with a primary or secondary clinical claim of SCD with crisis.

The study identified a sample of approximately 21,000 patients, with 17% who had two or more hospitalisations for VOCs (from Table 3, Shah et al. 2019), i.e. similarly defined to participants in the CLIMB SCD-121 study. Shah et al.[63] applied stepwise regression to quantify the hazard of each complication, for patients who had ≥1 VOC requiring inpatient stay during the half-year baseline period. The authors concluded that *" Patients who had a follow-up VOC had a 1.55 higher hazard of death than those without a follow-up VOC (95% CI [1.19, 2.05]; p value=0.0014). Patients with VOC were also more likely to develop life-threatening complications including ACS (HR=58.67; 95% CI [50.21, 68.55]; p value <0.0001), splenic sequestration (HR=34.99; 95% CI [30.65, 63.13]; p value<0.0001), pulmonary hypertension (HR=4.12; 95% CI [3.14, 5.41]; p value <0.0001), pulmonary embolism (HR=2.82;*

95% CI [2.21-3.58]; p value<0.0001), and stroke (HR=2.26; 95% CI [1.94, 2.63]; p value <0.0001)”,[63]

A careful reading of the wording explaining the stepwise regression in Table 2 in the Shah et al. article shows that the regression equations estimated in the study found a quantifiable relationship between VOCs at baseline and time to death (HR=1.56) and time to stroke (HR=2.26) only.[63]

Table 6: [redacted]

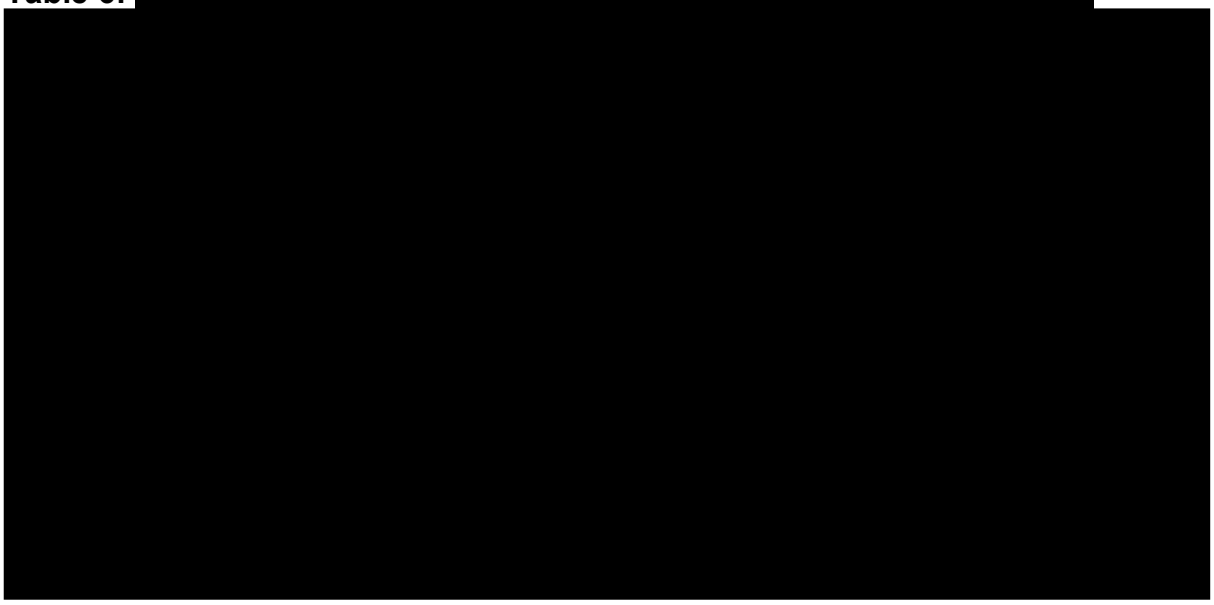


Table 6 also shows that in the stepwise regression failed to retain “number of VOCs” as a determinant of HR for all other SCD complications. A hazard obtained from an equation where VOC fails the significance test means:

1. the hazard for a particular complication does not differ between people that have a VOC and people that have no VOCs, and
2. the quantification of risk of acute events based on the number of VOCs failed.

Finally, a significantly higher hazard for death for people with VOCs (1.56) results from a contrast between people with (any) VOCs and those with no VOCs, therefore a contrast between people with or without VOCs, not a quantification of the relationship between number of VOCs and death. The increased hazard for time to splenic sequestration (HR=43.99) was associated with “baseline pain crisis” not otherwise specified. We interpret this hazard to be applicable to the contrast “people with any pain crisis (whether it is a VOC or other).

In the company model, people that have no VOCs (i.e., the exa-cel cured) are assigned zero risk of events, however the Shah et al. results contradicts this conclusion. Therefore, the overarching assumption in the model that zero VOCs imply no acute or chronic complications is not grounded in evidence.[63]

Whilst there is consensus that VOCs are associated with poor outcomes, the Shah study failed to quantify a relationship between VOCs and acute and chronic complications, in that it failed to show “number of VOCs” as a significant independent variable associated with the risk of most complications.

Therefore, the use of VOCs in the model to predict such outcomes is not corroborated by the available evidence.

A second additional point is that the Shah study used a different definition of VOCs than the CLIMB SCD-121 study. Shah et al. defined VOCs as hospitalisations associated with VOCs, whilst the CLIMB SCD-121 study used all VOCs, either leading to hospitalisations or not.[63]

The rates of severe VOCs, and the rate of VOCs that lead to hospitalisation are reported in Figure 8 (excerpt from Table 10-3 of CLIMB SCD-121 CSR, page 60).

Figure 8:

Therefore, the endpoints in Shah and CLIMB SCD-121 are not fully comparable. When HRs from Shah et al. are used, these should be applied to the annualised rate

of hospitalisations associated with VOCs in CLIMB SCD-121, not to overall VOC rates.[63]

The bias in estimation is likely to affect the comparator more, with respect to estimating event rates, yet the largest effect is likely to be seen in the intervention arm, where the risk of acute and chronic events is set to zero when no VOCs are reported, whilst according to Shah et al., event rates are likely to be positive in the exa-cel cohort. The Shah paper does not allow for the quantification of such rates.

For some computations, the number of VOCs is handled like a probability, i.e., the number (or proportion) of people that experience VOCs, whilst the number is a rate, i.e., mean number of VOCs for people alive in the model

A rate of 0.035 per cycle means that all people in the cohort have on average 0.035 VOCs, not that 3.5% of people have a VOC. Yet, when calculating the risk of acute events (Stroke, ACS, Infection, AKI, gallstones, PE, Leg ulcers) the number of VOCs is incorporated as risk of the event for people without VOCs, i.e., HR multiplied by 1-rate of VOC. See Figure 9 for an illustration.

	A	O	P	Q	R	S	T
17							
18		**Patient disposition (use in trace)**			**VOC trajectory**		**Acute complication events per cycle**
19		Alive	Death		Alive		Stroke
20		100.00%	0.00%		0.350		0.00%
21		99.99%	0.01%		0.350		0.2990306053%
22		99.96%	0.04%		0.350		0.2989469843%
23		99.92%	0.08%		0.350		0.2988264774%

Figure 9: Excerpt from the economic model illustrating the acute stroke events per cycle

Cell T21 is calculated with the following formula:

T21 = $O21*($R21*comp_base_stroke*comp_voc_hr_stroke+(1-$R21)*comp_base_stroke)

where:

comp_base_stroke = stroke [probability] in people without VOCs

comp_voc_hr_stroke = hazard for stroke in people with VOCs

Because all people in the cohort have VOCs (at this cycle), the EAG believes that the state occupancy for stroke at this cycle should be

$O21*($R21*comp_base_stroke*comp_voc_hr_stroke)

without the term (1-$R21)*comp_base_stroke)

The company model estimates a risk of stroke equal to 0.30% in that cycle, while the proposed calculations recommended by the EAG would result in a risk of stroke equal to 0.16%

3.2.6.2 Calculation of acute and chronic complications in the model (clinical parameters)

The range of acute and chronic complications included in the model is large, but clinical parameters, particularly efficacy (risk reduction) is overwhelmingly based on assumptions. The evidence base also appears selected; US data are preferred to available UK data.

It is accepted practice that modelling of cost-effectiveness can rely on assumptions around certain parameters when evidence is missing. Nonetheless, the credibility of a model structure conceptualisation is a qualitative evaluation based on the extent of grounding in evidence, as well as on the biological plausibility of clinical relationships hypothesised in the model structure. The extent of structural uncertainty in a cost-effectiveness model should be such that it is not overwhelming, and that the relationships there hypothesised can be translated into the model in such ways that the logic, flow, and plausibility not just of cost-effectiveness results, not just with respect to evidence but also to internal logic.

Here below is the list of clinical complications (acute and chronic) included in the company's model structure, with evidence source.

Table 7: List of clinical parameters included in the model, with sources

Endpoint	Source of evidence		
	Monthly rate when VOC = 0	**HR by VOC occurrence**	**Monthly rate among patients cured from SCD**
Acute kidney injury/infarction	Yeruva 2016[64]	Yeruva 2016[64]	Assumption
Chronic kidney disease	Bradt 2020[65]	Bradt 2020[65]	Assumption
Stroke	Shah 2019[63]	Shah 2019[63]	Assumption
Acute chest syndrome	Shah 2019[63]	Shah 2019[63]	Assumption
Pulmonary embolism	Shah 2019[63]	Shah 2019[63]	Assumption
Pulmonary hypertension	Shah 2019[63]	Shah 2019[63]	Assumption
Acute infections	Shah 2019[63]	Assumption (same as stroke)	Assumption
Gallstones	Shah 2019[63]	Assumption (same as stroke)	Assumption
Leg ulcers	Singh 2016[66]	Assumption (same as stroke)	Assumption
Avascular necrosis	Shah 2019[63]	Assumption (same as pulmonary hypertension)	Assumption
Heart failure	Bradt 2020[65]	Assumption (same as pulmonary hypertension)	Assumption
Neurocognitive impairment	Cahill 2019[67]	Assumption (same as pulmonary hypertension)	Assumption
Sickle retinopathy	American Academy of ophthalmology: Incidence of proliferative retinopathy among HbSS patients	Assumption (same as pulmonary hypertension)	Assumption
Liver complications	Assumption; 5 times of the risk among general population	Assumption (same as pulmonary hypertension)	Assumption
Post-stroke	NICE SCD guideline 143 (appendix F)	Assumption	Assumption

Table 7 shows that:

- Most baseline rates are taken from Shah et al (2019)[63] study and other literature.
- Of the clinical effectiveness parameters, nine are based on assumptions, four are taken from Shah et al (2019)[63] and two from other literature sources.
- Monthly rates among cured patients are entirely derived based on assumptions.

It is apparent that the extent of assumptions in the model is overwhelming, particularly when applied to event rates when patients are “cured”. Whilst modelling serves the purpose of estimating longer term outcomes when (some) cannot be directly observed, the extent of assumptions is such that the model appears informed by a very limited number of evidence sources, to the point that the credibility of the entire model conceptualisation cannot, in large part, be supported. It is acknowledged that the burden of disease in the SCD population is very large and very complex, however, the choice of clinical events in a model should also be balanced, in such a way that the model is at least based on reasonable evidence.

In particular, the model relies heavily on events reported in the study by Shah et al (2019).[63] The company conducted a burden of illness study, using similar methods to Shah et al.[63] yet with data from the UK. Although the BOI study has not applied statistical analyses comparable to those in Shah et al (2019),[63] the nature of the data (UK) and the relatively large sample size (n=[redacted]), as well as the presence of a subgroup of patients selected based on inclusion criteria matched to those of the CLIMB SCD-121 study, warrant that at least for some parameters, the BOI study should be used. It is unclear why the company’s study is entirely disregarded in this model.

In addition, the Shah et al.[63] study included evidence for a limited range of clinical endpoints. A more in-depth analysis and interpretation of the Shah et al study is provided in section 5.1.1.

Rates of chronic complications may be biased as a result of the methods of computation

The state-transition Markov structure handles events as competing events, whilst in this company model, they are calculated for each event in isolation. The Shah et al. (2019) study did not use competing events statistical models. The company's model does not include a dependency structure for these events, therefore the HRs generated in the study generate correlation biases when incorporated in the model.

The current version of the model tracks the number of people who had an event (by type) however, these rates are calculated based on rates from the previous cycle, adjusted by overall mortality and not by event-specific mortality. This means that all people alive are continuously at risk of any acute or chronic complication, regardless of whether they had an event already, either of the same type or of a different type. This results in a very high number of acute or chronic complications. Indeed, in the "no benefit" cohort, the model estimates 15 acute events (stroke, ACS, infection, AKI, gallstones, PE, leg ulcers) and 5.8 chronic complications will be reported over the course of lifetime.

In the original study, the risk was for the first event. As people with the first event are taken out of the pool of people at risk, the risk should reduce over time. In addition, the death rate applied to people with acute or chronic complications is the total death rate, and not disease specific. This means that rates for a particular state are not mutually exclusive with respect to the event "death", which results in people with a type of complication to become at risk of death for all other complications at the same time, in such way that the risk of death is applied multiple times for the same people (*see* Section 3.2.9). This introduces uncontrollable bias in the calculation of complication event rates in the model. Given that these extrapolations are calculated based on a chain of assumptions and populated with data from literature, the estimation appears highly uncertain.

On a similar note, the computation of independent rates for complications also means that when accounting for costs, each acute event is costed independently, whilst in practice, costs of hospitalisations with two causes of hospitalisation or more are not costed as twice the cost. This bias leads to possible inflated costs. This is likely to affect the comparator arm more than the intervention arm as VOCs are assumed to stop within one year from the use of exa-cel.

3.2.7 Adverse events

The cost-effectiveness analysis includes a very limited, restricted set of adverse events; all adverse events are applied to the SoC arm only. Adverse events from CLIMB SCD-121 and CLIMB-131 were not considered.

From Table 14.3.1.1.1b (page 1945-49 of the CLIMB SCD-121 CSR), it is possible to rebuild rates of adverse events associated with exa-cel. The table provides data for adverse events associated with apheresis (plerixafor), conditioning (busulfan) and exa-cel, covering the period from enrolment at the time of apheresis to post-exa-cel follow-up.

Table 8: Number of subjects with adverse events and number of adverse events, by severity, grade, CLIMB SCD-121 trial phase and by relation with each of the study drugs (plerixafor, busulfan and exa-cel).

In addition, the CLIMB SCD-121/CLIMB-131 CSR (Table 14.3.1.1.3b page 1948-58) also reports the number of subjects with SCD related complications (n=[redacted], in the FAS sample of N=[redacted], [redacted]%), subjects with new or worsening haematological disorders (n=[redacted], [redacted]% of [redacted]). Finally, Table 14.3.1.2.3b reports that, of the [redacted] evaluable subjects in the FAS, [redacted] ([redacted]%) subjects reported AEs related to busulfan; [redacted] ([redacted]%) reported AEs related to busulfan and CLIMB SCD-121, [redacted] ([redacted]%) reported AES related to CLIMB SCD-121 only, giving a total of [redacted] subjects ([redacted]%) who reported AEs related to CLIMB SCD-121.

Of these, [redacted] subjects ([redacted]%) reported AEs of grade 3 or above (Table 14.3.2.2.3b, page 2308). These were:

- Investigations due to CD4 lymphocytes decreased (n=[redacted], [redacted]%);
- Investigations due to platelet count decreased (n=[redacted], [redacted]%)
- Investigations due to blood alkaline phosphatase increased (n=[redacted], [redacted]%)
- Thrombocytopenia (n=[redacted], [redacted]%)
- Anaemia (n=[redacted], [redacted]%)

Table 9: Overview of adverse events for participants from Study 121 for the enroll to M24 interval SCD-safety set

AEs data are available for AEs of new or worsening haematological disorders associated with CLIMB SCD-121 (Table 14.3.2.5.3b, CSR CLIMB SCD-121/CLIMB-131, page 2320), reported by [redacted] of [redacted] subjects. (*see* Table 10)

Table 10: Adverse Events of New or Worsening Hematologic Disorders for Subjects from CLIMB SCD-121 by Preferred Term Cumulative from Study 121 Infusion SCD-Safety Set

[redacted]

Finally, data are reported by System Organ Class and Preferred Term (Table 14.3.1.2.5b; Table 14.3.2.2.3b; Table 14.3.2.2.5b; Table 14.3.2.5.1b), both in association with busulfan and CLIMB SCD-121.

Table 11: Adverse Events of SCD-Related Complications for Subjects from CLIMB SCD-121 by Preferred Term for the Enrol to M24 Interval SCD-Safety Set

[redacted]

The CLIMB SCD-121/CLIMB-131 CSR also provides patient level data (i.e., listings) for vaso-occlusive pain crises reported over the course of the study. Specifically, VOCs data were collected as safety endpoints for the period between enrolment (apheresis) and conditioning (busulfan) covering the time from trial enrolment to receipt of exa-cel.

It is unclear why these data were not used as VOC rates in the model, whilst the number of VOCs per year in the model was set to [redacted] (as discussed in Sections 2.2.2 and 3.2.6) taken from the two years before enrolment, given that trial data (collected prospectively and in this case, adjudicated) are generally more reliable than retrospective data collected from medical records (affected by precision in event coding as well as by the interpretation of the treating physician, in addition to recording errors).

Table 12: Listing of adverse events related or possible related to CLIMB SCD-121 for participants from Study 121 SCD-enrolled set

[redacted]

3.2.8 Health related quality of life

Table 13 shows the utility values collected alongside the trial period, provided in Table 22 in Document B (page 108). Data at baseline correspond to data at administration of exa-cel.

The company argues that at month 24, utility data show a change of [redacted] and proceeds to assign a value of [redacted] (cured SCD, adding [redacted] (change at month 24) to [redacted] (at exa-cel administration) to the period from exa-cel transplant until the end of the model (adjusted by age as per Ara et al.).[68]

The change value chosen, however, is measured in [redacted] patients, approximately [redacted]% of the sample who provided baseline values, i.e., a loss to follow-up of [redacted]%.

The value of [redacted] for change is therefore the result of two distinct effects: the (real) change in utilities over time, and the (artificial) bias introduced by the exclusion of the [redacted] individuals who formed part of the baseline but for whom there are no values at month 24. Therefore, the incorporation of utilities in the model made by the company suffers from selection bias.

Table 13: UK Health Utility Index Score (PES)

Visit (at month)	Baseline	Month 3	Month 6	Month 12	Month 18	Month 24
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PES, primary efficacy set; SD, standard deviation						

On the other hand, utility values at months 6 and 12 do not suffer from biases due to loss of follow-up, given the stability of the sample size in whom those utilities are measured. Given the similarity of average values of utilities from month 6 to month 24, and that such values are highly unlikely to be shown statistically different should such test be conducted, the EAG concluded that the use of the mean utility value of [redacted] is preferred for the longer term, equivalent to a utility gain of [redacted] over the course of therapy.

The utility value at baseline ([redacted]) is also preferred for the utility between apheresis (at enrolment) and administration of exa-cel, covering the period not modelled in the company base-case.

3.2.9 Mortality

Rates of mortality may be biased due to computation methods

Mortality is applied in two stages.

1. The first stage, background mortality is applied using data from ONS tables for the general population (cured rate). In addition, an SCD specific mortality rate (SCD rate) is applied at any cycle when the model population is assumed "not cured". Reflecting the distinction between cured and non-cured, in the

"Cured" cohort, the SCD specific mortality rate is applied in the first year only, after which the population reverts to the general population mortality rate plus a further increased risk of mortality, applied with a HR adjustment of 1.25.

2. The second component of mortality in the model is the risk of death assigned to both acute complications and chronic complications, "incremental mortality" in the language of Document B. These disease-specific death rates are applied to the following states:

    - VOCs
    - ACS
    - AKI
    - Pulmonary embolism
    - Stroke
    - Leg ulcers
    - Acute infections
    - CKD
    - Pulmonary hypertension
    - Heart failure
    - Liver complications

Table 14: Hazard/risk rates of death for acute and chronic events

Event	Value	Type of parameter	Applied to
VOC	1.56	HR	Number of VOCs per cycle
ACS	1.27	HR	Rate of acute event per cycle
AKI	9.5	RR	Rate of acute event per cycle
Pulmonary embolism	2.75	HR	Rate of acute event per cycle
Stroke	7.7%	HR	Rate of acute event per cycle (first event)
Leg ulcers	1.66	HR	Rate of acute event per cycle
Infection	1.00	HR	Rate of acute event per cycle
CKD	9.57	RR	Cumulative state occupancy
Pulmonary hypertension	12.57	HR	Cumulative state occupancy
Heart failure	12.57	HR	Cumulative state occupancy
Liver complications	2.53	HR	Cumulative state occupancy

ACS, acute chest syndrome; AKI, acute kidney injury, CKD, chronic kidney disease; HR, hazard ratio; RR, risk ratio; VOC, vaso-occlusive crisis

Hazard rates are applied to the general death rate, either of the general population or SCD specific when VOCs rates are >0, multiplied by the number of VOCs, and multiplied by a factor equal to the hazard -1.

This is incorrect for five reasons:

1. It is unclear why some event-specific death rates are applied to incident events only (stroke, leg ulcers), implying that survivors revert to good health at the end of each cycle with return to the risk of general mortality only, and not to the cumulative state occupancy for people with a history of that event (as per Markov logic), with appropriate parameters for subsequent events.
2. It is unclear why hazard rates of acute events are multiplied by the number of VOCs (see critique of use of Shah et al in Section 3.2.6.1)
3. It is unclear why the HR is applied subtracting 1 (HR -1)
4. It is unclear why a probability of death is applied to a state that represents "event counts" and not the (conditional) probability of moving to "death" given state occupancy for the specific event, i.e., number of people that report the particular event, as per Markov logic. This flaw affects both the application of the probability of dying to both VOC rates and to acute and chronic events rates.
5. Finally, the application of distinct cause-specific death rates to non-mutually exclusive states causes the estimation of total deaths in the model to be over 100%.

The calculation of overall mortality appears flawed. Model traces do not provide cumulative “incremental” mortality for the population overall and over all cycles in the model. When calculating the overall cumulative mortality using column “Overall mortality”, (column CA), i.e., the “incremental mortality” at each cycle, the model returns cumulative mortality rates that go above 100% starting from cycle 743 (82 years age in the model cohort).

Nonetheless, the model incorporates such rates in the model calculations. The model then calculates total deaths (column H, distinct from column “Overall mortality”) using a formula that constrains the cumulative number of deaths to 1. For

example, cell H27 (state occupancy for death overall in the model) is calculated as follows:

H27 = MIN(1,CA27+H26)

At each cycle, deaths are the minimum between 1 and the sum of total deaths at the previous cycle (H26) summed to the overall “incremental” deaths (CA26) as explained in this section. When such constraint is released, the cumulative sum of total deaths in the model becomes higher than 100%. In this manner, “incremental” mortality enters the calculation of people alive (obtained subtracting the number of total deaths from 1) and because total deaths are forced to 100% max, people alive are also forced between 0 and 100%.

This approach invalidates extrapolation of all event rates and extrapolation of death rates in the model, to the point that any estimation made using this model structure is not credible.

The solution would be to rebuild the model using a proper Markov structure (*see* Section 3.2.2) to constrain the population to 100% over the course of the model as the result of the Markov internal logic.

Underestimation of uncertainty in modelling of overall survival in exa-cel and SoC

The CS section B 3.3.4 describes the generation of survival curves as follows: “Patients are at risk of death throughout the modelled lifetime horizon. Outside of general population mortality, risk of death is dependent on the patients’ VOC status, frequency of VOCs and occurrence of complications and other transplant-related events.” And “In the base-case analysis, mortality risks were combined multiplicatively, which inherently assumes that the mortality risks related to transplantation, VOC occurrence, and complications are independent of each other.” Many “complications” were included in this modelling leading to a complex procedure to reach mortality estimates.

In clarification the EAG requested presentation of OS curves generated by the Markov model because these were absent from the company submission Document B. The OS curves embedded in the economic model are shown in Figure 10. A median age for survival of the age/gender adjusted general population was 83 years and medians for exa-cel and SoC approximately 74 years and 43 years,

respectively. The model cycle was one month and surviving proportions in the graph appear to be presented at yearly intervals.

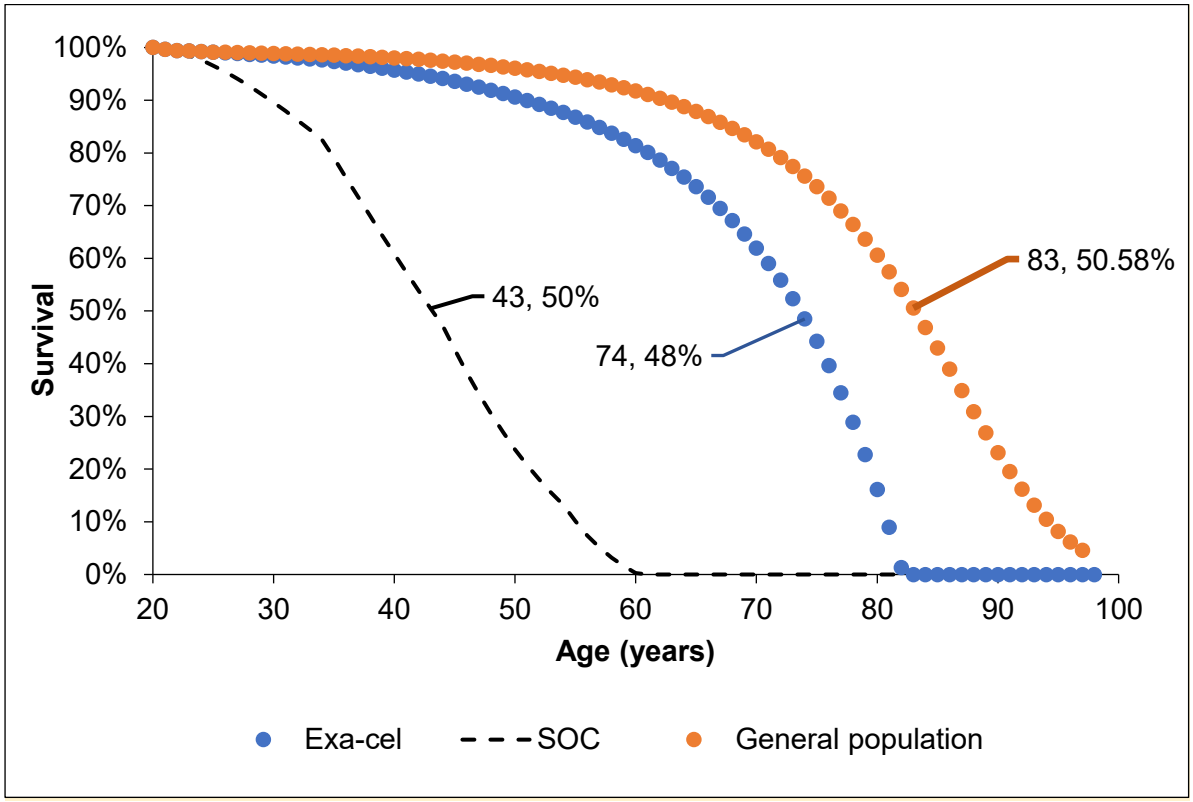


Figure 10: Markov model survival for study arms and for the age/gender matched general population. General population data was from life tables for England and Wales 2018 to 2020.

The shape of the curve for exa-cel was somewhat different to that for both the general population and SoC, however all three conform to a Gompertz distribution indicating some proportionality. Figure 11 shows Gompertz distributions fit well to the data reported within the economic model and generate very similar results to those reported for the Markov model (*see* Table 15).

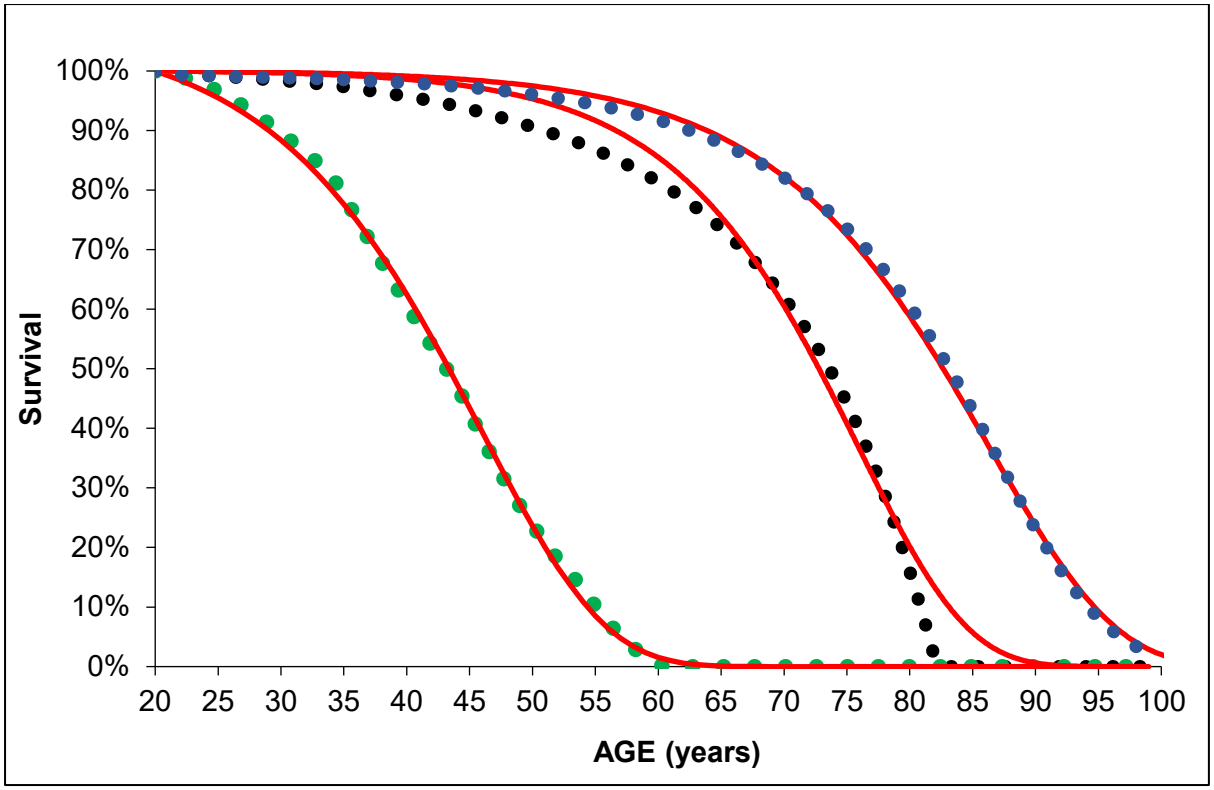


Figure 11: Gompertz models fit to Markov model study arms survival and to the age/gender matched general population data.

Table 15: Values generated using Gompertz distributions versus those from the Markov model

Survival	Exa-cel	SoC
Total life-years (no discounting)	49.06	22.36
Total life-years (1.5% discounting)	34.43	18.07
Total life-years (no discounting and Gompertz distribution)	51.08	23.05
Total life-years (1.5% discounting and Gompertz distribution)	35.36	19.17
Median age of death (years)	74.5	44
Median age of death (years) and Gompertz distribution	72.8	43.1
Exa-cel, LY, life-years, SoC; standard of care		

Very similar curves are generated when hazard ratios are applied to the Gompertz general population model to generate curves that approximate closely to the Markov outputs for the SoC and exa-cel survival outputs (shown in Figure 12).

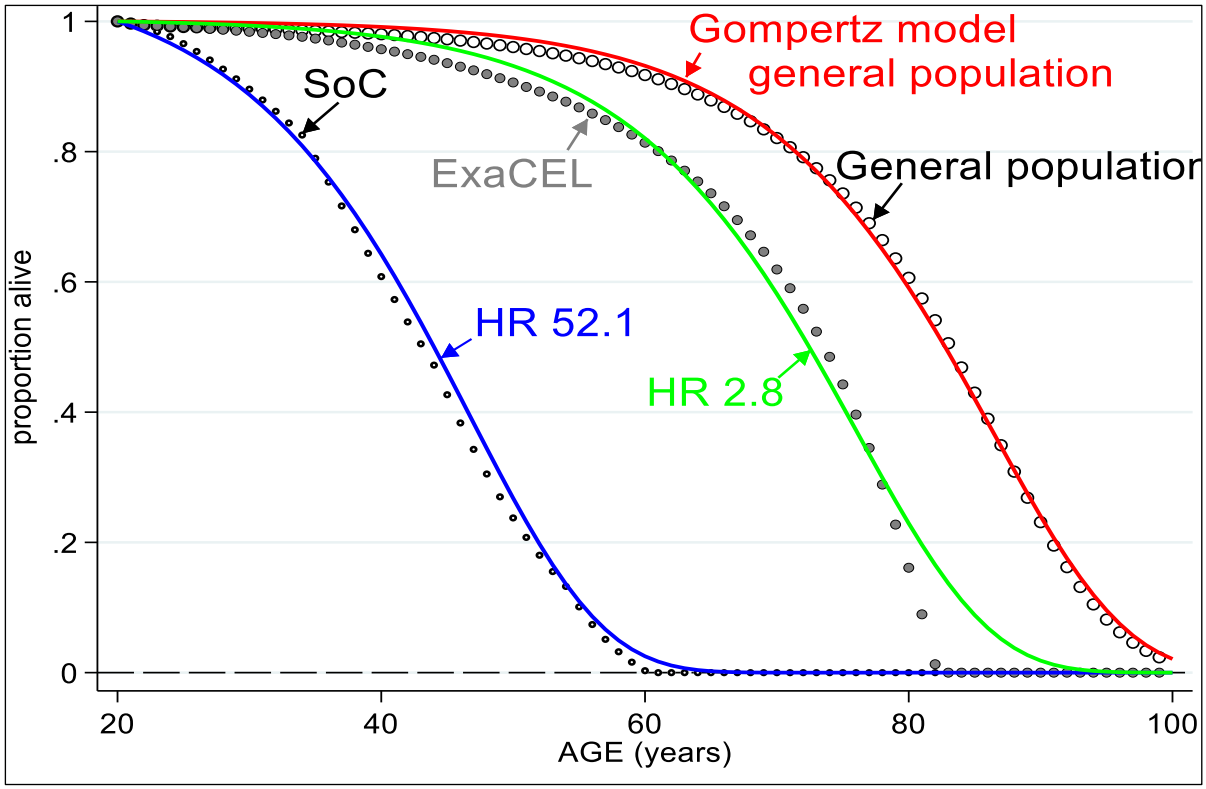


Figure 12: The general population data and "Markov" outputs for CLIMB SCD-121 study arms are shown as circles; models generated by applying hazard ratios to the general population Gompertz model are shown as solid lines.

The results from the "Markov" models and the Gompertz distributions do not validate the company's mortality modelling (they merely indicate that the "Markov" models for the study arms follow a Gompertz distribution as would be expected for the age and gender adjusted general population). It is very difficult to validate the Markov survival models generated because of the complexity of their production.

The company submission argues that the "Markov" output for the SoC arm is reasonable because *"An overall SMR of 5.21 versus the age- and gender- matched general population is predicted from the model from the SoC arm."* This lies between the SMRs of 4.9 and 7.4 in the overall and 2014-2018 cohorts of the Vertex Pharmaceuticals burden-of-illness study, respectively (0.78 person-years in the SCD overall cohort versus 0.16 general population and 0.81 person-years in the SCD 2014-2018 cohort versus 0.11 general population).[33] The model therefore appears to predict mortality in line with the UK. The range from ref (4) is 4.9 to 7.4 and has been calculated from: 0.78/0.16 = 4.9 and 0.81/0.11 = 7.4.

Prima facie the 5.21 SMR (SoC versus general population) was surprising in view of the large HR between SoC, and general population seen with Gompertz models. The CS does not explain how the SMR of 5.21 was derived and the EAG was unable to replicate the 5.21 SMR value quoted in the CS.

The EAG used the method of Guyot et al. (2012)[69] to obtain IPD for [redacted] individuals (FAS data set N = [redacted]) in the age/gender adjusted general population and the Markov model outputs for the SoC and exa-cel populations.[69] Kaplan-Meier plots derived from IPD are shown in Figure 13 and closely follow the respective data in the CS economic model.

Figure 13: Kaplan Meir survival plots of [redacted] with the same survival as the general population (adjusted for age and gender); with the same survival as the Markov model of patients receiving exa-cel treatment; and with the same survival as the Markov model of patients receiving SoC treatment.

The stptime command in Stata calculates person-time, incidence rates, and SMR using IPD data. Table 16 summarises the output from the stptime command.

Table 16: Estimated person-time and incidence rates using the data shown in Figure 13.

Population	Person-time	Failures	Rate	LCI	UCI
General Population	2610	43	0.016475	0.012219	0.022214
SoC	974.08	43	0.044144	0.032739	0.059523
Exa-cel	2153.64	43	0.019966	0.014808	0.026922
Total	5737.72	129	0.022483	0.018919	0.026717
LCI, lower confidence interval; UCI, upper confidence interval; SoC, standard of care					

These results suggest a SMR of 2.68 for SoC versus age- and gender-adjusted general population; this is outside the range 4.9 to 7.4 and lower than the CS value of 5.21. For exa-cel, stptime delivered an SMR of 1.21. Roessler et al. indicated that SMR values using hospital data are affected by case-mix and that this hampers valid assessment of performance based on SMR values.[70]

The EAG conclude that the CS SMR estimate of 5.21 for SoC is likely incorrect and that the correct SMR is probably outside the range 4.9 to 7.4 that the CS deems reasonable.

Because of assumptions made about complications, particularly chronic complications that are assumed to last until death, and additional other assumptions there is inevitably considerable uncertainty in modelling mortality to the lifetime horizon. As far as EAG can ascertain in the base-case economic modelling such uncertainty has not been incorporated into PSA. This absence has resulted in strikingly bunched PSA scatterplots within the cost-effectiveness plane embedded in the company's economic model and illustrated in Figure 14.

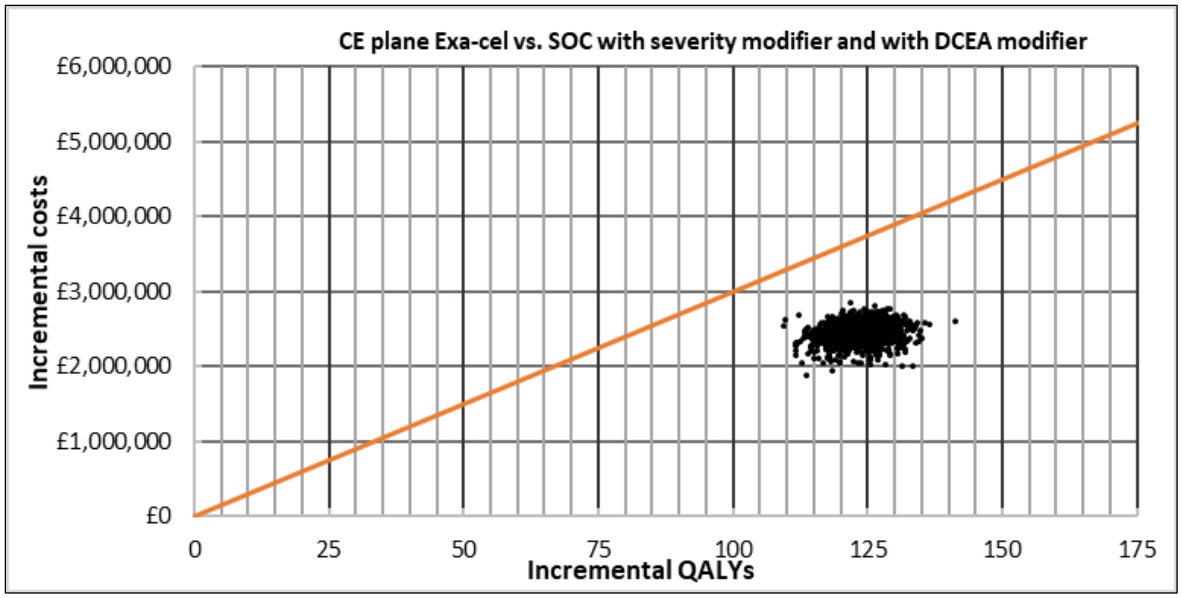


Figure 14: Incremental cost-effectiveness scatterplot for exa-cel compared to SoC with severity modifier and DCEA

This underestimation of uncertainty has in turn resulted in the CS CEAC plots such as in CS Document B Figure 28.

The company employ PSA to explore uncertainty in their economic model. Unusually, the base-case PSA incremental cost-effectiveness plane was absent from CS Document B and was only present embedded in the economic model. In the PSA, all iterations resided in the north-east quadrant and are shown in Figure 14. The span of uncertainty ranges from approximately 110 to 135 incremental QALYs and the mean is reported as 124.15 (CS Document B, Table 65). The mean incremental QALYs are greater than 100 years of perfect health because of the application of adjustments (DCEA and severity modifier).

Since many expected uncertainties are associated with the generation of this result the EAG suspect that uncertainty in incremental QALYs may be underestimated. One potential source of underestimation may be the modelling of overall survival in exa-cel and SoC arms since these are derived from multiple inputs, many obtained from the literature, each susceptible to selection bias and each associated with considerable uncertainty.

When the PSA is run with no discounting, no severity modifier and no DCEA the mean incremental LYs were [redacted] and mean incremental QALYs [redacted]. The 95%CI

associated with the IPD Kaplan-Meier (KM) overall survival are shown in Figure 15. These suggest substantial uncertainty in the difference between arms.

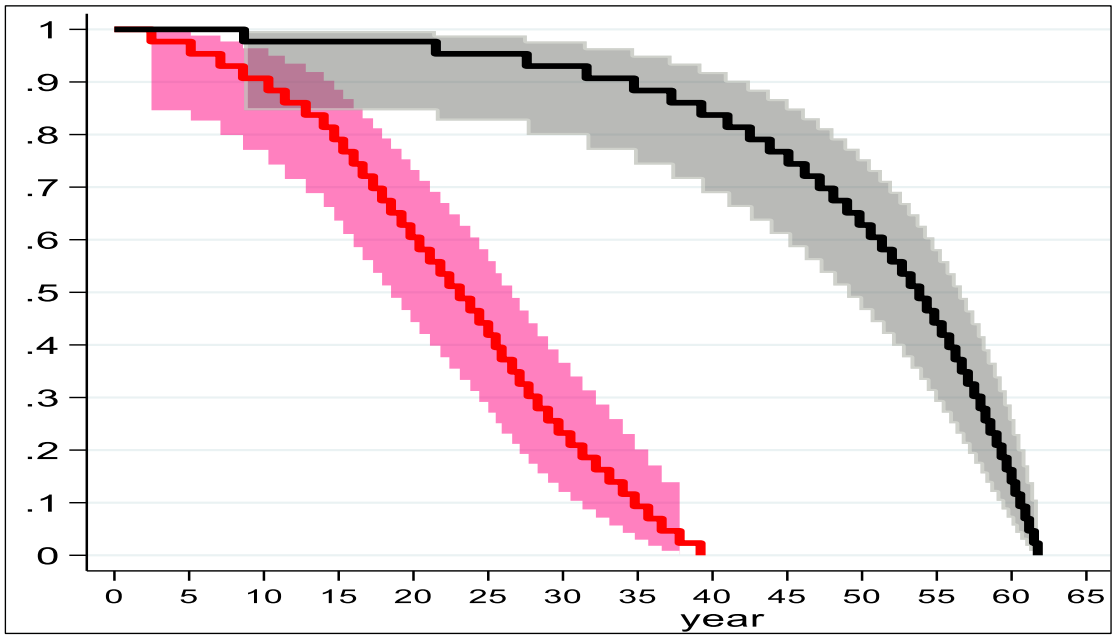


Figure 15: 95% CI associated with IPD KM plots for overall survival (black exa-cel, red SoC)

Figure 16A shows the corresponding PSA LY on an incremental cost-effectiveness plane and the associated mean-centred 95%CI shown as an ellipse. Figure 16B shows the mean-centred 95%CI ellipse based on the IPD KM plots for survival. The mean incremental LYs ([redacted]) is similar to that for the PSA Markov model ([redacted]). However, the uncertainty based on IPD is considerably greater than that associated with the Markov model and suggests the latter is likely an underestimate.

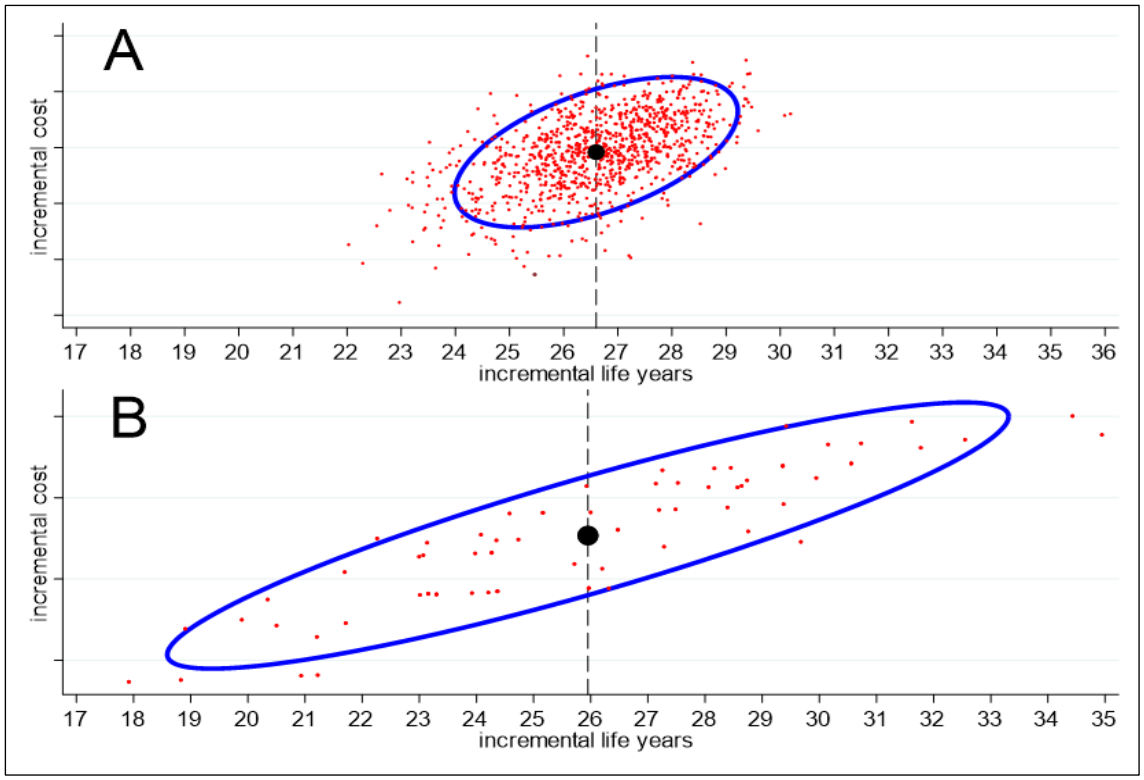


Figure 16: Incremental cost-effectiveness scatterplot displaying incremental life-years for exa-cel compared to SoC, by applying no discounting, severity modifier or DCEA. A: Mean centred 95% CI associated with the company's base case IPD. B: Mean centred 95% CI based on the IPD KM plots shown in Figure 15. *Note: incremental cost has arbitrary units

3.2.10 Resources and costs

[redacted]

The cost of apheresis (plerixafor) is calculated for the average patient not for patient distribution of weight; the company's computation does not include wastage

For plerixafor, the model considers an average weight per patient of 72KG. However, the cost of therapy is dependent on patient weight, similarly to BSA. This weight was calculated by adjusting the dose in each cycle based on the average weight of the SCD cohort adjusted to age. The cost per patient dosed is therefore £5018 and not £3269.6 as per company model. Each patient requires 4 days of plerixafor (£13,078.4 company, £20,071 EAG).

The company calculation of the cost of plerixafor (apheresis) assuming no wastage, is as follows:

- Cost of plerixafor is equal to:
  - plerixafor dose/kg (0.24 mg/kg) * patient weight (67kgs) / plerixafor units per vial (24)
  - Multiplied by plerixafor vial cost (£4,880) and by the number of days on treatment (4).

Therefore, the company calculates the cost of 16mg of plerixafor, equivalent to 0.67 vials, at £3,270 x 4, £13,078.

The correct cost should be calculated based on the distribution of weight for the patient sample, because the distribution determines how much wastage should be included in the cost.

A vial of plerixafor (24mg) can treat a patient of up to 100KG; for heavier patients, 2 vials are necessary. Using the weight distribution from CTX001-121, assuming that weight follows a normal distribution with mean 67kgs, SD 17.3, 93% of patients will be treated with one vial and 3% with 2 vials, resulting in 1.03 vials (including wastage) at a mean price per patient of £5,018, or a total of £20,071 over 4 days.

The total cost of apheresis is inappropriately calculated

The total cost of apheresis in the model is the sum of the cost of plerixafor, of pre-mobilisation costs (£2,554) including costs of fertility preservation, cost of

hospitalisation (£10,749), physician visits (assumed 0). The sum of these cost components is then multiplied by 2.2 average number of apheresis cycles. In the company model, the total of these components amounts to £55,214, whilst in the EAG's recalculation, the total cost is £70,667. The difference is due to the incorrect calculation of the plerixafor cost.

However, the company model applies a cost of £65,685 for mobilisation, adding a factor of £10,471 for the 19% of patients who receive apheresis but do not proceed to exa-cel. The company assumes that all apheresis costs (successful or not) are accrued before exa-cel. Such cost only in part covers the true costs to the NHS but excludes the cost of exa-cel for those people.

Finally, the model includes functionality for repeated apheresis; such value is set to 0; nonetheless, the addition is incorrect because it does not account for the fact that all repeated apheresis must also include the cost of exa-cel.

The model does not correctly account for the cost of supportive blood transfusions given before and alongside exa-cel

The company base-case assumes a cost of transfusions based on clinical opinion, and incorporates the cost of 5 transfusions (3 before and 2 after) exa-cel transplant (Details in Table 17)

Table 17: Transfusion model parameter, excerpt.

Blood transfusion costs	
	Active in model
Number of transfusions per month among SCD patients	0.7
Number of RBC units per administration	10.0
Cost per RBC unit	£260.80
Administration cost per transfusion	£89.6
Staff time	£49.1
Disposables	£40.5

The cost per transfusion applied in the model is £2698 (rounded), £13,800 in total; some people are also assumed to receive transfusions in the 12 months post exa-cel (£313 per month).

Yet, the CLIMB SCD-121 trial prescribes that patients should receive RBC exchange or simple transfusions for at least 8 weeks before mobilisation, to be continued until conditioning (CLIMB SCD-121 CSR, page 29-30). This was because [redacted]. Indeed, failure to receive such transfusions was a protocol deviation in the trial (CLIMB SCD-121 CSR, page 66).

There is no reason to believe that when exa-cel will be administered in clinical practice, supportive transfusions will stop or decrease. Therefore, resource use in the model should be based on trial data rather than clinical opinion; besides, such discrepancy would invalidate efficacy data (engraftment efficacy) as transfusions have a direct impact on VOC rates observed during exa-cel engraftment and follow up.

The CSR does not report the number of transfusions between exa-cel and month 12 but only reduction at 12 months.

The EAG replaced the number of transfusions in the company base case (5) by that reported in the trial (9 annualised number, taken from annualised baseline data from CLIMB SCD-121 mean number of units (not 10 but 11.6, SD 18.5, proportional to weight and clinical status)[71] yielding a similar number of transfusions per month (0.75) applied to 12 months after start of apheresis, to all treatment cohort and 1 month after exa-cel treatment (as per Figure 11-4 , CLIMB SCD-121 CSR, page 77), to those that receive exa-cel only, but a higher cost per transfusion (£1980).

The model should be run as a probabilistic base-case

In this model, key efficacy parameters are assumed 100% - therefore with certainty, either based on clinical opinion or on clinical trial data. These parameters are affected by sampling error (as all parameters from clinical trials) therefore the deterministic base-case overestimates certainty and the base-case is in fact an extreme, generated by the absence of a control and using surrogate endpoints in the study.

In addition, the model uses a 100% efficacy rate for exa-cel. Nonetheless, the trial also reports that two patients had VOCs after exa-cel. This rate, albeit small, should be incorporated in the model as “relapse”.

3.2.11 Severity

The company states that exa-cel meets the criteria for a 1.2x severity modifier at the base-case discount rate of 3.5% and 1.7x at a 1.5% discount rate. The company applied the severity modifier to the incremental QALYs, based on the proportional and QALY shortfall analysis. The QALY shortfall was calculated using the discounted QALYs yielded by the economic model for SoC, which was calculated relative to the age – and gender- matched UK population using the online QALY shortfall tool. In addition to the critique mentioned in Section 1.3.7, calculating a QALY shortfall from the economic model for SoC, which was calculated relative to the age- and gender matched UK population is likely to result in double counting/weighting of differences in QALY associated with lower IMD. Additionally, NICE stipulates that applying absolute and proportional shortfall calculations should include discounting at the reference-case rate, which is 3.5% per annum.

4 COST EFFECTIVENESS RESULTS

4.1 *Company's cost effectiveness results*

The following section presents the company's cost-effectiveness results reported in CS (Document B). The company reported deterministic and probabilistic results, as well as sensitivity and scenario analyses for the comparison between exa-cel versus SoC. Main outcomes are reported in terms of LY and QALY; results are reported in the form of an ICER expressed as cost per LY and cost per QALY.

4.1.1 Company's deterministic base-case results

The company presented a co-base-case that includes severity modifiers and DCEA weighting using 1.5% and 3.5% discount rates, respectively. Considering these modifiers, the ICERs reported were approximately [redacted] (*see* Table 18) and [redacted] per QALY (*see* Table 19), based on 1.5% and 3.5% discount rates, respectively.

Table 18: Deterministic base-case results, using a 1.5% discount rate with/without severity modifier or with/without DCEA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) without severity modifier	ICER with 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]
DCEA, distributional cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years								

Table 19: Deterministic base-case results, using a 3.5% discount rate with/without severity modifier or with/without DCEA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) without severity modifier	ICER with 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]
DCEA, distributional cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years								

4.1.2 Company's PSA results

Probabilistic sensitivity analysis was undertaken for the outcome of cost per QALY only. In PSA, each parameter is assigned a distribution to reflect the pattern of its variation and the ICER results are re-calculated based on randomly selecting values from each distribution. Tabulated PSA results are reported in Table 20 and Table 21 based on 1.5% and 3.5% discount rates, respectively. The EAG notes that PSA results were similar to the deterministic results.

Table 20: PSA results, using a 1.5% discount rate

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) without severity modifier	ICER with 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]
DCEA, distributional cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years								

Table 21: PSA results, using a 3.5% discount rate

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) without severity modifier	ICER with 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]
DCEA, distributional cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years								

Each iteration of the incremental costs and associated incremental QALYs for exa-cel compared to SoC were graphed/plotted on an incremental cost-effectiveness plane as shown in Figure 17, along with corresponding cost-effectiveness acceptability curves (CEAC), as shown in Figure 18 and Figure 19. In Figure 17, these results show that considering the uncertainty about the chosen parameters to be included in the PSA (and along with the distributions), there was little variation in the iterations.

Figure 17:

In Figure 18 and Figure 19, we report the company's CEACs for the comparison between exa-cel based on the severity modifier and DCEA weights at 1.5% and 3.5% discount rates, respectively. These results show that at a willingness-to-pay threshold (WTP) of £30,000 per QALY, exa-cel when compared to SoC has a probability of 1 of being cost-effective, when considering severity modifier and DCEA weighting at 1.5% discount rate. Conversely, at a WTP threshold at £30,000 per

QALY, using a 3.5% discount rate with severity modifier and DCEA weighting, exacel has a [redacted] probability of being cost-effective compared to SoC.

Figure 18: [redacted]

Figure 19: [redacted]

For reasons explained in Section 3.2.9 on mortality (Underestimation of uncertainty in modelling of overall survival in exa-cel and SoC), in Section 3.2.10 (The model should be run as a probabilistic base-case) and not all key input parameters were included in the PSA, the EAG consider that the uncertainty is highly likely to be underestimated and not captured appropriately in the PSA.

4.1.3 Company's sensitivity analyses

Several deterministic one-way sensitivity analyses were undertaken to explore the impact on the ICER (cost per QALY) by making changes to key model input parameters. Parameters were varied according to the lower and upper bounds of their respective 95% CIs or by assuming uncertainty of ±20% of the point estimate where the standard errors or confidence intervals were missing. The results were presented in the form of tornado diagrams. In Figure 20 and Figure 21, the results for the comparison between exa-cel and SoC with severity modifier and DCEA weighting, based on 1.5% and 3.5% discount rate, respectively. These results showed that the assumption of cured sickle cell disease utility value of [redacted] had the greatest impact to the cost per QALY ICER.

Figure 20: [redacted]

Figure 21:

4.1.4 Model validation and face validity check

Several validity checks of the economic analyses were undertaken by the company, which included internal validity, face validity and external validity. Internal validation included cross-checking model inputs, calculations, visual basic code, as well as model structure, data, and assumptions by an independent researcher and health economist. Face validity checks included comparing the model's predicted survival output against real-world estimates. The company acknowledged that due to the limited evidence face validity for exa-cel could not be assessed. The EAG considers that the company's economic model lacks structural face validity as discussed in Sections 3.2.9 and 5.

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG considered that the company's model does not fulfil basic, essential structural face validity, because of the extensive use of non-mutually exclusive death rates which have the consequence of violating the basic Markov assumption of constant number of people in the model. The model does not take the NHS and PSS perspective, in that it excludes outcomes for up to approximately 20% off the relevant model population in the exa-cel arm. The model includes a large range of events based on assumed clinical effectiveness estimates; it is very unclear whether

the model relies on plausible theoretical propositions around which endpoints may or may not be relevant for the modelling of cost-effectiveness of this intervention.

Furthermore, the model is organised in such a way that the results are based on a weighted average of costs and outcomes of four cohorts, “Cured”, “Cured with waning”, “Improved” and “No benefit”. The consolidation of these four groups into the exa-cel and SoC arms is not explained; because of the factual structuring of the model flow, it is very difficult for the EAG to operate adjustments to reflect the critique conducted so far.

5.1 *Exploratory and sensitivity analyses undertaken by the EAG*

The EAG believes that the company’s model structure lacks credibility, because of the violation of basic Markov models assumptions. In addition, the model is hard to modify because all cost calculations are inbuilt in traces, where unit costs are calculated for each costing element. In addition, costs and QALYs for each model arm appear to result from a weighted average of the four clinical modules, yet the methods used to consolidate these data is that of adding each cell from the original four sheets into a cell in the exa-cel or SoC arm. Therefore, any potentially relevant change can only be implemented by means of an extensive rebuilt of the model.

The EAG prefers a model structure that would reflect the basic conventions used in Markov models. In the sections 5.1 to 5.1.2.15, the ERG provides a detailed critique of model parameters and assumptions. However, major changes necessary to improve the face validity of the model are hard to implement. The rebuild of the model using a proper Markov structure and appropriate assumptions regarding the incorporation of the data is recommended.

5.1.1 Potential alternative model structure

When determining a model structure to extrapolate longer-term patient-relevant clinical endpoints, using an intermediate outcome such as VOCs, it is important to determine which outcomes have been shown functionally related to such intermediate outcomes.

The EAG built a model structure that considered relationships between VOCs and clinical endpoints that have at least some bases of evidence. The Shah et al.[63] paper was used to determine which endpoints have at least some evidence of functional

relationships with VOCs, to be able to apply efficacy data from the CLIMB SCD-121 study.

The Shah et al.[63] study provides very little in terms of methodology used to derive risk equations for the five endpoints for which they present evidence of relationships with VOCs (*see* Table 6). However, the study does provide a complete list of predictors that were found significant in the analysis.

Table 22: List of statistically significant predictors of hazard ratios for chronic complications

Dependent variable	Death	ACS	Splenic sequestration	PE	stroke	Pulmonary hypertension
Statistically significant predictors (risk equations not provided)						
By patient characteristics	Age	Age	Age	Age	Age	Age
	Sex	Sex		Sex	Sex	
	Region	Region		Region	Region	
	Race	Race				
By resource use	CCI	Baseline iron chelation	Baseline Hydroxyurea	CCI	CCI	CCI
	Baseline opioid	Folic acid		Opioids	Baseline NSAIDs	Opioids
	NSAID	Baseline transcranial doppler			Iron chelation	Folic acid
	Iron chelating therapy	Baseline all cause HRU			Tricyclic AD	Blood transfusions
					Acetaminophen	All cause HRU
	Baseline all cause HRU				Baseline blood transfusions/pneumococcal vax	
By SCD-related clinical events	Baseline VOC		Baseline pain crisis		Baseline VOCs	
	Follow-up PE	Follow-up PE		PE	PE	Follow up PE
	Stroke			Stroke		Stroke
	Pulmonary hypertension					
				Follow up ACS	Follow up ACS	ACS

Dependent variable	Death	ACS	Splenic sequestration	PE	stroke	Pulmonary hypertension
Statistically significant predictors (risk equations not provided)						
	Baseline neoplasm			Baseline fever	Baseline fever and seizures	
ACS, Acute chest syndrome; HRU, Healthcare resource use; NSAIDS, Non-steroidal anti-inflammatory drugs; PE, Pulmonary embolism; SCD, Sickle cell disease; VOC, Vaso-occlusive crisis;						

The findings from Shah et al.[63] showed that a quantifiable relationship can be drawn as follows (see Figure 22):

1. Baseline VOCs are significant predictors for deaths, splenic sequestration, and stroke only.
2. However, all events are predicted by other SCD-related clinical events:
    a) All events are predicted by pulmonary embolism,
    b) Death, pulmonary embolism, and pulmonary hypertension are predicted by stroke,
    c) Pulmonary embolism, stroke and pulmonary hypertension are predicted by acute chest syndrome,
    d) Death is predicted by pulmonary hypertension.

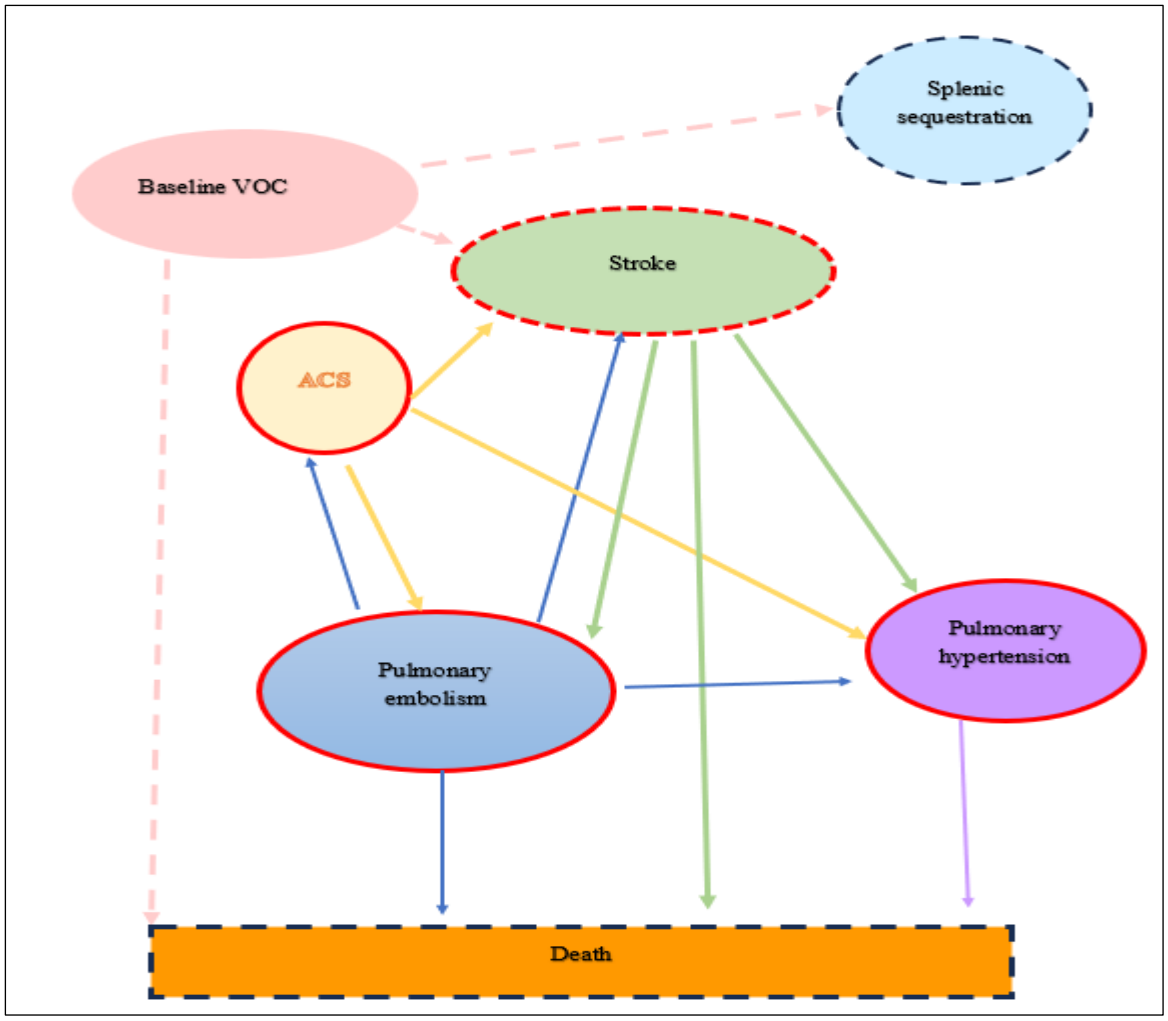


Figure 22: Illustrative structure of the dependency between events from Shah et al (2019)[63]

Figure 22 shows the dependency relationships that can be derived from Shah et al (2019) study.

The Shah et al. data provide clear quantifiable evidence that can be applied to exacel and SoC, via the hazard ratios provided in the study, and can support a Markov structure. An important assumption that underpins this structure is that other relevant patient characteristics, and determinants related with resource use, are applicable to the UK. The EAG acknowledges the limitation, however the impact cannot be verified, since Shah et al.[63] does not provide risk equations that can be used to adjust the hazard to the specific model population for this appraisal. However, this limitation affects all applications of the Shah et al data, which have been extensively relied upon in the company's model.

Two model arms could be modelled:

- Exa-cel
- SOC

Each including clinical events identified by Shah et al (2019).[63]

An important point, the Shah study does not provide a specific coefficient for VOCs at baseline, in other words, it is unclear whether Shah used the number of VOCs as a dichotomous variable in the statistical model (i.e., any VOCs vs No VOCs) or the actual number of events per patient. Because the paper does not provide the specific equation coefficients, there is a need to choose how to apply the rates from the study. This means that in the exa-cel arm, two cohorts should be modelled:

1. People who receive exa-cel, with zero VOCs at the start, and VOCs accrued as time in the model passes as a result of VOC-relapse rates from CLIMB SCD-121,
2. People who do not receive exa-cel, that report a baseline VOCs rate as per the company's model (despite its limitations), and that follow the clinical course of SoC.

In addition, other clinical events in the model (both arms) could be added, external to the Markov structure, but applied as concurrent (non-mutually exclusive) event rates for the following endpoints:

- Heart failure
- Infections [new cases] (assume no cause specific deaths)
- Gallstones
- Leg ulcers
- Avascular necrosis
- Liver complications
- Neurocognitive impairment
- Sickle retinopathy
- VOC rates (recurrence)

VOC rates should be applied independently from other endpoints, as concomitant events. This is because in the SoC arm, the entire cohort reports VOCs. In the exa-cel arm, VOC rates apply to dropouts and relapse rates.

The remaining events can be applied as concomitant events (i.e., non-mutually exclusive) outside the Markov structure, i.e., rates are calculated for the entire alive population, to provide a realistic picture of the burden of disease in the model population. Unlike the company's model, these events should be assumed to not impact mortality because:

1. There is no evidence of quantifiable association, or causal relations that link VOCs to these events other than the fact that they are "concomitant" and as SCD severity increases, so do VOC rates and rates of other events: this does not mean that VOCs and other events are in a causal relationship, as Shah et al[63] clearly show.
2. To avoid the violation of the Markov assumption as in the company's model.

Other clinical manifestations of SCD could be added, yet:

1. As in the company's submission, there are limited data for all other endpoints, in terms of baseline rates and above all, efficacy of exa-cel: there is no evidence that links quantitatively other SCD clinical endpoint to a validated definition of VOCs (however variable)
2. As for "concomitant" events, an attempt to expand the model structure for events not included in the chain of relationships in the Shah study, it is difficult to assume whether these events apply to all the population in the model or not. The attempt to include non-functionally related endpoints in the Markov structure, showed the limitation of the Markov assumption for this population with such high and varied disease burden. When such events become part of the computation of mortality rates, the assumption of mutually exclusive states has to be respected; it also means that these events become "competing events" with respect to the cardiovascular events from Shah,[63] because no variance-covariance matrix can be applied in the model. This means that these events can only be applied to the otherwise "healthy" population state in the model, with the result that as the exa-cel efficacy is incorporated in the model, the" otherwise health" population increases and the rates for these

concomitant events become much higher in the exa-cel arm than in the SoC arm, causing counterintuitive reduction in life years modelled with exa-cel and much higher death rates for these events than in the SoC arm.

5.1.2 Clinical and efficacy parameters

5.1.2.1 Exa-cel transplant

The outcomes of the procedures associated with receipt of exa-cel can be modelled as a simple decision tree based on CLIMB SCD-121 data. The probability of failing to receive exa-cel ([redacted]%) is taken from CLIMB SCD-121.

Table 23: Rates of withdrawal from the exa-cel pathway, CLIMB SCD-121

	Cases withdrawn	Total in CLIMB SCD-121	Percentage, %
Overall	[redacted]	[redacted]	[redacted]
At apheresis	[redacted]	[redacted]	[redacted]
Before conditioning (technical)	[redacted]	[redacted]	[redacted]

An alternative parametrisation can be done based on the mean dose of exa-cel implanted (data from CLIMB SCD-121), which provided a mean dose of [redacted]. The proportion of people who would receive less than the lower bound of the therapeutic range ([redacted]) can be estimated using the log-normal distribution, providing an expected value of [redacted]%.

Figure 23: Exa-cel decision tree schematic

The proportion of people who fail apheresis has been assigned the cost of apheresis only; the proportion who fails to receive exa-cel is assigned the cost of apheresis, the cost of the drug, but not the cost of conditioning and the cost of supportive blood transfusions that are started before conditioning. This is a conservative assumption as it reduces the cost of exa-cel.

At this point, the model population proceeds either into the long-term Markov structure (█%) for exa-cel or to the long-term Markov structure for SoC (█%). (*see* Figure 23)

5.1.2.2 Longer term Markov structure

The longer-term Markov structure is made of a Markov cohort (mutually exclusive states, constant population over time) and a set of clinical events, superposed to the "alive" population of the Markov structure. The latter is made up of non-mutually exclusive states that allow to estimate the major components of the burden of disease for SCD, with no added death rates.

The Markov structure comprises the following clinical events:

- Alive, SCD or otherwise healthy

- Acute chest syndrome
- Pulmonary embolism
- Stroke
- Pulmonary hypertension
- Splenic infarction

Rates for these events, taken from the Vertex BOI study, which provides UK specific rates, and in addition, rates specific to the subgroup in the BOI study that fulfils inclusion/exclusion criteria for the CLIMB SCD-121 trial. This group is termed “12-35 years with no exclusion conditions (Also known as the exa-cel clinical trial like patient population)” in the report.

Table 24: Rate per year (Vertex BOI study, Table 44) Acute complications per-patient per year (PPPY) over the follow-up

Model state	Mean (SD) Vertex BOI study (N=578)	Hazard, with VOCs (from Shah et al (2019)[63]	Probability, per month	
			SoC arm	Exa-cel arm
Strokes	0.01 (0.08)	2.26	0.083%	0.037%
Pulmonary embolism	0.03 (0.21)	2.82	0.250%	0.089%
Acute chest syndrome	0.49 (0.68)	58.67	4.001%	0.070%
Splenic infarction	* (*)	43.99	0.083%	0.002%
Renal failure	0.03 (0.16)	n/a	0.250%	0.250%
Gallstones	0.26 (0.94)	n/a	2.143%	2.143%
Infections (any)	0.21 (1.24)	n/a	1.735%	1.735%
Leg ulcers	0.17 (1.07)	n/a	1.407%	1.407%
BOI, Burden of illness; PPPY, per-patient per-year; SD, Standard deviation; SoC, Standard of care; VOC, Vaso-occlusive crisis				

Table 25: Rate per year (Vertex BOI study, Table 44) Chronic complications per-patient per year (PPPY) over the follow-up

Model state	Rate (100 person-years) Vertex BOI study (N=578)	Hazard, with VOCs (from Shah et al (2019)[63]	Probability, per month	
			SoC arm	Exa-cel arm
Pulmonary hypertension (from chronic complications)	0.730	4.12	0.061%	0.015%
Bone and joint problems (Avascular necrosis)	2.420	n/a	0.201%	0.201%
Liver complications (any)	0.590	n/a	0.049%	0.049%
Neurocognitive impairment	0.560	n/a	0.047%	0.047%
Retinopathy	1.900	n/a	0.158%	0.158%
Heart failure	0.350	n/a	0.029%	0.029%
BOI, Burden of illness; PPPY, per-patient per-year; SD, Standard deviation; SoC, Standard of care; VOC, Vaso-occlusive crisis				

5.1.2.3 VOC rates

The EAG rejected the application of VOC rates in the model as a quantitative predictor of event rates. The application of VOC rates instead can be done as a non-mutually exclusive event rate, used to apply utilities and costs for that event.

The baseline company VOC rate ([redacted] VOCs per year) can be applied in the model to the SoC arm (overall alive population), and in the exa-cel arm, to the proportion of people who did not receive exa-cel and those who relapsed on VOCs. In the exa-cel arm, [redacted] VOCs should be applied consistently with the CLIMB SCD-121 data. The company model applies VOCs rates in the exa-cel arm for the first year only but does not make provisions for VOC relapse rates and relevant costs.

The relapse rate for exa-cel can also be applied to the exa-cel recipients in the exa-cel arm, [redacted]% ([redacted] months follow up), a cycle probability of [redacted]%.

5.1.2.4 Death rates

A range of death rates can be applied to these events, reflecting the possible causes of death for the SCD population.

- General population background mortality can be obtained from ONS data, as applied in the company model.
- In the SoC arm, an increased risk of death should be applied to background mortality rates to adjust for VOCs, so effectively it is framed as “VOC” specific death rates. Following the logic of the analysis from Shah, the HR from the study should be applied to the general mortality rates in the SoC arm and the percentage that do not receive exa-cel in the exa-cel arm, but not in the proportion that receive exa-cel.
- ACS, PE, PH and stroke specific death rates can be applied to the respective states.
- In addition, an SCD specific mortality rate can be applied, as included in the company’s model. This rate is applied to the entire “alive” population but limited to the SoC arm and to the SoC proportion in the exa-cel arm. An alternative SCD mortality rate is also available from the Vertex BOI study ([redacted] deaths in [redacted] person-years)

These rates, and the VOC specific rate applied to general mortality, are the mechanisms by which the therapeutic efficacy of exa-cel can be incorporated into the model, limited to tangible, available evidence. When the HR from Shah et al are applied to the probability of developing each specific complication, the reduction of these rates propagates directly to the probability that the cohort will suffer deaths from each complication (i.e., indirect pathway). A direct reduction in the general mortality rates can also be applied, in relation to the evidence from Shah et al.[63] that absence of VOCs reduces (general) death rates (direct pathway). Finally, the general SCD mortality should be applied in both model cohorts, since there is no hard evidence that death rates for SCD-related causes overall will be reduced; the death rate in Shah et al.[63] is insufficiently characterised or separated from general mortality in the study sample to operate such distinction.

5.1.2.5 Model costs

The model should apply costs to each of the acute and chronic events in the Markov trace, as well as additional therapy costs in the exa-cel arm relating to exa-cel and related procedures.

In both arms, the costs of blood transfusions (supportive peri-procedure transfusions in exa-cel and therapeutic, alongside other therapies, in SoC), as well as the cost of iron chelation regimens, monitoring and terminal care costs should be applied.

5.1.2.6 Cost of apheresis

The cost of cells mobilisation to produce exa-cel should be applied to the entire cohort of people eligible to receive exa-cel, at the time of entry into the model. The cost of apheresis was estimated by the EAG to be £70,667 based on plerixafor units consumed, hospitalisation costs and number of mobilisation cycles. With respect to the company's model, the cost of plerixafor was recalculated using the weight distribution (rather than the cost for the average weight-patient) to account for wastage. Because the cost of apheresis is calculated with formulae directly in the model trace, it is not possible to input an alternative cost in the current model structure.

5.1.2.7 Cost of exa-cel

The cost of [redacted] per dose of exa-cel should be applied in the model to people who were expected to undergo conditioning but didn't because of insufficient exa-cel yield.

5.1.2.8 Cost of hospitalisation associated with exa-cel transplant

The cost of transplant for exa-cel is calculated as the cost of one hospitalisation and the cost of supportive blood transfusions received before and after conditioning.

The cost of hospitalisation in the model is appropriate (£25,387, corresponding to the Elective Inpatient Peripheral Blood Stem Cell Transplant SA26A and SA26B HRG codes, weighted by CLIMB SCD-121 age distribution) as per company's model. The cost of blood transfusions should be estimated using CLIMB SCD-121. This cost differs from that used in the company's model in that the company used clinical opinion on resource use, whilst the EAG prefers to use data from the CSR of CLIMB SCD-121 as the EAG deems unlikely that supportive transfusions will be lower in clinical practice.

5.1.2.9 Cost of hydroxyurea and cost of chelation

The EAG prefers the computation of costs of hydroxyurea and chelation regimens based on the distribution of patients' weight. The company's model uses a rate of

utilisation of approximately 35% whilst the Vertex BOI study [Table 45, page 145] stated that chelation was rarely if not at all used.

The EAG recalculated the costs of the three products used in the company's model to reflect the distribution of patient weight and wastage. The difference between these costs and the costs applied by the company is not large.

5.1.2.10 Monitoring costs

The cost of monitoring SCD applied in the company's model seems appropriate. The cost should be applied to the entire SCD alive cohort, and in addition, to every VOC occurrence (as applied in the SoC and exa-cel cohorts).

5.1.2.11 Cost of terminal care

Terminal care costs was applied in relation to the number of incident deaths in both model arms. A cost of £12,149 per event seems appropriate.

5.1.2.12 Cost of VOCs

The cost of VOCs applied in the model, proportionally to the VOC rate, is appropriate, £1,567 taken from the National Schedule of NHS Cost (SA36A-C, Sickle-Cell Anaemia with Crisis).

5.1.2.13 Costs of longer-term events

Long term acute and chronic events costs in the company's model were derived from standard UK NHS cost sources. The company added the cost of blood transfusions to HRG costs, against the logic that the average HRG costs normally already include all costs pertinent to the episode. The EAG did not correct this deviation as the impact is likely to not alter the main cost-effectiveness conclusions.

5.1.2.14 Model utilities

Model utilities used in the model are reported here below. With respect to data from CLIMB SCD-121, the utility of "alive with exa-cel" should be adjusted (from 0.92 to 0.88) to reflect a less biased selection of data from CLIMB SCD-121.

5.1.2.15 Model extrapolation

All parameters should be applied throughout the model, i.e., extrapolated over the time horizon of the model, which was set to 100 years of age.

5.2 *Impact on the ICER of additional clinical and economic analyses undertaken by the EAG*

The EAG did not undertake any additional analyses using the company's model.

5.3 *EAG's preferred assumptions*

In Table 26, we present a list of or key issues and corresponding preferred assumptions.

Table 26: EAG's preferred model assumptions

Issues, by group	Details	EAG preferred assumption
Company base-case		
The model does not use the NHS-PSS perspective	Model does not account for costs and outcomes of treatment failures between apheresis and myeloablation.	The outcomes of the procedures associated with receipt of exa-cel can be modelled as a simple decision tree based on CLIMB SCD-121 data. The probability of failing to receive exa-cel ([redacted]%) is available from CLIMB SCD-121. The proportion of people who fail apheresis should be assigned the cost of apheresis only; the proportion who fails to receive exa-cel should be assigned the cost of apheresis, the cost of the drug, but not the cost of conditioning.

Issues, by group	Details	EAG preferred assumption
Model structure - The model does not follow a Markov structure	VOC rates used to model complications as non-mutually exclusive states. Death rates are applied to each complication – independently from all other complications; independently from rates of acute events. Rates of chronic complications seem excessive - may be unreliable because of the methods of computation. Rates of mortality may be biased due to computation methods – affected by independent computation of death rates for each complication. Model totals constrained to be 100% by definition, cohort reaches 500% as a result of independently applied death rates. For some computations, the number of VOCs is handled like a probability, i.e., the number (or proportion) of people that experience VOCs, whilst the number is a rate, i.e., mean number of VOCs for people alive in the model. The application of mortality rates for some events is affected by errors	The model structure should be redesigned as a proper Markov structure, with mutually exclusive and exhaustive mortality rates.
Modelling of acute events based on the number of VOCs - entirely speculative	Used as equation term, in contradiction with evidence from sources	VOC rates should not be used as in independent variable in a risk equation but as risk modifier
Modelling of adverse events is partial to exa-cel – very short list and selected events	Whilst the SOC arm has VOCs and events associated with SCD, VOCs, acute chest syndrome and other SCD acute events (infections, catheter infestations etc.) in the exa-cel arm are not appropriately considered, possibly because the company assigned these events to pre-exa-cel period OR considered them as 'non related'. VOC rates in the model are speculative; there are SCD-related complications (VOCs and other) data from the CLIMB SCD-121 trial. AEs also detail which events required treatment – not considered	All AEs from the CLIMB SCD-121 study should be used in the model, particularly when details on resource use are also available VOC data from CLIMB SCD-121 should be used and if excluded, justified.

Issues, by group	Details	EAG preferred assumption
The total cost of apheresis is inappropriately calculated	Cost of apheresis applied as retroactive lump sum including people who do not proceed to conditioning. The cost of plerixafor is calculated for the average patient not for patient distribution of weight; the company's computation does not include wastage	The methods used to incorporate the cost of apheresis and conditioning should be adjusted to incorporate appropriate rates and costs of dropouts; the cost of drugs (plerixafor, iron chelators and hydroxyurea) should be computed using the distribution of patient weight, the model should be able to take alternative total costs for apheresis and drug costs used in the longer term.
The model does not correctly account for the cost of supportive blood transfusions given before and alongside exa-cel	The cost of five transfusions only are included, not representing the administration protocol for exa-cel.	A clarification is required regarding whether supportive transfusions will be part of the therapeutic protocol for exa-cel implantation; such costs should be included in the model fully
Cost of adverse events not considered appropriately		AEs related with exa-cel from CLIMB SCD-121 should be appropriately costed and incorporated in the model.
Underestimation of uncertainty in modelling overall survival in exa-cel and SoC	Distributions not appropriately parameterised PSA not reliable	Distributions should be included in the PSA for all death rates used in the model.
The model should be run as a probabilistic base-case	Efficacy rates of 100% interpreted as 'certain' but the evidence suggests otherwise.	Base case ICER estimates should be probabilistic, i.e., the ratio of mean costs and mean QALYs from the PSA
Inclusion of severity modifier, implementation of 1.5% discount rate and DCEA	Considering these modifiers as they have been applied in the company's base-case is likely to result in double counting.	Base-case ICER estimates using an appropriate severity modifier which is based on 3.5% discount rate.
AE, Adverse events; DCEA, Distributional cost-effectiveness analysis; ICER, Incremental cost-effectiveness ratio; PSA, Probabilistic sensitivity analysis; QALY, Quality adjusted life-years; SCD, Sickle cell disease; SoC, Standard of care; VOC, Vaso-occlusive crisis		

5.4 *Conclusions of the cost effectiveness section*

Because the company's model lacks face validity, the EAG suggests that a model rebuild should be undertaken. The overwhelming number of assumptions around model parameters also provides a challenge in the interpretation of results.

At this time, it is futile to attempt model changes and re-parameterisation, because of the difficulty to assess the resulting changes in the ICER, other than those related with the discount rate. Changes to cost assumptions and efficacy rates are likely to be swamped by flaws in the model structure. Nonetheless, it is observed that,

because all exa-cel costs are supported upfront, the following three factors are likely to drive model results:

- the choice of discount rate has a very large, major impact on the ICER. Such reactivity warrants a careful analysis.
- this also affects the case pro or against the application of severity modifiers.
- the use of DCEA and the value attached to inequality aversion also have a major effect on the company's base-case.

6 References

1. Howard J, Hart N, Roberts-Harewood M, Cummins M, Awogbade M, Davis B. Guideline on the management of acute chest syndrome in sickle cell disease. *British Journal of Haematology* 2015;**169**(4):492-505. http://dx.doi.org/10.1111/bjh.13348

2. National Institute for Health and Care Excellence. *CG143 Sickle cell disease: managing acute painful episodes in hospital*. 2012. URL: https://www.nice.org.uk/guidance/cg143 (Accessed).

3. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, *et al.* Sickle cell disease. *Nat Rev Dis Primers* 2018;**4**:18010. http://dx.doi.org/10.1038/nrdp.2018.10

4. Dormandy E, James J, Inusa B, Rees D. How many people have sickle cell disease in the UK? *J Public Health (Oxf)* 2018;**40**(3):e291-e5. http://dx.doi.org/10.1093/pubmed/fdx172

5. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. *Lancet* 2017;**390**(10091):311-23. http://dx.doi.org/10.1016/s0140-6736(17)30193-9

6. Alsultan A, Ngo DA, Farrell JJ, Akinsheye I, Solovieff N, Ghabbour HA, *et al.* A functional promoter polymorphism of the δ-globin gene is a specific marker of the Arab-Indian haplotype. *Am J Hematol* 2012;**87**(8):824-6. http://dx.doi.org/10.1002/ajh.23239

7. Vertex Pharmaceuticals Inc. Data on file. Exa-cel UK HTA Advisory Board. In; 2022.

8. Udeze C, Ly, N. F., Ingleby, C. et al. Mortality and clinical complications among patients with sickle cell disease with recurrent VOCs in England. *British Journal of Haematology* 2023.

9. Brandow AM, Zappia KJ, Stucky CL. Sickle cell disease: a natural model of acute and chronic pain. *Pain* 2017;**158 Suppl 1**(Suppl 1):S79-s84. http://dx.doi.org/10.1097/j.pain.0000000000000824

10. Nolan VG, Zhang Y, Lash T, Sebastiani P, Steinberg MH. Association between wind speed and the occurrence of sickle cell acute painful episodes: results of a case-crossover study. *Br J Haematol* 2008;**143**(3):433-8. http://dx.doi.org/10.1111/j.1365-2141.2008.07354.x

11. Veluswamy S, Shah P, Denton CC, Chalacheva P, Khoo MCK, Coates TD. Vaso-Occlusion in Sickle Cell Disease: Is Autonomic Dysregulation of the Microvasculature the Trigger? *J Clin Med* 2019;**8**(10). http://dx.doi.org/10.3390/jcm8101690

12. National Haemoglobinopathy Panel (NHP). *National Haemoglobinopathy Panel Guidelines. Available at https://www.nationalhaempanel-nhs.net/nhpguidelines*. 202224 April 2023, 2023).

13. Darbari DS, Wang Z, Kwak M, Hildesheim M, Nichols J, Allen D*, et al.* Severe painful vaso-occlusive crises and mortality in a contemporary adult sickle cell anemia cohort study. *PloS one* 2013;**8**(11):e79923-e. http://dx.doi.org/10.1371/journal.pone.0079923

14. Elmariah H, Garrett ME, De Castro LM, Jonassaint JC, Ataga KI, Eckman JR*, et al.* Factors associated with survival in a contemporary adult sickle cell disease cohort. *Am J Hematol* 2014;**89**(5):530-5. http://dx.doi.org/10.1002/ajh.23683

15. Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. *New England Journal of Medicine* 2017;**376**(16):1561-73. http://dx.doi.org/10.1056/NEJMra1510865

16. Elguero E, Délicat-Loembet LM, Rougeron V, Arnathau C, Roche B, Becquart P*, et al.* Malaria continues to select for sickle cell trait in Central Africa. *Proc Natl Acad Sci U S A* 2015;**112**(22):7051-4. http://dx.doi.org/10.1073/pnas.1505665112

17. Global Health Data Exchange. *GBD Results Tool*. 2019. URL: http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/4de92fcc7248e0cb8937ce7e383e735c (Accessed 7 March 2022).

18. GBD Sickle Cell Disease Collaborators. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000-2021: a systematic analysis from the Global Burden of Disease Study 2021. *Lancet Haematol* 2023;**10**(8):e585-e99. http://dx.doi.org/10.1016/S2352-3026(23)00118-7

19. NHR Information service. *Number of Patients by Diagnosis*. 2019. URL: http://nhr.mdsas.com/wp-content/uploads/2019/04/NumberPatientsDiagnosis.pdf (Accessed 9 March 2022).

20. Kato GJ. Priapism in sickle-cell disease: a hematologist's perspective. *The journal of sexual medicine* 2012;**9**(1):70-8. http://dx.doi.org/10.1111/j.1743-6109.2011.02287.x

21. National Heart Lung and Blood Institute. *Evidence-Based Management of Sickle Cell Disease. Available at https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf*. 2014).

22. Kenyon M, Babic A. The European Blood and Marrow Transplantation Textbook for Nurses. 2018; 10.1007/978-3-319-50026-3. http://dx.doi.org/10.1007/978-3-319-50026-3

23. Wingard JR, Hsu J, Hiemenz JW. Hematopoietic stem cell transplantation: an overview of infection risks and epidemiology. *Infect Dis Clin North Am* 2010;**24**(2):257-72. http://dx.doi.org/10.1016/j.idc.2010.01.010

24. National Health Service. *The National Haemoglobinopathy Register. Available at https://nhr.mdsas.com/*. URL: https://nhr.mdsas.com/ (Accessed 2023).

25. de Montalembert M, Voskaridou E, Oevermann L, Cannas G, Habibi A, Loko G*, et al.* Real-Life experience with hydroxyurea in patients with sickle cell disease:

Results from the prospective ESCORT-HU cohort study. *Am J Hematol* 2021;**96**(10):1223-31. http://dx.doi.org/10.1002/ajh.26286

26. Gardner RV. Sickle Cell Disease: Advances in Treatment. *Ochsner J* 2018;**18**(4):377-89. http://dx.doi.org/10.31486/toj.18.0076

27. Matte A, Zorzi F, Mazzi F, Federti E, Olivieri O, De Franceschi L. New Therapeutic Options for the Treatment of Sickle Cell Disease. *Mediterranean journal of hematology and infectious diseases* 2019;**11**(1):e2019002-e. http://dx.doi.org/10.4084/MJHID.2019.002

28. Rai P, Ataga KI. Drug Therapies for the Management of Sickle Cell Disease. *F1000Research* 2020;**9**:F1000 Faculty Rev-592. http://dx.doi.org/10.12688/f1000research.22433.1

29. European Medicines Agency. *Adakveo (crizanlizumab)*. 2023. URL: https://www.ema.europa.eu/en/medicines/human/EPAR/adakveo (Accessed 13 June 2022).

30. Gragert L, Eapen M, Williams E, Freeman J, Spellman S, Baitty R*, et al.* HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med* 2014;**371**(4):339-48. http://dx.doi.org/10.1056/NEJMsa1311707

31. Day S. *Dictionary for clinical trials*. New York;Chichester;: John Wiley & Sons; 1999.

32. National Institute for Health and Care Excellence. *Exagamglogene autotemcel for treating sickle cell disease*
Final scope. London: National Institute for Health and Care Excellence; 2023. URL: https://www.nice.org.uk/guidance/gid-ta11249/documents/final-scope (Accessed).

33. Vertex Pharmaceuticals Inc. Data on file. Sickle Cell Disease with recurrent VOCs and Transfusion-dependent β-thalassaemia: Economic and Clinical Burden of Disease in England. In; 2023.

34. Robson M, O'Donnell, O., Van Ourti, T. *Aversion to Health Inequality - Pure, Income-Related and Income-Caused*: Tinbergen Institute; 2023.

35. Frangoul H, Altshuler D, Cappellini MD, Chen Y-S, Domm J, Eustace BK*, et al.* CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia. *New England Journal of Medicine* 2020;**384**(3):252-60. http://dx.doi.org/10.1056/NEJMoa2031054

36. Locatelli F, Frangoul H, Corbacioglu S, Fuente J, Wall D, Cappellini MD*, et al.* Efficacy and Safety of a Single Dose of Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease. Paper presented at: 27th Congress of the European Hematology Association (EHA); Virtual.

37. Soni S, Frangoul H, Bobruff Y, Cappellini MD, Corbacioglu S, Fernandez CM*, et al.* Safety and Efficacy of CTX001 in Patients with Transfusion-Dependent β-Thalassemia (TDT) or Sickle Cell Disease (SCD): Early Results from the Climb THAL-111 and Climb SCD-121 Studies of Autologous CRISPR-Cas9-Modified

CD34+ Hematopoietic Stem and Progenitor Cells (HSPCs). *Transplantation and Cellular Therapy* 2021;**27**(3, Supplement):S72-S3. http://dx.doi.org/https://doi.org/10.1016/S2666-6367(21)00101-9

38. de la Fuente J, Locatelli F, Frangoul H, Corbacioglu S, Wall D, Cappellini M*, et al.* 5612617 EFFICACY AND SAFETY OF A SINGLE DOSE OF EXAGAMGLOGENE AUTOTEMCEL FOR TRANSFUSION-DEPENDENT-THALASSEMIA AND SEVERE SICKLE CELL DISEASE. *HemaSphere* 2023;**7**(S1).

39. Vichinsky E, Neumayr L, Gold JI, Weiner MW, Kasten J, Truran D*, et al.* A Randomized Trial of the Safety and Benefit of Transfusion Vs. Standard Care In the Prevention of Sickle Cell-Related Complications In Adults: a Preliminary Report From the Phase II NHLBI Comprehensive Sickle Cell Centers (CSCC) Study of Neuropsychological Dysfunction and Neuroimaging Abnormalities In Neurologically Intact Adult Patients with Sickle Cell Disease. *Blood* 2010;**116**(21):3221. http://dx.doi.org/https://doi.org/10.1182/blood.V116.21.3221.3221

40. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J*, et al.* Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. *N Engl J Med* 2017;**376**(5):429-39. http://dx.doi.org/10.1056/NEJMoa1611770

41. Niihara Y, Miller ST, Kanter J, Lanzkron S, Smith WR, Hsu LL*, et al.* A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. *New England Journal of Medicine* 2018;**379**(3):226-35. http://dx.doi.org/10.1056/NEJMoa1715971

42. Howard J, Ataga KI, Brown RC, Achebe M, Nduba V, El-Beshlawy A*, et al.* Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Haematol* 2021;**8**(5):e323-e33. http://dx.doi.org/10.1016/s2352-3026(21)00059-4

43. Kanter J, Walters MC, Krishnamurti L, Mapara MY, Kwiatkowski JL, Rifkin-Zenenberg S*, et al.* Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease. *N Engl J Med* 2022;**386**(7):617-28. http://dx.doi.org/10.1056/NEJMoa2117175

44. Frangoul H, Bobruff Y, Cappellini MD, Corbacioglu S, Fernandez CM, de la Fuente J*, et al. Safety and Efficacy of CTX001™in Patients With Transfusion-Dependent β-Thalassemia or Sickle Cell Disease: Early Results From the CLIMB THAL-111 and CLIMB SCD-121 Studies of Autologous CRISPR-CAS9-Modified CD34+Hematopoietic Stem and Progenitor Cells*. 2020. URL: https://crisprtx.com/assets/uploads/2020-ASH-Presentation-Frangoul_CTX001-HEME.pdf (Accessed).

45. Grupp S, Bloberger N, Campbell C, Carroll C, Hankins JS, Ho TW*, et al.* CTX001™ for Sickle Cell Disease: Safety and Efficacy Results from the Ongoing CLIMB SCD-121 Study of Autologous CRISPR-Cas9-Modified CD34+ Hematopoietic Stem and Progenitor Cells. Paper presented at: The European Hematology Association; Virtual.

46. Locatelli F, Lang P, Corbacioglu S, Li A, de la Fuente J, Wall D*, et al.* Transfusion Independence and Elimination of Vaso-Occlusive Crises After Exagamglogene Autotemcel in Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease. EHA, abstract no. 579.

47. Frangoul H, Locatelli F, Bhatia M, Corbacioglu S, de la Fuente J, Wall D*, et al.* Efficacy and Safety of a Single Dose of ExagamglogeneAutotemcelfor Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease. ASH, abstract no. 474.

48. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;**52**(6):377-84. http://dx.doi.org/10.1136/jech.52.6.377

49. Vertex Pharmaceuticals Inc. Data on file. CLIMB-131 Interim Clinical Study Report. In; 2022.

50. Hooper P, Jutai JW, Strong G, Russell-Minda E. Age-related macular degeneration and low-vision rehabilitation: a systematic review. *Can J Ophthalmol* 2008;**43**(2):180-7. http://dx.doi.org/10.3129/i08-001

51. Joseph GJ, Latremouille-Viau D, Sharma VK, Gagnon-Sanschagrin P, Bhor M, Khare A*, et al.* Vaso-Occlusive Crises and Costs of Sickle Cell Disease from a Commercial Payer's Perspective. *Blood* 2019;**134**(Supplement_1):3464-. http://dx.doi.org/10.1182/blood-2019-124920

52. Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A*, et al.* A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. *New England Journal of Medicine* 2019;**381**(6):509-19. http://dx.doi.org/10.1056/NEJMoa1903212

53. VanWagner LB, Green RM. Evaluating Elevated Bilirubin Levels in Asymptomatic Adults. *JAMA* 2015;**313**(5):516-7. http://dx.doi.org/10.1001/jama.2014.12835

54. Vertex Pharmaceuticals Incorporated. Data on file - CTX001 SCD PRO Review for MAA D120 Update. In: Vertex Pharmaceuticals Incorporated; 2023.

55. Phillippo D, Ades, T., Dias, S., Palmer, S., Abrams, K. R., & Welton,, Nagalli S. *NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. (Technical Support Documents)*. NICE Decision Support Unit; 2016. URL: https://research-information.bris.ac.uk/ws/portalfiles/portal/94868463/Population_adjustment_TSD_FINAL.pdf (Accessed).

56. Beaudoin F, Richardson M, Richardson M, Synnott P, Lancaster V, Fluetsch N*, et al. Betibeglogene Autotemcel for Beta Thalassemia: Effectiveness and Value; Evidence Report*. Institute for Clinical and Economic Review; 2022. URL: https://icer.org/wp-content/uploads/2021/11/ICER_Beta-Thalassemia_Evidence-Report_060222-1.pdf (Accessed March 1, 2023).

57. Heeney MM, Ware RE. Hydroxyurea for children with sickle cell disease. *Hematol Oncol Clin North Am* 2010;**24**(1):199-214. http://dx.doi.org/10.1016/j.hoc.2009.11.002

58. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV*, et al.* Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med* 1995;**332**(20):1317-22. http://dx.doi.org/10.1056/nejm199505183322001

59. Voskaridou E, Christoulas D, Bilalis A, Plata E, Varvagiannis K, Stamatopoulos G*, et al.* The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). *Blood* 2010;**115**(12):2354-63. http://dx.doi.org/10.1182/blood-2009-05-221333

60. Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Kantor E, Bao Y*, et al.* Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics* 2010;**28**(10):935-45. http://dx.doi.org/10.2165/11538370-000000000-00000

61. Clarivate. *Are Embase and MEDLINE the same?* ; 2021. URL: https://clarivate.com/blog/embase-vs-medline-faq/#:~:text=Embase%20is%20a%20completely%20separate,can%20be%20found%20in%20MEDLINE. (Accessed 6 Nov 2023).

62. National Institute for Health and Care Excellence. *NICE health technology evaluations: the manual*. London: National Institute for Health and Care Excellence; 2022. URL: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation (Accessed).

63. Shah N, Bhor M, Xie L, Halloway R, Arcona S, Paulose J*, et al.* Evaluation of Vaso-occlusive Crises in United States Sickle Cell Disease Patients: A Retrospective Claims-based Study. *J Health Econ Outcomes Res* 2019;**6**(3):106-17. http://dx.doi.org/10.36469/9667

64. Yeruva SL, Paul Y, Oneal P, Nouraie M. Renal Failure in Sickle Cell Disease: Prevalence, Predictors of Disease, Mortality and Effect on Length of Hospital Stay. *Hemoglobin* 2016;**40**(5):295-9. http://dx.doi.org/10.1080/03630269.2016.1224766

65. Institute for Clinical and Economic Review. *Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value*. 2021. URL: https://icer.org/wp-content/uploads/2021/02/ICER_SCD_Evidence-Report_031220-FOR-PUBLICATION.pdf (Accessed 18 March 2022).

66. Singh A, Minniti C. Leg Ulceration in Sickle Cell Disease: An Early and Visible Sign of End-Organ Disease. In: *Sickle Cell Disease - Pain and Common Chronic Complications*; 2016. http://dx.doi.org/10.5772/64234

67. Cahill CR, Leach JM, McClure LA, Irvin MR, Zakai NA, Naik R*, et al.* Sickle cell trait and risk of cognitive impairment in African-Americans: The REGARDS

cohort. *EClinicalMedicine* 2019;**11**:27-33. http://dx.doi.org/10.1016/j.eclinm.2019.05.003

68. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;**13**(5):509-18. http://dx.doi.org/10.1111/j.1524-4733.2010.00700.x

69. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;**12**:9. http://dx.doi.org/10.1186/1471-2288-12-9

70. Roessler M, Schmitt J, Schoffer O. Can we trust the standardized mortality ratio? A formal analysis and evaluation based on axiomatic requirements. *PLoS One* 2021;**16**(9):e0257003. http://dx.doi.org/10.1371/journal.pone.0257003

71. Vertex Pharmaceuticals Inc. Data on file. CLIMB SCD-121 Interim Clinical Study Report. In; 2022.

Title: Exagamglogene autotemcel for treating sickle cell disease- appendix with additional scenarios

Produced by Warwick Evidence

Authors

Jo Parsons, Assistant Professor[1]
Emanuela Castelnuovo, Senior Health Economist[1]
Naila Dracup, Information Specialist[1]
Martin Connock, Honorary Senior Research Fellow[1]
Xavier Armoiry, Honorary Senior Research Fellow and Professor of Pharmacy[1,2,3]
Amy Grove, Professor of Health Technology Assessment and Implementation Science[1]
Peter Auguste, Assistant Professor in Health Economics & Decision Modelling[1]

[1]Warwick Evidence, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, CV4 7AL
[2]Claude Bernard University Lyon, Villeurbanne 69100, France
[3]Lyon University Hospitals- Hôpital Edouard Herriot Pharmacy department, 69003 Lyon, France

Correspondence to

Mr Peter Auguste
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry, CV4 7AL.

Date completed 01/12/2023

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/60/84.

Declared competing interests of the authors

Description of any pecuniary relationship with sponsors, both personal and of the TAR Centre. If there are none, please state 'none'.

Acknowledgements

We would like to thank Professor Baba PD Inusa, consultant paediatric haematologist, King's College, London and Dr Elizabeth Rhodes, consultant haematologist, St. George's University Hospitals NHS Foundation Trust who provided clinical support. Emeritus Professor Aileen Clarke, Professor of Public Health, and Health Services research, University of Warwick who quality assessed the EAG report.

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.

This report should be referenced as follows:

Parsons J, Castelnuovo E, Dracup N, Connock M, Armoiry X, Auguste P. Exagamglogene autotemcel for treating sickle cell disease, Warwick Evidence, 2023: A Single Technology Appraisal.

Contributions of authors

Jo Parsons (Assistant Professor), Martin Connock (Honorary Senior Research Fellow), Xavier Armoiry (Honorary Senior Research Fellow and Professor) and Amy Grove (Professor) reviewed and critiqued the clinical effectiveness evidence. Martin Connock reviewed and critiqued the statistics and undertook any additional statistical analyses. Xavier Armoiry reviewed and critiqued the mixed treatment comparisons. Naila Dracup (Information Specialist) critiqued the company's searches and undertook additional searches. Emanuela Castelnuovo reviewed and critiqued the cost-effectiveness evidence and undertook additional economic analyses. Baba Inusa (Paediatric Haematologist) and Elizabeth Rhodes provided expert clinical advice. Peter Auguste (Assistant Professor) reviewed the cost-effectiveness evidence and co-ordinated the project and the report.

Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

Table of Contents

Table of Tables

Table of Issues

No table of figures entries found.

Table of Figures

Content of appendix

In this appendix we outline the EAG's concerns with regards to the company's not related to the company's Markov structure and Markov structural concerns. The structure of this appendix is as follows:

- Concerns not related to Markov structural concerns.
- Impact of non-Markov structural changes to the company's base-case results (without severity modifier)
- Concerns related to the company's Markov structure.
- Changes related to the Markov structure and their impact to ICER

The EAG implemented two groups of changes / modifications:
One set of changes concerns parameters or assumptions that are not related with the Markov structure of the model. These changes affect cost calculations for some drugs, costs and outcomes for the exa-cel cohort and choice of discount rate. These changes have been operated keeping the ***structure of the model as is***. They should be understood not as the EAG base-case but rather, as possible illustrations of the reactivity of the ICER to parameters changes. They remain affected by the overall lack of validity of the model structure.

The second set of changes were an attempt to assess the reactivity of the model structure to changes in the features that the EAG believes inappropriate. These changes should not be interpreted as "fixes" to make the model structure valid; rather, they are a way to test the severe inadequacies highlighted by the EAG, or a way to illustrate why the EAG deems the model structure invalid. Some of these changes show that under the current structure, the model displays behaviours that are hard to interpret. The EAG obtained some indicative ICERs, that at best help to understand the direction of the cost-effectiveness analysis should a proper Markov structure be implemented. In view of the additional analyses undertaken, the EAG reiterates that the model structure appears invalid for the purposes of this STA.

1.1 *Concerns not related to Markov structural issues*

The EAG expressed concerns regarding the following features / model choices:

- Exclusion of 19% of people who received apheresis but not exa-cel
- Exclusion of exa-cel costs for those who have insufficient cells yield.
- Cost of plerixafor (used during apheresis) calculated for the average patient (72kgs in originals model, weight increases in time up to 83kgs, then decreases).

- Cost of blood transfusions with exa-cel and SoC as per Vertex burden-of-illness study.
- Cost of chelation and other drugs calculated by average weight (as for plerixafor).
- Utility for alive state selected- higher than that reported in trial.
- Discount rate of 1.5% on both costs and benefits

1.1.1 Impact of non-related changes to Markov structure to company's results

In Table 1, we report the EAG unrelated to the Markov structure and their impact to the company's base-case results. Results are based on excluding the severity modifier. Considering these cumulative change results in an ICER of approximately [redacted] per QALY.

Table 1: Impact of EAG non-Markov structural changes related to company's base-case results, without severity modifier

Issues, parameters and non-related with Markov structural issues	EAG changes	Company's ICER	Change in company's ICER, vs company's base case	
Base case, company	-	[redacted]	in £	%
Base case, company, updated with EMIT prices	-	[redacted]	[redacted]	[redacted]
Exclusion of 19% people who receive apheresis but not exa-cel	Addition of outcomes for dropouts, who are assigned costs and outcomes as in SoC	[redacted]	[redacted]	[redacted]
Exclusion exa-cel costs for those (approximately 10%) who have insufficient cells yield	Addition of costs of exa-cel for those who do not receive conditioning	[redacted]	[redacted]	[redacted]
	• Minor issue: use of distribution to assess the probability of not having viable quantities of exa-cel (using log normal for CD4+m/kg) - EAG preferred: use in distribution	[redacted]	[redacted]	[redacted]
	Addition of blood transfusion costs for those who do not receive conditioning (exa-cel)	[redacted]	[redacted]	[redacted]
Cost of apheresis calculated for the average patient (72kgs in original model, weight increases in time up to 83kgs then decreases again)	Recalculation of cost of apheresis, using weight distribution for plerixafor	[redacted]	[redacted]	[redacted]
Cost of blood transfusions with SoC as per Vertex BOI study	Recalculation of blood transfusion frequency	[redacted]	[redacted]	[redacted]
Costs of chelation and other drugs calculated by (increasing) average weight	By weight distribution, constant weight	[redacted]	[redacted]	[redacted]
Utility for alive state selected - higher than that reported in trial	Use of trial utility value at 12 months (as per use of VOC rates as in primary endpoint in CLIMB SCD-121)	[redacted]	[redacted]	[redacted]
Discount rate set to 1.5%	Discount rate set to 3.5%	[redacted]	[redacted]	[redacted]
Total, Cumulative changes to company's base case			[redacted]	[redacted]

EAG, Evidence assessment group; ICER, Incremental cost-effectiveness ratio; SCD, Sickle cell disease; SoC, Standard of care; VOC, vaso-occlusive crisis

1.2 *Concerns related to the Markov structure*

The following section presents the issues identified by the EAG with the company's Markov structure.

- Imposed mortality constraints to make cohort 100% over time.
- No rationale for the choice of which sickle cell disease complications are included (e.g., splenic infarction has data but was not considered in the structure)
- States for which there is no evidence of baseline rate and treatment effect – treatment effects are mutated across clinical states with no underpinning clinical rationale – example: is it clinically valid to apply the hazards of pulmonary embolism to clinical events such as "gallstones" and "neurocognitive impairment"?
- Use of vaso-occlusive crisis as a risk equation predictor
- Exclusion of relapse rate. A similar issue concerns the assumption of lifetime benefits with exa-cel.

1.2.1 Impact of changes related to Markov structural issues

In Table 2, we outline the Markov structural issues and the cumulative impact on addressing these changes.

Table 2: Changes related to the Markov structure and impact to company's results

EAG concerns	Concerns explained	Proposed implementation with given model structure	Impact
Starting from cumulative parameter changes (in company's model) (see Table 1)	-	All changes implemented in Table 1	[redacted]
Imposed mortality constraints to make cohort 100% over time.	The ICER reflects alive states that go negative, and consequently, rates of complications that go negative. This means that removing clinical health states (i.e., gallstones, infections etc..) not based on evidence may have an unpredictable effect improving the ICER (i.e., negative utility weight become positive, costs become negative), although for the chronic states this did not happen (see below).	Replace the constraint formula applied to mortality rates in the model.	[redacted]
No rationale for the choice of which sickle cell disease complications are included (e.g., splenic infarction has data but was not considered in the structure)	Most complications are included based on assumptions Splenic infarction can happen in children (literature case reports). The company has done no work in term of locating relevant literature or addressing this endpoint using perhaps clinical opinion.	None	Qualitative issue
States for which there is no evidence of baseline rate and treatment effect – treatment effects are mutated across clinical states with no underpinning clinical rationale – example: is it clinically valid to apply the hazards of pulmonary embolism to clinical events such as "gallstones" and "neurocognitive impairment"?	**Corrective changes should be in the direction of eliminating states for which evidence is not available or clinical opinion has not been sought.** The ICER resulting from the EAG modifications should not be interpreted to mean that this change is favouring SoC, because complication rates in exa-cel are set to zero by definition in the exa-cel-treated in the company's model; as a result, event rates improve, because the EAG added to the exa-cel arm a 19% proportion of people that .turn to SoC as they fail the apheresis-conditioning process in the exa-cel arm. Conversely, outcomes in the SoC arm are heavily driven by longer term complications so SoC picks up the largest benefit from this change. The decrease in event rates in SOC is also not inclusive of chronic states, so likely underestimated	**Issue pertaining to evidence.** The EAG has attempted to delete some of these states (e.g., infections, AKI, gallstones, leg ulcers, CKD) from the model setting the relevant state occupancy to 0s throughout in the exa-cel and SoC arms/acute complications only. This approach could be taken for all chronic events – the impact on the ICER seems to increase (caveated with the rates of people alive becoming positive)	[redacted]
Use of vaso-occlusive crisis as a risk equation predictor	The modification is made challenging because of company's model methods. All states' hazards at baseline and for treatment are geared up with the rate of VOCs embedded in		[redacted]

EAG concerns	Concerns explained	Proposed implementation with given model structure	Impact
	the traces' formulae. Replacing the number of VOCs (0.035 per cycle) with 1 (as is logical, given the use as if in a risk equation) decreases the ICER. Setting this parameter to zero makes the ICER shoot up to [redacted] because the company geared up the VOC rate as a probability and included a term for those who have no VOCs in the "cured" state. This means that one term of the equation serves to apply the baseline rate of events to all the population (1-cohort_m_bvoc) but this also has the effect of setting to zero all acute events in the exa-cel arm, and by reflection to set to zero all biases in the mortality rates underpinning the model. Overall, it is unclear what the differential impact of each of these separate effects amount to, this modification should be taken with extreme care. In addition, this modification is not sufficient to address the mortality issue in the model, which remains affected by overestimation based on background death rates and SCD-specific rates; this also confirms that a quick fix of mortality is unlikely to be feasible or useful given the model structure.		
Exclusion of relapse rate. A similar issue concerns the assumption of lifetime benefits with exa-cel.	-	This requires a time-dependent modification to the model structure, to add rates of people that enter SoC as they relapse or as they lose response. This is very time consuming. The likely impact is that the ICER will increase.	-
AKI, Acute kidney injury; CKD, Chronic kidney disease; EAG, Evidence assessment group; ICER, Incremental cost-effectiveness ratio; SCD, Sickle cell disease; SoC, Standard of care; VOC, vaso-occlusive crisis			

In Figure 1 and Figure 2, we show the cumulative model outputs for people who are alive/dead, in the exa-cel arm and SoC arm, respectively. Vertical axis displaying the percentage of people alive/dead in the model and the horizontal axis is age.

Figure 1:

Figure 2:

As a result of alive state occupancy that goes negative, chronic complication rates (shown in Figure 3 and Figure 4, for exa-cel and SoC, respectively) also goes to negative (i.e., when death rates go above 100%). This occurs around the age of [redacted] years of age in the model for SoC and [redacted] years of age in the model for exa-cel.

Figure 3:

Figure 4: [redacted]

Title: Exagamglogene autotemcel for treating sickle cell disease- appendix of the company base-case results using NICE preferred prices

Produced by Warwick Evidence

Authors

Jo Parsons, Assistant Professor[1]
Emanuela Castelnuovo, Senior Health Economist[1]
Naila Dracup, Information Specialist[1]
Martin Connock, Honorary Senior Research Fellow[1]
Xavier Armoiry, Honorary Senior Research Fellow and Professor of Pharmacy[1,2,3]
Amy Grove, Professor of Health Technology Assessment and Implementation Science[1]
Peter Auguste, Assistant Professor in Health Economics & Decision Modelling[1]

[1]Warwick Evidence, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, CV4 7AL
[2]Claude Bernard University Lyon, Villeurbanne 69100, France
[3]Lyon University Hospitals- Hôpital Edouard Herriot Pharmacy department, 69003 Lyon, France

Correspondence to

Mr Peter Auguste
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry, CV4 7AL.

Date completed 01/12/2023

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/60/84.

Declared competing interests of the authors

Description of any pecuniary relationship with sponsors, both personal and of the TAR Centre. If there are none, please state 'none'.

Acknowledgements

We would like to thank Professor Baba PD Inusa, consultant paediatric haematologist, King's College, London and Dr Elizabeth Rhodes, consultant haematologist, St. George's University Hospitals NHS Foundation Trust who provided clinical support. Emeritus Professor Aileen Clarke, Professor of Public Health, and Health Services research, University of Warwick who quality assessed the EAG report.

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.

This report should be referenced as follows:

Parsons J, Castelnuovo E, Dracup N, Connock M, Armoiry X, Auguste P. Exagamglogene autotemcel for treating sickle cell disease, Warwick Evidence, 2023: A Single Technology Appraisal.

Contributions of authors

Jo Parsons (Assistant Professor), Martin Connock (Honorary Senior Research Fellow), Xavier Armoiry (Honorary Senior Research Fellow and Professor) and Amy Grove (Professor) reviewed and critiqued the clinical effectiveness evidence. Martin Connock reviewed and critiqued the statistics and undertook any additional statistical analyses. Xavier Armoiry reviewed and critiqued the mixed treatment comparisons. Naila Dracup (Information Specialist) critiqued the company's searches and undertook additional searches. Emanuela Castelnuovo reviewed and critiqued the cost-effectiveness evidence and undertook additional economic analyses. Baba Inusa (Paediatric Haematologist) and Elizabeth Rhodes provided expert clinical advice. Peter Auguste (Assistant Professor) reviewed the cost-effectiveness evidence and co-ordinated the project and the report.

Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

Table of Contents

Table of Tables

Table of Issues

No table of figures entries found.

Table of Figures

Content of appendix

The company's economic analyses use the list prices in the base-case. In this appendix all analyses include using the eMIT prices that are in place for comparator and other treatment-related costs. Where there are eMIT prices available, the EAG will use the list price. The appendix is structure as follows:

- Re-run of the company's base-case analyses, as well as the main sensitivity analyses (including probabilistic sensitivity analysis) based on the NICE preferred prices.

Given the concerns raised by the EAG about the company's economic model, these analyses do not reflect the EAG's validation of the company's model but simply a re-run of the company's model using commercial agreements.

1.1 *Cost effectiveness results*

The following section presents the cost-effectiveness results using eMIT prices in place. The company reported deterministic and probabilistic results, as well as sensitivity and scenario analyses for the comparison between exa-cel versus Soc. Main outcomes are reported in terms of LY and QALY; results are reported in the form of an ICER expressed as cost per LY and cost per QALY.

1.1.1 Deterministic base-case results

The company presented a co-base-case that includes severity modifiers and DCEA weighting using 1.5% and 3.5% discount rates, respectively. Considering these modifiers, the ICERs reported were approximately [redacted] (*see* Table 1) and [redacted] per QALY (*see* Table 2), based on 1.5% and 3.5% discount rates, respectively.

Table 1: Deterministic base-case results, using a 1.5% discount rate with/without severity modifier or with/without DCEA and eMIT and prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) without severity modifier	ICER with severity modifier
Standard of care	£347,943	18.70	10.71	-	-	-	-	-
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted incremental results				[redacted]		[redacted]	[redacted]	[redacted]
DCEA, distributional cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years								

Table 2: Deterministic base-case results, using a 3.5% discount rate with/without severity modifier or with/without DCEA and eMIT and prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) without severity modifier	ICER with severity modifier
Standard of care	£276,831	15.15	8.94	-	-	-	-	-
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted incremental results				[redacted]		[redacted]	[redacted]	[redacted]
DCEA, distributional cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years								

1.1.2 PSA results

Probabilistic sensitivity analysis was undertaken for the outcome of cost per QALY only. In PSA, each parameter is assigned a distribution to reflect the pattern of its variation and the ICER results are re-calculated based on randomly selecting values from each distribution. Tabulated PSA results are reported in Table 3 and Table 4 based on 1.5% and 3.5% discount rates, respectively. The EAG notes that PSA results were similar to the deterministic results.

Table 3: PSA results, using a 1.5% discount rate and eMIT and prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) without severity modifier	ICER with severity modifier
Standard of care	£345,121	18.49	10.63	-	-	-	-	-
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted incremental results				[redacted]		[redacted]	[redacted]	[redacted]
DCEA, distributional cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years								

Table 4: PSA results, using a 3.5% discount rate and eMIT and prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) without severity modifier	ICER with severity modifier
Standard of care	£284,035	15.00	8.87	-	-	-	-	-
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted incremental results				[redacted]		[redacted]	[redacted]	[redacted]
DCEA, distributional cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years								

Each iteration of the incremental costs and associated incremental QALYs for exa-cel compared to SoC were graphed/plotted on an incremental cost-effectiveness plane as shown in Figure 1, along with corresponding cost-effectiveness acceptability curves (CEAC), as shown in Figure 2 and Figure 3. In Figure 1, these results show that considering the uncertainty about the chosen parameters to be included in the PSA (and along with the distributions), there was little variation in the iterations.

Figure 1:

In Figure 2 and Figure 3, we report the CEACs for the comparison between exa-cel based on the severity modifier and DCEA weights at 1.5% and 3.5% discount rates, respectively. These results show that at a willingness-to-pay threshold (WTP) of £30,000 per QALY, exa-cel when compared to SoC has a probability of [redacted] of being cost-effective, when considering severity modifier and DCEA weighting at 1.5% discount rate. Conversely, at a WTP

threshold at £30,000 per QALY, using a 3.5% discount rate with severity modifier and DCEA weighting, exa-cel has a [redacted] probability of being cost-effective compared to SoC.

Figure 2: [redacted]

Figure 3: [redacted]

1.1.3 Sensitivity analyses

Several deterministic one-way sensitivity analyses were undertaken to explore the impact on the ICER (cost per QALY) by making changes to key model input parameters. Parameters were varied according to the lower and upper bounds of their respective 95% CIs or by assuming uncertainty of ±20% of the point estimate where the standard errors or confidence intervals were missing. The results were presented in the form of tornado diagrams. In Figure 4 and Figure 5, the results for the comparison between exa-cel and SoC with severity modifier and DCEA weighting, based on 1.5% and 3.5% discount rate, respectively. These results showed that the assumption of cured sickle cell disease utility value had the greatest impact to the cost per QALY ICER.

Figure 4:

Figure 5:

ERG Summary

Using the company's model and assumptions with the pricing agreements, the deterministic results generated approximate ICERs between [redacted] to [redacted] per QALY, under the 1.5% discount rate and under the 3.5% discount rate ICERs between [redacted] to [redacted] per QALY.

Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

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 20 November** 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 information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Short follow-up of trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Inconsistency between statements reporting duration throughout document: (i.e., previous sections state that results *>12 months* are limited by small sample size numbers, whereas Section 2.2.2.3, pg 56 states: *'Interpretation of results beyond Month 24 is severely limited by small sample size.')*	EAG to update wording to ensure consistency on duration throughout	Alignment of wording required to ensure consistency. We propose use of *Interpretation of results beyond Month 24 is severely limited by small sample size.', given that the sample size at Month 12 and Month 15 is the same, and so use of Month 12 is not appropriate.*	The EAG do not consider this to be a factual error, and do not feel that it merits a change to the EAG report. All analyses are limited by small sample size irrespective of timing of analyses.

Issue 2 CLIMB SCD-131

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Executive Summary, Section 1.4, pg 19, the EAG states that: *'Currently, CLIMB SCD-131 is hardly relevant for the decision problem.'*	Clarification of why CLIMB-131 study is not relevant for the decision problem.	A total of 13 patients were in the CLIMB-131 study at the time of the D120 data cut-off, providing longer-term follow up data for the efficacy and safety of exa-cel. Therefore, it is unclear as to why CLIMB-131 is considered not relevant.	"CLIMB SCD-131" is only mentioned three times in CS document B

Issue 3 Representation of severe SCD definition and associated co-morbidities

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Definition of severe SCD missing - Section 1.1.1, pg 31: *'The mean age of death in the UK amongst patients with severe SCD is 40.2 years.'*	Suggest addition of the following: *'The mean age of death in the UK amongst patients with severe SCD is 40.2 years.* ***Patients with at least 2 VOCs per year for two consecutive years were classified as having severe SCD****.'*	Clarification of severe SCD definition to ensure alignment throughout response	The EAG considers that this is unimportant. No change made. Two VOCs per year is synonymous with severe SCD.

Issue 4 Critique of company's definition of decision problem

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, pg 33: *'At the time of writing Marketing authorisation has yet to be granted and it is not known if the proposed MHRA authorisation will be adopted. Irrespective of the defined population, alignment with marketing authorisation is not yet established.'*	Update paragraph with ***'marketing authorisation has been granted'*** and ensure this is reflected throughout report.	MHRA recently granted marketing authorisation for exa-cel in the UK.	The EAG do not consider that this is a factual error; The MHRA was made on 16th November 2023, after the EAG report deadline. The EAG retain this wording.
Section 1.3.1, pg 34: *'Given that VOC definitions vary, as do concepts of SCD severity, multiple selections of patients might satisfy such criteria. Results emanating from several data sets are presented in the submission. The company consider the FAS encompassing 43 individuals is adequate for decision making.'*	Suggest rewording to provide further clarity on VOC definition and SCD severity (i.e., listing CLIMB SCD-121 trial inclusion criteria).	There were strict trial inclusion criteria to define VOC and SCD severity. Whilst we agree that VOC definitions can vary, within the CLIMB SCD-121 trial, they are fully defined in the trial inclusion criteria.	Unimportant. No change.
Incorrect statement (missing relevant information) – Section 1.3.1, pg 34: 'CS states *"In the UK only 24 SCD*	Suggest rewording statement to match pg 39 of EAG report which states: *'pg. 52 states "The total number of patients with all haemoglobinopathies to undergo allo-SCT in the UK in 2021 was just 36,*	The year '*2021*' is omitted from the EAGs statement which is highly relevant in relation to the statement provided, in the context of the COVID	No factual error. No change made

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
patients, the majority likely paediatric, have received allo-SCT" implying indeed that very few UK adult severe SCD patients would have a matched donor.'	*including 24 SCD patients, the majority of which are likely to have been paediatric (134).'*	pandemic and implications for procedures.	

Issue 5 Clarity on population fit for exa-cel treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3.1, pg 34: *'The company suggest (CS Document B pg. 53 Figure 10 "Epidemiological cascade for SCD in the UK") that 1750 ([redacted]%) of 2,150 UK severe SCD patients fit for exa-cel treatment would lack a matched HLA donor.'*	Suggest rewording to: *'The company suggest (CS Document B pg. 53 Figure 10 "Epidemiological cascade for SCD in the UK") that 1750 ([redacted]%) of 2,150 UK severe SCD patients fit for exa-cel treatment would* ***have no*** *matched HLA donor.'*	The phrase *'would lack a matched HLA donor'* implies that a suitable donor is likely to become available in the future, whereas exa-cel is for those with no suitable donor available.	No factual error, unimportant. No change
Section 1.3.1, pg 34: *'In view of the low number of UK allo-SCT interventions performed and the NHS perspective of the analyses, in EAG opinion [redacted]% is likely a considerable overestimate.'*	Suggest correction to: *'In view of the low number of UK allo-SCT interventions performed and the NHS perspective of the analyses, in EAG opinion [redacted]% is likely a considerable overestimate* ***of the number of patients who have a matched HLA donor****.'*	To provide clarity on '*a considerable overestimate*' and what this relates to.	No factual error, unimportant. No change

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3.1, pg 34: '*This seems a very small number relative to the 1,750 itemised in the burden-of-illness (BoI) study in CS Figure 10, and in the context of the company's equity concerns and DCEA approach appears disappointingly low.'*	EAG to correct as follows: '*This seems a very small number relative to the 1,750 itemised in the **epidemiological cascade** in CS Figure 10, and in the context of the company's equity concerns and DCEA approach appears disappointingly low.'*	Incorrect reference to '*burden-of-illness (BoI) study*'.	Thank you. We have amended to the suggested text.

Issue 6 Safety analysis endpoints

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3.4, pg 36: *'CS Section B2.4.3.4 "Safety analysis" lists "Mortality, including all-cause mortality and transplant-related mortality" as "endpoints". Results for these outcomes seem absent from the submission.'*	Suggest rewording to: *'CS Section B2.4.3.4 "Safety analysis" lists "Mortality, including all-cause mortality and transplant-related mortality" as "endpoints". Results for these outcomes seem absent from the submission, **except those for transplant-related mortality.**'*	Results for transplant-related mortality were detailed in submission based upon data from CLIMB SCD-121: *'Patients treated with exa-cel were assumed to have no risk of 100-day transplant-related mortality based on the CLIMB SCD-121 FAS data, where no patients experienced treatment-related death.'*	Thank you. We have amended to the suggested text.

Issue 7 Definition of primary efficacy and key secondary efficacy outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incorrect definition of primary efficacy outcome. Section 1.3.4, pg 37: *'The EAG notes that the primary/key efficacy outcome or endpoint in CLIMB SCD-121 was the proportion of patients that achieved VF12, defined as freedom from VOCs for twelve months after the last RBC transfusion support.'*	EAG to update their definition of the primary outcome with the following rewording: *'The EAG notes that the primary/key efficacy outcome or endpoint in CLIMB SCD-121 was the proportion of patients that achieved VF12, defined as* ***absence*** *from* ***severe*** *VOCs for* ***at least*** *twelve months* ***after exa-cel infusion. Patient evaluation starts 60 days after the last RBC transfusion for post-transplant support or SCD management.****'*	Alignment of VF12 definition with company submission for clarity.	No factual error The EAG report mentions the 60-day provision later in the EAG text.
Section 2.2.1, pg 48: *'…key secondary endpoint of proportion of patients free from inpatient hospitalisation for severe VOCs (HF12) were measured with the PES, and all other efficacy endpoints were measured with the FAS.'*	Suggest correction to: *'…key secondary endpoint of proportion of patients free from inpatient hospitalisation for severe VOCs* ***for at least 12 months after exa-cel infusion*** *(HF12) were measured with the PES, and all other efficacy endpoints were measured with the FAS.'*	Alignment of HF12 definition with company submission.	No factual error These are different ways of expressing the same thing.
Section 2.2.2.1, pg 53: *"'…defined as free from (VOC or hospitalisation)…".'*	Correct to: *"'…defined as free from (****severe*** *VOC or* ***inpatient*** *hospitalisation)…".'*	Alignment of VF12 and HF12 definitions with company submission.	Text changed to '*defined as free from (****severe*** *VOC or* ***inpatient*** *hospitalisation)…".*

Issue 8 Critique of trials of the technology of interest, the company's analysis and interpretation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2, pg 47: *'The clinical evidence presented in the CS for the efficacy and safety of exa-cel was obtained by one source, the CLIMB SCD-121 study. CLIMB SCD-121 was a Phase 1/2/3 single-arm, open-label, multi-site, single-dose study.'*	Suggest correction to: *'The clinical evidence presented in the CS for the efficacy and safety of exa-cel was obtained from **two sources**, the CLIMB SCD-121 study **and CLIMB-131 study**. CLIMB SCD-121 is an **ongoing** Phase 1/2/3 single-arm, open-label, multi-site, single-dose study. **CLIMB-131 is a multi-site, open-label, Phase 3 rollover study.**'*	CLIMB SCD-121 is not completed and is still ongoing. Clinical evidence obtained from two sources, CLIMB SCD-121 and CLIMB-131.	Text changed to read *'The clinical evidence presented in the CS for the efficacy and safety of exa-cel was obtained from **two sources**, the CLIMB SCD-121 study **and CLIMB-131 study**. CLIMB SCD-121 is an **ongoing** Phase 1/2/3 single-arm, open-label, multi-site, single-dose study. **CLIMB-131 is a multi-site, open-label, Phase 3 rollover study.**'*
Section 2.2.1, pg 52: *'…change of F-cells…'*	Suggest correction to: *'…change in **proportion of** F-cells…'*	Alignment to CLIMB SCD-121 secondary endpoint.	The EAG have amended section 2.2.1, pg 52 to read '*change in **proportion of** F-cells.'*
Section 2.2.1, pg 52: *'Safety was evaluated using adverse events, rate and time of engraftment and mortality.'*	Suggest correction to: *'Safety was evaluated using adverse events, **the presence of successful engraftment, time to engraftment, incidence of transplant-related mortality and all-cause mortality.**'*	Alignment to CLIMB SCD-121 safety endpoints.	The EAG have amended section 2.2.1, pg 52 to read '*Safety was evaluated using adverse events, **the presence of successful engraftment, time to engraftment, incidence of transplant-related***

			mortality and all-cause mortality.’

Issue 9 Critique of efficacy results from CLIMB SCD-121

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.2.1 (Figure 3), pg 54: Incorrect information *(‘VH12 and HF12 ‘start’ 2 months after last RBC.’*) and unclear what *‘Patient variable span.’* Means	Correct to: ‘*VF12 and HF12 ‘start’* ***60 days*** *after last RBC.’* Further clarification required in relation to definition of *‘Patient variable span.’*	Alignment with company submission wording.	No factual error.
Section 2.2.2.1, (Figure 3), pg 54: Incorrect information *(‘The EAG note that most of these events in the PES will occur in the US where practice for VOC identification and inpatient hospitalisation may not accurately reflect that in the UK.’)*	Suggest rewording to: ‘*The EAG note that most of these events in the PES will occur in* ***other European countries as well as the*** *US where practice for VOC identification and inpatient hospitalisation may not accurately reflect that in the UK.’* Suggest addition of the CLIMB SCD-121 trial definition of VOC.	There are clear definitions for VOC within the trial (to ensure similarities between different countries) and there is an endpoint committee to verify consistency. *‘The evaluation of VF12 starts 60 days after last RBC transfusion for post-transplant support or SCD disease management’.* The start of observation 60 days following the last RBC transfusion is consistent with sufficient time to allow for the known lifespan of	The EAG reworded section 2.2.2.1, pg 54 to read ‘*The EAG note that most of these events in the PES will occur in* ***other European countries as well as the*** *US where practice for VOC identification and inpatient hospitalisation may not accurately reflect that in the UK.’* The EAG added the definition of VOC as presented in CS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		transfused red blood cells as well as the resolution of transient increases in HbF associated with the transplant procedure. A minimum of 12 months' duration of absence of severe VOC is robust and considered to be highly unlikely to be due to chance, in patients who have 2 or more severe VOCs per year in the 2 years prior to screening.	Document B section B.1.1 as: *'comprising any of the following: acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] nonsteroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions, acute chest syndrome, Priapism lasting > 2 hours and requiring a visit to a medical facility or Splenic sequestration)'*
Section 2.2.2.1, pg 55: (*'Of 43 FAS patients 13 had insufficient follow up to achieve VF12, two of these 13 experienced a VOC and if followed for 12 months would classify as a VF12 failures. Of the remaining 30 FAS patients: one failed VF12, one died before 12 months, 28 achieved VF12 one of whom*	Suggest incorporating the following information and rewording to provide clarity: *'43 FAS patients, 29 PES patients, one patient died, and 13 additional patients who can be evaluated.'* Removal of *'would classify as VF12 failures'*.	The Statistical Analysis Plan (SAP) for CLIMB SCD-121 indicates the following: Patients require at least 12 months VOC-free follow-up within the lifetime of the CLIMB SCD-121 trial. This period of 12-months does not need to start immediately following the washout period; therefore the '*2 of 13 patients*' who would '*classify as VF12 failures*' is an	No factual error. EAG prefers EAG wording. This section is based on interpretation of data presented in CS Figure 15.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
experienced a VOC during post 12-month follow-up.')		inaccurate statement since these patients may still meet the primary endpoint.	
Section 2.2.2.1, pg 55: *'one failed VF12, one died before 12 months'*	Suggest correction to: *'one patient **did not achieve** VF12, one died before 12 months'*	Alignment with company submission wording.	There is no factual error; the EAG prefers and retains our wording.
Clarification required of patient data set - Section 2.2.2.1, pg 55: '*Of the remaining 29 FAS patients…*'	Suggest correction to: '*Of the remaining 29 **PES** patients…*'	Alignment with CLIMB SCD-121 trial results.	We have updated section 2.2.2.1, p55 to read '*Of the remaining 29 **PES** patients…*'
Clarification required since the following statement is unclear – Section 2.2.2.3, pg 57: *'The EAG were uncertain of the position of "baseline" in the patients' treatment pathway (depicted in CS Figure 3), and whether "patients available for analysis" represents numbers remaining at risk.'*	EAG to provide further clarification on '*…numbers remaining at risk.'*	It is unclear what is meant by '*…patients available for analysis'* and '*numbers remaining at risk.' w*ith reference to figure 3 in the CS, which is a schematic of the treatment procedure with no mention of patients available for analysis.	No factual error. No change. This is statement of EAG opinion.
Incorrect evaluation of the following data –	Suggest removing the elements of this text that relate to one or two patients.	As the EAG make such a strong case against interpretation of	The text has been changed to '*By month four*

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.2.3, pg 57: *'By month four HbF peaks at almost 6 g/dL. Thereafter to month thirty (when five patients were available) mean HbF is maintained above 5 g/dL but exhibits a tendency to decline slightly from the four-month peak. Months 33 and 36 (two patients available) show a decline of approximately 10% in total Hb and in HbF. The remaining patient at month 42 recovers HbF and Hb to earlier levels.'*		data from small sample sizes throughout, it would be inconsistent to draw attention to data pertaining to one or two patients. There are different numbers of patients included at different timepoints. Therefore, the mean HbF is less at some points, but this is because there are different patients (i.e., if the patients with longest follow up had lower HbF throughout - the fact that the mean HbF is lower at Months 33 and 36 just represents that the patients at this point of follow up have a lower mean Hb – not that there is a decline in HbF). Likewise, the remaining patient does not *'recover HbF and Hb levels'* necessarily – this may just represent that they have a higher HbF and Hb than the mean at the previous time point.	*HbF peaks at a mean of about 6 g/dL. Thereafter to month thirty (when five patients were available) mean HbF is above 5 g/dL Months 33 and 36 (two patients available) have a mean HbF approximately 10% lower than the peak at month 4. The remaining patient at month 42 has a mean near that of the peak value.'*
Section 2.2.2.5, pg 59, the EAG state that: *'The EAG question this assertion of permanence because of*	Unclear why EAG question this assertation of permanence, further justification proposed.	See Issue #1.	No factual error. No change

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
diminishing number of patients monitored beyond one year.'			
Section 3.2.4. pg.82 The assumption that occurrence of VOC equates to relapse.	Removal of the term 'relapse' throughout when referring to a patient experiencing a VOC.	Relapse implies that the graft has failed and HbS levels are increasing/HbF is decreasing. This is not so. These are patients who have no impairment of engraftment, still have high HbF, but have VOC (usually secondary to other disease e.g., virus, or in those with chronic pain). Therefore, this should not be termed as relapse but as post treatment VOC or similar.	In the EAG's view, this is neither a factual inaccuracy nor an error. The EAG has sometimes used the term "relapse" to designate the occurrence of a VOC. In usual terms, a relapse is "the return of ill health after an apparent or partial recovery" (Collins English Dictionary), which is in line with what a VOC corresponds to. Moreover, the term "relapse" has not been used to designate another clinical event in the company submission which means there can't any confusion for readers. No change made
Section 3.2.5.1. pg.82,83 and Section 5.1.2.1 pg 127 The assumption that the dose of (2.9×10^6 CD34+ cells/kg)	While the mentioned dose is lower than the protocol-specified minimum; however, it is a therapeutic dose. As specified in the clarification questions, the reason for this is that early in the study, an adjustment was	Misinterpretation of D120 Report	Thank you. We have now amended to "slightly lower than the lower bound of the dose range".

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
slightly lower than the minimum therapeutic range.	made to the exa-cel drug product calculation to account for the density coefficient of the final formulation medium and doses were recalculated, including for some patients who had previously received exa-cel. Upon recalculation, it was determined that 3 patients who had already received exa-cel in Study 121 received a dose of 2.9×10^6 CD34+ cells/kg.		
Section 3.2.6.1. pg. 84 Assuming that the use of supportive transfusions is being used to avert VOC	The transfusions are not being used to avert VOCs. They are supportive treatment during the recovery from myeloablation. Likewise, exa-cel will not have an impact at this time as it precedes engraftment.	Misinterpretation of CLIMB SCD-121 results	We have now deleted this sentence.
Section 3.2.6.1, pg 88: *Assuming that CLIMB SCD-121 study used all VOCs, either leading to hospitalisations or not.*	The CLIMB SCD-121 study VOCs definition included the requirement that patients had to attend a healthcare facility.	Misinterpretation of CLIMB SCD-121	We do not consider that a change is needed. Unless otherwise specified, "healthcare facility" means any facility that provides healthcare- including hospitals or other facilities.
Section 5.1.1 pg 125: *'VOC rates (relapses)'*	Suggest correction to: *'VOC rates (recurrence)'*	Wrong information	Thank you we have replaced 'relapses' with 'recurrence'.

Issue 10 Incorrect description of modelling methods

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.1. pg.75 “The model did not consider an NHS and PSS perspective, since the costs supported by the NHS during the apheresis and conditioning phase are included only for patients who finally receive a per protocol dose of exa-cel” and rest of table cell. As acknowledged in the EAG report in section 3.2.10 page 112 a cost uplift was included to capture the costs of people who underwent mobilization but did not receive exa-cel.	Suggest replacing with “the model considers the NHS and PSS perspective”.	Inaccurate explanation – contradicted in later section of EAG report.	We do not consider this to be a factual error and hence, no change needed. The omission of outcomes afferent to procedures that are paid for by the NHS is a significant departure from the NHS -PSS perspective; in other words, the NHS-PSS perspective is not limited to the inclusion of costs. The cost uplift is incomplete as it does not include the cost of goods and services associated with missing the conditioning step.
Section 3.2.6.1 pg.87 & pg. 88 “The increased hazard for time to splenic sequestration (HR=43.99) was associated with “baseline pain crisis” not otherwise specified.” ; “..>in that it failed to show “number of VOCs” as a significant independent variable…”	Although the study did not report the relationship between the number of VOCs and the incidence of acute and chronic complications, it did report a statistically significant relationship between the presence of VOC at follow-up and the incidence of complications.	Inaccurate explanation	We do not consider this to be a factual error and hence, no change needed. The terminology used in the Shah paper for this endpoint is “baseline pain crisis”. A definition for ‘baseline pain crisis’ is not provided; neither the Shah

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			study considered adjudication of events. The paper otherwise defines a "VOC" as an event related with a hospitalisation; the equivalence between "VOC with hospitalisation" and "baseline pain crisis" is not provided. Therefore, the interpretation of the equivalence of the two events is not possible.
Section 3.2.7. pg.94 "all adverse events are applied to the SoC arm only. "	Suggest replacing with "all adverse events are applied to the SoC arm. For patients receiving exa-cel, all AEs are assumed to occur during the hospital stay that patients undergo as part of the transplant procedure. "	Inaccurate explanation	We do not consider this to be a factual inaccuracy and hence, no change needed. Currently, transplant procedures do not include exa-cel therefore any data pertaining to transplant do not cover adverse events with exa-cel. Not a factual inaccuracy.
Section 3.2.8 pg.98 "Therefore, the incorporation of utilities in the model made by the company suffers from selection bias."	The decrease in patient numbers does not indicate a loss to follow-up but rather reflects that not all patients have reached the 24-month mark at the time of the data cut.	Inaccurate explanation	We do not consider this to be a factual inaccuracy and hence, no change needed. Patients' data at 24 months do not include data for all

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			patients which are part of baseline and month 12 measurements. The reason why these data are not included in the estimate at 24 months does not alter the fact that there is a mismatch with respect to the patient groups whose values are included in these two measurements.
Section 3.2.9. pg.99 "…after which the population reverts to the general population mortality rate. "	Suggest replacing with "……after which the population reverts to the general population mortality rate plus a further increased risk of mortality, applied with a HR adjustment of 1.25"	Inaccurate explanation	We have amended this statement.
Section 3.2.10. pg.111 "For plerixafor, the model considers an average weight per patient of 67KG."	Suggest replacing with "For plerixafor, the model considers an average weight per patient of 72 kg. This weight was calculated by adjusting the dose in each cycle based on the average weight of the SCD cohort adjusted to age."	Inaccurate explanation	Amendment accepted. The nature of the EAG's statement is not a factual inaccuracy but a substantial modelling issue. It regards the failure to calculate drug doses using patients weight distribution as is established practice in NICE appraisals.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.1.2.7 pg.132 “The cost of [redacted] per dose of exa-cel should be applied in the model to people who received exa-cel and to people who proceeded to conditioning but failed to receive the product because of insufficient yield.” No patient would be permitted to proceed to conditioning without sufficient yield as they would otherwise die without cells to replace those depleted.	Suggest replacing with “The cost of [redacted] per dose of exa-cel should be applied in the model to people who received exa-cel and to people who underwent mobilization but did not receive exa-cel.”	Inaccuracy in feasible treatment pathway.	Partially accepted. Changed as “[..] people who were expected to undergo conditioning but didn’t because of insufficient exa-cel yield”. These people did not undergo conditioning – therefore they did not accrue the corresponding cost - but received supportive care in view of conditioning, i.e., blood transfusions. These costs are accrued almost entirely before conditioning. The CLIMB SCD-121 CSR, page 29-30 states: “Stage 1: After eligibility was confirmed, subjects began RBC exchange or simple transfusions for a minimum of 8 weeks before the planned start of mobilization and continued receiving these transfusions until they

			began busulfan conditioning. The goal of these RBC transfusions was to maintain an HbS level of <30% of total hemoglobin (Hb) while keeping total Hb concentration ≤11 g/dL". And "Stage 3A: After the exa-cel product was received at the site and the backup CD34+ stem cells. were confirmed available and in acceptable condition to be administered if needed, the subject began busulfan conditioning". The cost of transfusions is supported before conditioning, when it is not known whether a patient will be in the material position to undergo conditioning or not (i.e., having a sufficient exa-cel quantity).

Issue 11 Typographical errors & further clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Mentioned throughout - *'HST assessments'*	Clarification required as unclear why reference is made to *'HST assessments'* throughout	ID4016 is not a HST assessment	The EAG has removed HST throughout. We have changed to: *"Relative to a standard cost-effectiveness analysis encountered in Single Technology Appraisals (STAs) the SCD submission introduces …"* *"The NICE program considers drugs for rare conditions…"* *"In the context of orphan disease assessments…"* *"…relative to previous orphan disease assessments…"*

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Executive Summary, Section 1.1, pg 12: *'exagamglogene auototemcel'*	Correct to: *'exagamglogene **autotemcel**'*	Typographical error	Thank you. Change made.
Executive Summary, Section 1.1, pg 14: *Reference to 'CLIMB-121 study'*	Suggest correction to: *'**CLIMB SCD-121** study'*	Typographical/ nomenclature error	Thank you. Change made.
Executive Summary, Section 1.4, pg 18: *'The FAS supplies data for more patients (42)…'*	Suggest correction to: *'The FAS supplies data for more patients (**N**=42)…'*	Typographical error	Thank you. Change made.
Executive Summary, Section 1.4, pg 19 *'CLIMB SCD-131'*	Suggest correction to: *'**CLIMB-131'***	Typographical error, the open-label extension is not SCD-specific	Thank you. Change made throughout the EAG report.
Executive Summary, Section 1.6, pg 24: Issue 8 table is missing a *'report section'* heading	EAG to add a *'report section'* heading	Typographical error	We have now included a cross reference.
Executive Summary, Section 1.6, pg 26: *'The costs supportive blood transfusions…'*	Correct to: *'The costs **of** supportive blood transfusions…'*	Typographical error	Thank you. Change mage.
Section 1.1, pg 30 Section 1.2.3 pg 32	Suggest correction to: 'β^S/β^S, β^S/β^0 or β^S/β^+'	Typographical error	Changes mage.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3.1 pg 34 '*βS/βS, βS/β0 or βS/β+*'			
Section 1.1, pg 30: '*Submission was made to the MHRA*'	Suggest rewording to: '***A regulatory** submission*'	Further clarity on submission type	Amended
Section 1.1, pg 30: '*in hospital (NICE 2012)*'.	Suggest correction to: '*in hospital (NICE **CG143**, **published in June 2012 and updated in October 2022**)'*	Further clarity on publication dates	Amended for further clarification.
Section 1.1.1, pg 30: '*characterised by episodes of severe pain, chronic haemolytic anaemia, organ damage and shortened life expectancy.'*	Suggest rewording to: '*characterised by **unpredictable** episodes of severe pain, chronic haemolytic anaemia, **widespread** organ damage and shortened life expectancy.'*	Alignment to company submission	Amended to be more aligned to the company submission.
Sections 1.1.1 & 1.2.1, pg 31: (Alsultan et al. 2012, Vertex Pharmaceuticals 2022) (Udeze et al. 2023, Vertex Pharmaceuticals 2023) (GBD Sickle Cell Disease Collaborators 2021)	Vancouver style referencing should be followed, with each reference assigned a unique number and written as superscript. Reference issues likely relate to a need to update citations and bibliography.	Incorrect reference formats	Thank you. We have now provided the appropriate references in this section.
Section 1.2.2, pg 32: '*Established therapies address some of the disease symptoms but do not offer a cure for SCD.*'	Suggest rewording to: '*Established therapies, **like hydroxycarbamide and RBC transfusions**, address some of the*	Alignment to company submission	Amended to be more aligned to the company submission.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	disease symptoms but do not offer a cure for SCD. '		
Section 1.2.2, pg 32: '*subsequent recommendations to revoke conditional marketing authorisation may reduce available treatment options…'*	Suggest rewording to: '*subsequent **EMA decision** to revoke conditional marketing authorisation **has reduced** available treatment options…'*	This is no longer a recommendation, EMA has revoked the licence following guidance from the CHMP.	Thank you we have reworded.
Section 1.3, pg 33: *'hydrocarbamide'*	Correct to: *'**hydroxycarbamide**'*	Typographical error	This has been corrected.
Section 1.3.1, pg 34: *'The company suggest (CS Document B pg. 53 Figure 10 "Epidemiological cascade for SCD in the UK") that 1750 ([redacted]%) of 2,150 UK severe SCD patients fit for exa-cel treatment would lack a matched HLA donor.'*	Suggest rewording to state that the [redacted]% is based on published data from Gragert *et al.,* (2014)	Reference missing	Thank you. We have now included a reference to this study.
Section 1.3.3, pg 35: '*The wording of comparators in NICE scope differs somewhat from that addressed in the company submission*.'	Suggest correction to: '*The wording of comparators in **the** NICE scope differs somewhat from that addressed in the company submission*.'	Typographical error	We have included 'the'.
Section 1.3.3, pg 35: *'In Table 1 of CS Document B, the*	Suggest correction to: *'In Table 1 of CS Document B, the company lists two*	Typographical error, no need for capital letters.	De-capitalisation corrected. No double

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
company lists two comparators: Best Supportive care (SoC) and Hydroxycarbamide.'	*comparators: **b**est **s**upportive care (SoC) and **h**ydroxycarbamide.'*	Double spacing.	space in our version of the EAG report.
Section 1.3.4, pg 36: *'That the treatment pathway (as depicted in CS Figure 3) might predispose severe SCD patients to virus infection(s) or other life-threatening events that might impact on mortality appears not to have been adequately considered or discussed in the CS…'*	Suggest correction to: *'**Indication that** the treatment pathway (as depicted in CS Figure 3) might predispose severe SCD patients to virus infection(s) or other life-threatening events that might impact on mortality appears not to have been adequately considered or discussed in the CS…'*	Typographical error	Included for clarity.
Section 1.3.7, pg 40: *'The EAG notes firstly that the matching applied to the general population only encompassed age and gender and may have missed other attributes that would influence survival and secondly that multiple inputs were required to deliver the "Markov" SoC survival model each of these associated with uncertainty.'*	Suggest correction to: *'The EAG notes firstly that the matching applied to the general population only encompassed age and gender and may have missed other attributes that would influence survival**,** and secondly that multiple inputs were required to deliver the "Markov" SoC survival model, each of these **is** associated with uncertainty.'*	Punctuation error Typographical error	Sentence reads clearly to the EAG. No change needed.
Section 1.3.7, pg 40: *'…for estimation severity modifier…'*	Suggest correction to: *'…for estimation **of the** severity modifier…'*	Further clarification	Change made for better readability.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1, pg 43: *'Eligible comparators (CS Appendix D, Table 70) were Lovotibeglogene autotemcel, lovo-cel, Crizanlizumab, Voxelotor, L-glutamine (not approved in EU), hydroxycarbamide, allogeneic stem cell transplantation, red blood cell transfusions and other types of transfusions (simple/exchange), iron chelation therapy, placebo, or best medical care.'*	Suggest correction to: *'Eligible comparators (CS Appendix D, Table 70) were* ***l****ovotibeglogene autotemcel,* ***(lovo-cel)****,* ***c****rizanlizumab,* ***v****oxelotor, L-glutamine (not approved in EU), hydroxycarbamide, allogeneic stem cell transplantation, red blood cell transfusions and other types of transfusions (simple/exchange), iron chelation therapy, placebo, or best medical care.'*	Typographical error	Changes made.
Section 2.1.1, pg 43: *'A search filter was applied to identify randomised controlled and single arm trials in accordance with the inclusion criteria…'*	Suggest rewording to: *'A search filter was applied* ***during study selection*** *to identify randomised controlled and single arm trials in accordance with the inclusion criteria…'*	Alignment to company submission	No change required.
Section 2.1.1, pg 44: '*Ovid'*	Suggest correction to '*Ovid* ***SP****'*	Typographical error	Included 'SP' for clarity.
Section 2.1.1, pg 44: *'The search terms and numbers of results from searching conference abstracts are provided for the update search…'*	Suggest correction to *'The search terms and numbers of results from searching conference abstracts are provided for the update****d*** *search…'*	Typographical error	Corrected for grammatical error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1.1, pg 44: *'However, the EAG note that the search terms differ from the update congress abstract SLR update search terms.'*	Suggest correction to: *'However, the EAG note that the* ***search terms differ from the updated SLR conference abstract search terms****.'*	Typographical error	Amended for clarity.
Section 2.1.1, pg 44: *'One addition record was retrieved from this review';'*	Suggest correction to: *One addition**al** record was retrieved from this review."*	Typographical error	We have amended.
Section 2.1.1, pg 45: '(CS Document B Table 3)'	Suggest correction to: '(CS **Clarification Response** Table 3)'	Cross referencing error	Thank you. We have corrected.
Section 2.1.1, pg 45: *'The PRISMA flow-diagram for the update search (CS Appendix D, Figure 37) accurately reports the number of results of the database searched.'*	Suggest correction to: *'The PRISMA flow-diagram for the updated search (CS Appendix D, Figure 37) accurately reports the number of results* ***identified in*** *the database searched.'*	Typographical error	Amended for clarity.
Section 2.1.3, pg 46: *'The company reports (D.11) that the searches resulted in 100 results included in the SLR, and an additional 12 eligible conference abstracts.'*	Suggest correction to: *'The company reports (CS Appendix* ***D1.1****) that the searches resulted in 100 results included in the SLR, and an additional 12 eligible conference abstracts.'*	Cross referencing error	We have corrected for clarity.
Section 2.1.3, pg 46: *'CLIMB SCD1-121'*	Suggest correction to: *'****CLIMB SCD-121'***	Typographical/ nomenclature error	Thank you. We have corrected this typo.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.1, pg 48: (Vertex Pharmaceuticals Inc. 2022)	Vancouver style referencing should be followed, with each reference assigned a unique number and written as superscipt	Incorrect reference format	Thank you. We have now provided the reference to this study.
Section 2.2.1, pg 49: *'CLIMB SCD-131'*	Suggest correction to: ***'CLIMB-131'***	Typographical/ nomenclature error	Thank you. We have corrected to CLIMB-131.
Section 2.2.1, 52: *'The EAG notes again that as a single-arm study, there are no randomised comparators or control groups in the CLIMB SCD-121 trial, all patients in the received exa-cel infusion and therefore only the outcomes under the intervention treatment can be observed.'*	Suggest correction to *'The EAG notes again that as a single-arm study, there are no randomised comparators or control groups in the CLIMB SCD-121 trial, all patients in the **FAS** received exa-cel infusion and therefore only the outcomes under the intervention treatment can be observed.'*	Typographical error (missing information)	We have included 'FAS' for clarity.
Section 2.2.2, pg 53: *'CS pg . 84'*	Suggest correction to: *'CS pg . **81**'*	Cross referencing error	Thank you. We have corrected.
Section 2.2.2.1, pg 53: *'…a key secondary analysis…'*	Suggesting rewording to: *'…a key secondary **efficacy endpoint**…'*	Alignment to company submission	Thank you. We have amended for clarity.
Section 2.2.2.1 (Figure 3), pg 54: *'CRISPR/Cass 9 editing'* *'RBS transfusion'*	Suggest correction to: ***'CRISPR/Cas-9 editing'*** *'**RBC transfusion**'* *'**VF12**'*	Typographical errors Alignment to company submission	Thank you. We have made these changes.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
'VH12' *'Measurement: % or proportion free of severe VOCs or inpatient hospitalisations'* *'Statistical test: VH12 and HF12 versus null of 50%'*	*'Measurement: % or proportion free* ***of patients with*** *severe VOCs or inpatient hospitalisations'* *'Statistical test: VH12 and HF12 versus null* ***hypothesis of 50 response rate****%'*		
Section 2.2.2.2, pg 56: *'A US study reported a 1.52 mean annual rate of severe VOCs resulting in hospitalisation (these approximate to severe VOCs because of the requirement for ED or inpatient hospitalisation).'*	EAG to provide source for US study	Reference missing	Thank you. We have now included
Section 2.2.2.3, pg 57: '*CS Figure 20 (see* ***Error! Reference source not found.****) presents the mean g/dL of HbF and of total Hb at various months for 42 FAS patients extending to a maximum of 42 months together with numbers "available for analysis" at the designated time points.'*	Suggest correction to: '*CS Figure 20 (see* ***Error! Reference source not found.****) presents the mean g/dL of HbF and of total Hb at various months for 42 FAS patients extending to a maximum of 42 months together with numbers* ***of patients*** *"available for analysis" at the designated time points.'*	Typographical error (missing information)	Amended for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.2.3, pg 57: *'CLIMB SCD-131'*	Suggest correction to: *'**CLIMB-131**'*	Typographical error	Thank you. We have corrected.
Section 2.2.2.3, pg 57: *'CS pg.20'*	Suggest correction to: *'CS Document B pg. **17**'*	Cross referencing/ typographical error	We have now provided the correct page number.
Section 2.2.2.5, pg 58: *'…reported for visits patient visits at…'*	Suggest correction to: *'…reported for patient visits at…'*	Typographical error	We have amended
Section 2.2.2.6, pg 60: *'At one-year post-baseline units…'*	Suggesting rewording to: *'At one-year post-baseline **mean** units…'*	Typographical error (missing information)	Amended for clarity.
Section 2.2.2.6, pg 60: *'Mean values for Indirect Bilirubin were reported at yearly intervals (with no intermediate times reported); baseline of [redacted] µmol/L…'*	Suggest correction to: *'Mean values for Indirect Bilirubin were reported at yearly intervals (with no intermediate times reported); baseline of **55.4** µmol/L…'*	Typographical error	We have corrected this typo.
Section 2.2.2.6, pg 60: *'Normal range has been reported as 0 to 34 µmol/L.'*	EAG to provide source for normal range	Reference missing	We have now included the reference to support this statement.
Section 2.2.2.8, pg 60: *'The mean (SD) percentage of F-cells was 70.4% at month 3.'*	Suggest correction to: *'The mean (SD) percentage of F-cells was 70.4% (**SD: 14.0%**) at month 3.'*	Typographical error (missing information)	We have included the standard deviation.
Section 2.2.2.9, pg 61*: 'The change (mean (SD)) at one*	Suggest correction to: '*The change (mean (SD)) at one year for the 23 patients in*	Typographical error	We have amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
year for the 23 patients in PES of this age group was 20.8 (21.8) for EQ VAS and 0.08 (SD:0.11) for UK Health Utility score.'	*PES of this age group was 20.8 (21.8) for EQ VAS and 0.08 (SD:**0.16**) for UK Health Utility score.'*		
Section 2.2.2.9, pg 61: *'At month 18 the change for [redacted] monitored patients was [redacted] (25.5) for EQ VAS and [redacted] ([redacted]) for UK Health Utility score.'*	Suggest correction to: *'At month 18 the **mean (SD)** change for [redacted] monitored patients was [redacted] (25.5) for EQ VAS and [redacted] ([redacted]) for UK Health Utility score.'*	Typographical error (missing information)	Amended for clarity.
Section 2.2.2.9, pg 61: *'Numeric Pain Rating (NPR) scores…'*	Suggest correction to: *'Numeric Pain Rating scores (**NRS**)…'*	Typographical/ nomenclature error	Corrected this abbreviation.
Section 2.2.2.9, pg 61: *'The EAG note that 23 provide data at baseline and 15 at 24 months.'*	Suggest correction to: '*The EAG note that 23 **patients** provide data at baseline and 15 **patients** at 24 months.'*	Typographical error	Amended for clarity
Section 2.3.1, pg 63: *'According to the DSU TSD18…'*	EAG to provide definition of abbreviation	Abbreviation definition missing	We have now provided this definition for DSU TSD
Section 2.3.2, pg 64*: 'In Table 74 of the CS Appendix B…'*	Suggest correction to: *'In Table 74 of the CS Appendix **D**…'*	Cross referencing error	Correct Appendix cross-referenced.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3.3, pg 65: *'Although on page 79 of the CS…'*	Suggest correction to: *'Although on page 78 of the CS…'*	Typographical error	Correct page number cross-referenced.
Section 2.3.3, pg 65 & Section 2.3.5, pg 67: *'CLIMB-SCD 121'*	Suggest correction to: ***'CLIMB SCD-121'***	Typographical/ nomenclature error	Thank you. We have amended.
Section 2.3.5, pg 67: *'From pages 120 to 122 of the CS…'*	Suggest correction to: *'From pages 120 to 122 of the CS* ***Document B****…'*	Cross referencing error	Amended for clarity.
Section 2.4, pg 69: *'CLIMB-SCD 121'*	Suggest correction to: ***'CLIMB SCD-121'***	Typographical/ nomenclature error	Corrected this nomenclature error.
Section 3, pg 70: *'has undertaken'*	Suggest correction to: *'has not undertaken'*	Typographical	Thank you we have corrected.
Section 3, pg 77: *'knee'*	Suggest correction to: *'kidney'*	Typographical	Thank you. We have corrected.
Section 3.2.5.3, pg 84: *'VOCs relapse'*	Suggest correction to: *'recurrence of VOC'*	Terminology accuracy	Thank you. We have changed the terminology for accuracy.
Section 3.2.6.1, pg 86: *'mulitplier'*	Suggest correction to: *'multiplier'*	Typographical/ nomenclature error	Amended.
Section 3.2.10, pg 88: *'CX001-121'*	Suggest correction to: *'CTX001-121'*	Typographical/ nomenclature error	Amended.
Section 3.2.6.1, pg 90: *'the state occupancy for stroke at*	Suggest correction to: *'CTX001-121' the EAG believes that the state occupancy for*	More accurate clarifications	Amended for clarification.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
this cycle should be'; '…, whilst the correct value should be 0.16%'	*stroke at this cycle would be'; '…, while the proposed calculations recommended by the EAG would result in a risk of stroke equal to 0.16%.'*		
Section 3.2.6.2, pg 91&92: *'Acute kidney injury/infarction; Chronic kidney disease; Stroke; Acute chest syndrome' rows*	Duplicated in the same table	Duplication	Thank you. We have de-duplicated.
Section 3.2.6.2, pg 92: *'(1,117)'*	Suggest correction to: *'(n=1,117)'*	Typographical	Changes made.
Section 3.2.7, pg 94: *'CLIMB SCD-131'*	Suggest correction to: *'CLIMB-131'*	Typographical/ nomenclature error	Corrected nomenclature error
Section 3.2.7, pg 96: *'CLIMB SCD-131'*	Suggest correction to: *'CLIMB-131'*	Typographical/ nomenclature error	Corrected nomenclature error
Section 3.2.8, pg 99: *'[redacted]'*	Suggest correction to: *'[redacted]'*	Typographical	Corrected this typo.
Section 3.2.9, pg 100 table 14 'IR'	EAG to provide definition of abbreviation	Abbreviation definition missing	We have amended to 'HR'
Section 3.2.10, pg 111: *'CX001-121'*	Suggest correction to: *'CTX001-121'*	Typographical/ nomenclature error	Corrected nomenclature error
Section 3.2.10, pg 112: *'£ 2698'*	Suggest correction to: *'£2698'*	Typographical/ nomenclature error	Removed the space for consistency.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.10, pg 113: *'(£1.980)'*	*Suggest correction to: '(£1,980)'*	Typographical/ nomenclature error	Removed the '.' And changed to £1980 for consistency.
Section 3.2.10, pg 113: *'are assumed 100%'*	*Suggest correction to: 'are assumed to be 100%'*	Typographical/ nomenclature error	No change made.
Section 4.1 pg 114: *'Soc'*	*Suggest correction to: 'SoC'*	Typographical	Changed for consistency.
Section 5.1.1, pg 122: *'CLIMB-121'*	Suggest correction to: *'CLIMB SCD-121'*	Typographical/ nomenclature error	Corrected nomenclature error
Section 5.1.2.2. pg 130: 'retinopathy'	*Section 5.1.2.2. pg 130: 'Retinopathy'*	Typographical/ nomenclature error	We have made this change.
Section 5.3. pg 136: 'Base-case ICER estimates using an appropriate severity modifier which is based on 3.5% discount rate.'	*Wrong font size*	Formatting	The font size has been changed to be consistent with the text in this table.

Issue 12 Confidential data nomenclature

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 3 - '***Please note that:*** *Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections*	Remove: '*Sections highlighted in yellow and underlined are 'academic in confidence' (AIC).'*	Academic in confidence (AIC) nomenclature and markup has been superseded in latest NICE	Thank you. We have removed this text from page 3.

highlighted in aqua and underlined are 'commercial in confidence' (CIC).'		advice, with only CIC (now 'CON', or confidential) permitted.	

Issue 13 Confidential data markup

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.3.1, pg 34	*'The company suggest (CS Document B pg. 53 Figure 10 "Epidemiological cascade for SCD in the UK") that 1750 ([redacted]%) of 2,150 UK severe SCD patients fit for exa-cel treatment would lack a matched HLA donor.'*	*'The company suggest (CS Document B pg. 53 Figure 10 "Epidemiological cascade for SCD in the UK") that 1750 (81.4%) of 2,150 UK severe SCD patients fit for exa-cel treatment would lack a matched HLA donor.'*	We have removed this confidentiality marking.
Section	*'In view of the low number of UK allo-SCT interventions performed and the NHS perspective of the analyses, in EAG opinion [redacted]% is likely a considerable overestimate.'*	*'In view of the low number of UK allo-SCT interventions*	We have

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
1.3.1, pg 34		*performed and the NHS perspective of the analyses, in EAG opinion 18.6% is likely a considerable overestimate.'*	removed this confidentiality marking.
Section 1.3.4, pg 36	*'The Summary of safety (CS Doc B section B.2.10.2) mentions that ""[redacted]"."'*	*'The Summary of safety (CS Doc B section B.2.10.2) mentions that "One patient had a fatal AE, however it was not related to exa-cel. The patient died at Day 130 following Exa-cel infusion due to respiratory failure after COVID-19 infection, [redacted]"."'*	We have removed this confidentiality marking.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.3.8, pg 42	*'…offers a different value of 3.5…'*	*'…offers a different value of 3.5…'*	We have changed the confidentiality marking.
Section 2.2.1, pg 48 & pg 52	*'During clarification the company confirmed that [redacted] patients enrolled into the CLIMB SCD-121 at D120 were from the UK (with [redacted] patients from the UK included in the PES).'* *'([redacted] patients were from the UK were enrolled at D120, but [redacted] patients…'*	*'During clarification the company confirmed that [redacted] enrolled into the CLIMB SCD-121 at D120 were from the UK (with [redacted] from the UK included in the PES).'*	We have added additional confidentiality

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		'([redacted] were from the UK were enrolled at D120, but [redacted]…'	markings.
Section 2.2.2, pg 55	*'[redacted] failed VF12, [redacted] died before 12 months'*	*'[redacted], one died before 12 months'*	We have changed the confidentiality marking.
Section 2.2.2, pg 55	*'All PES patients are reported to have achieved HF12.'*	*'[redacted] PES patients are reported to have achieved HF12.'*	Confidentiality marking

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
			added.
Section 2.2.2, pg 55	*'A total of eleven VOC events were recorded amongst four patients; one patient died without a recorded VOC event.'*	*'A total of [redacted] VOC events were recorded amongst [redacted] patients; one patient died without a recorded VOC event.'*	Confidentiality markings added.
Section 2.2.2, pg 56	*'In the Appendix to Document B (pg.141) the life-time total VOC events output from the economic model in the SoC arm as 93.9; given a mean SoC survival output from the economic model of 22.36 years this provides an annualised rate of approximately 4.2.'*	*'In the Appendix to Document B (pg.141) the life-time total VOC events output from the economic model in the SoC arm as 93.9; given a mean SoC survival output from the economic model of 22.36 years this provides an annualised rate of approximately [redacted].'*	Confidentiality marking added.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 2.2.2.3, pg 57	*'Thereafter to month thirty (when five patients were available) mean HbF is maintained above [redacted] but exhibits a tendency to decline slightly from the four-month peak.'*	*'Thereafter to month thirty (when [redacted] patients were available) mean HbF is maintained above [redacted] but exhibits a tendency to decline slightly from the four-month peak.'*	Confidentiality marking added.
Section 2.2.2.5, pg 58	*'The mean value at 6 months was [redacted]% ([redacted]%) with [redacted] of 43 FAS patients monitored.'*	*'The mean value at 6 months was [redacted]% ([redacted]%) with [redacted] of [redacted] FAS patients monitored.'*	Confidentiality marking added.
Section 2.2.2.5,	*'The mean remained virtually the same at [redacted] and 24 months with [redacted] and [redacted] patients monitored respectively.'*	*'The mean remained virtually the same at 12 and 24 months with [redacted] and [redacted] patients monitored respectively.'*	Confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
pg 59			removed.
Section 2.2.2.6, pg 59	*'CS Figure 23 indicated a mean LDH at baseline of 463 U/L, above normal range of 103 to 223 U/L.'*	*'CS Figure 23 indicated a mean LDH at baseline of [redacted] U/L, above normal range of 103 to 223 U/L.'*	Confidentiality marking added.
Section 2.2.2.9, pg 61	*'At month 18 the change for [redacted] monitored patients was [redacted] (25.5) for EQ VAS and [redacted] ([redacted]) for UK Health Utility score.'*	*'At month 18 the change for [redacted] monitored patients was [redacted] ([redacted]) for EQ VAS and [redacted] ([redacted]) for UK Health Utility score.'*	Confidentiality marking added.

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
Section 2.2.2.9, pg 62	*'The EAG notes that only [redacted] of the 23 patients provide data at 24 months.'*	*'The EAG notes that only [redacted] of the [redacted] patients provide data at 24 months.'*	Confidentiality marking added.

DSU OPINION ON THE COMPANY'S MODEL STRUCTURE FOR THE SINGLE TECHNOLOGY APPRAISAL OF EXAGAMGLOGENE AUTOTEMCEL FOR TREATING SICKLE CELL DISEASE

REPORT BY THE DECISION SUPPORT UNIT

14th December 2023

Authors: Paul Tappenden[1], Mon Mon Yee[1]

[1] Sheffield Centre for Health and Related Research (SCHARR), University of Sheffield

ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) External Assessment Centre is based at the University of Sheffield with members at York, Bristol, Leicester and the London School of Hygiene and Tropical Medicine. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Centre for Health Technology Evaluation Programmes. Please see our website for further information www.nicedsu.org.uk.

The production of this document was funded by the National Institute for Health and Care Excellence (NICE) through its Decision Support Unit. The views, and any errors or omissions, expressed in this document are of the authors only. NICE may take account of part or all of this document if it considers it appropriate, but it is not bound to do so.

Conflicts of interest

Paul Tappenden is the lead health economist for the ongoing NIHR-funded REDRESS trial of haploidentical stem cell transplantation (SCT) for people with severe sickle cell disease (NCT05392894). This transplantation approach does not reflect current practice and haploidentical SCT is not listed as a comparator in the final NICE scope for the appraisal of exagamglogene autotemcel. Mon Mon Yee has no conflicts of interest to declare.

This report should be referenced as follows:

Tappenden, P., Yee, M. NICE DSU Report. DSU opinion on the company's model structure for the Single Technology Appraisal of exagamglogene autotemcel for treating sickle cell disease, 2023.

1. Introduction

In December 2023, the National Institute for Health and Care Excellence (NICE) asked the Decision Support Unit (DSU) to provide additional advice on the suitability of the economic model structure developed by Vertex Pharmaceuticals to inform the Single Technology Appraisal (STA) of exagamglogene autotemcel (exa-cel) for the treatment of sickle cell disease (SCD). Specifically, the External Assessment Group (EAG) report for this appraisal[1] raises serious concerns regarding several aspects of the company's model structure and concludes that a full model rebuild is required. Owing to their concerns regarding the company's model structure, the EAG has not undertaken any exploratory analyses. This DSU report provides a brief summary and discussion around the key model structure issues raised by the EAG, and provides recommendations for further analyses to address these concerns. This DSU report is not intended to supersede the EAG report, nor does it include a comprehensive critique of the company's model. Rather, it is intended to provide a second opinion on a limited set of issues raised by the EAG and to suggest potential solutions to ensure that the model is suitable for decision-making.

This report is set out as follows. Section 2 explains the general structure and logic applied in the company's economic model. Section 3 provides a summary of the EAG's concerns about the company's modelling approach and the DSU's opinion on these issues. Section 4 sets out recommendations from the DSU detailing potentially useful approaches for addressing these concerns.

2. Overview of the company's model structure

2.1 Limits on the structural issues covered by this report

The company's economic model includes two treatment groups: (i) exa-cel and (ii) standard of care (SoC). The model assumes that almost all patients in the exa-cel group are functionally cured and do not experience subsequent vaso-occlusive crises (VOCs) or additional new complications over and above those which are already present at the point of model entry. Health outcomes for this treatment group are largely driven by standardised mortality ratio (SMR) adjusted life tables and general population utility values. Given the short duration of follow-up in the CLIMB-SCD-121 study,[2] the EAG report[1] highlights considerable uncertainty around whether exa-cel results in a permanent cure for people with SCD. Notwithstanding the uncertainty around the durability of benefits for patients receiving exa-cel, the EAG's main concerns regarding the structure of the model mostly affect the SoC group, because these patients are assumed to experience continued VOCs, acute complications and chronic complications, which in turn, lead to negative impacts on patient survival, quality-adjusted life year (QALY) losses and additional disease management costs. As such, the issues discussed in this DSU report do not relate to the plausibility of the company's assumptions of functional cure for the exa-cel group, but instead focus more on whether the company's model structure could provide a sufficient basis for providing reliable estimates of overall survival, QALYs and costs for patients treated

with SoC. Additional consideration is also given to what the EAG refers to as a structural error in the company's calculations of overall survival for both treatment goups, and to further concerns regarding the exclusion from the model structure of the costs and outcomes for patients in whom exa-cel is planned but not delivered.

2.2 Model structure and logic

The company's model adopts a cohort-level state transition model approach, which includes two health states: (i) alive and (ii) dead. Within the alive state, the model includes the possibility of developing one or more of 7 acute complications and one or more of 8 chronic complications. In very broad terms, the model logic follows four linked steps which are described below. All calculations are applied using a monthly cycle length over a lifetime horizon (78.9 years; 947 monthly cycles).

Step 1 - Determine rate of VOCs and chronic complications at baseline. The probability of being alive at the beginning of cycle *n* is determined (initially this is assumed to be 1.0). In the SoC group (and for the small minority of exa-cel-treated patients who are not functionally cured), all surviving patients are assumed to have 4.2 VOCs per year (0.35 VOCs per month). The DSU is unsure whether the company's intended assumption is that 35% of patients have a VOC in every monthly cycle (and 65% do not have a VOC), or that amongst the surviving population, patients spend on average 35% of each month alive with a VOC (and 65% of each month without a VOC). A proportion of patients are assumed to have a history of neurocognitive impairment or retinopathy at the point of model entry. The initial prevalence of all other chronic complications is assumed to be zero.

Step 2a - Determine the number of acute complications. The model calculates the number of acute complications experienced (stroke, acute coronary syndrome [ACS], infection, acute kidney injury [AKI], gallstones, pulmonary embolism [PE] and/or leg ulcers) in the current monthly cycle. The numbers of events experienced are conditional on the probability of being alive and on the proportion of people with VOCs (or the proportion of time spent with VOCs; see ambiguity described above). The risks of experiencing these acute complications are based on estimates obtained from the literature[3-5] and assumptions, with higher risks assumed for patients with VOCs. The model assumes that patients can have multiple concurrent acute complications and that most of these events independently contribute to excess mortality risk amongst the surviving patients.

Step 2b - Determine the number of chronic complications. The model also estimates the number of patients who are alive and who have developed chronic complications (chronic kidney disease [CKD], pulmonary hypertension [PH], avascular necrosis, neurocognitive impairment, post-stroke [following a prior acute stroke event], retinopathy and liver damage) by the current monthly cycle. The number of patients with each chronic complication is dependent on the proportion of patients with a prior history

of that chronic complication, the proportion of patients without a prior history of the complication with or without VOCs, and the probability of being alive at cycle *n*. The risks of developing these chronic complications are based on estimates obtained from the literature[3, 6-8] and assumptions, with higher risks assumed for patients with VOCs. The model assumes that patients can have multiple concurrent chronic complications (as well as multiple co-occurring acute complications) and that several of these chronic complications independently contribute to excess mortality risk amongst the surviving patients. The model calculations detail how many alive patients currently have each complication in cycle *n* and how many have ever had each complication (the sum of which exceeds 1.0).

Step 3 - Determine the number dead and alive at end of model cycle. The cumulative probability of having died in each cycle in the SoC group is modelled as a function of two factors: (i) the baseline probability of dying with SCD (adjusted for risk factors)[6] plus (ii) additional excess mortality risks[4, 6, 9] linked to the number of specific complications in alive patients. These risks are added together and converted to a probability (note: the handling of rates, probabilities and numbers appears to be inconsistent in the company's model). A similar approach is used for the exa-cel group, except that the baseline mortality risk for functionally cured patients is modelled using general population life tables plus an SMR of 1.5.

The cumulative probability of being dead at the beginning of cycle *n*+1 is calculated as the cumulative probability of being dead in cycle *n* plus new deaths occurring in cycle *n*+1. The cumulative probability of being alive in cycle *n*+1 is then calculated as one minus the cumulative probability of being dead in cycle *n*+1. An =MIN() function is applied to the cumulative probability of death in each cycle to prevent this from exceeding 1.0.

Step 4 - Calculate QALYs and costs. QALYs and costs are calculated as a function of the time spent alive with and without acute complications (including VOCs) and chronic complications. The model also includes various other costs and effects, including pre-treatment and treatment costs and transplant-related disutility. These factors are not discussed here - further details can be found in the EAG report.[1]

The model repeats the calculations in Steps 1-4 in cycle *n*+1 until cycle *n*+947.

The company's model tracks the modelled cohort's history of chronic complications, but the way that it does this is partial at best. It tracks the proportion of the surviving cohort with chronic complications and estimates the overall excess complication-related mortality risk based on the number of complications in the alive population. However, the excess mortality risk attributable to each individual complication is not applied directly to those patients with those specific complications. Rather, the overall mortality risk (including baseline SCD-related mortality and complication-dependent excess mortality) given the total number of complications in each cycle is applied indiscriminately to all surviving patients.

3. Summary of key structural issues raised by the EAG and the DSU's view

The EAG report[1] (Section 3.2.2) states that the company's model structure is not organised as a Markov structure, and that owing to the computation methods applied by the company, the model may overestimate the incidence and mortality impact of SCD-related complications. The EAG report and an accompanying addendum prepared by the EAG both highlight that the company's model includes a mathematical constraint, which when removed, leads to a situation whereby the model predicts death rates of approximately 400% for the SoC group and over 500% for the exa-cel group by cycle 947. The EAG has suggested that the problems in the company's model structure are likely to invalidate the cost-effectiveness results and that a model rebuild using standard practices for state transition models is required. The EAG report also argues that costs and outcomes for patients who do not receive exa-cel should be accounted for in the model structure.

Below, we provide a brief commentary on these structural issues and the feasibility of a model rebuild.

The EAG report[1] also raises concerns about how the model uses the number of VOCs to estimate risks, whether the use of HRs from Shah *et al.*[3] adequately handles competing risks, and whether it is reasonable to assume that the number of VOCs represents a valid surrogate for predicting other complications. These issues relate more to the use of evidence in the model and are beyond the remit of this DSU report.

Issue 1: Probability of death exceeds 1.0

The EAG report[1] highlights that deaths in the model are calculated using an additive approach, whereby the number of new deaths in cycle n+1 are added to the number of prior deaths in cycle n, and the proportion of people alive in each cycle is calculated as one minus the cumulative probability of being dead. The company has applied a constraint to ensure that the probability of being dead in any cycle cannot exceed 1.0; this is contained in the formulae in column H of the model trace worksheets. When this constraint is removed, the cumulative probability of being dead patients exceeds 1.0 in both treatment groups. The EAG report describes this as *"an uncontrollable structural error."*

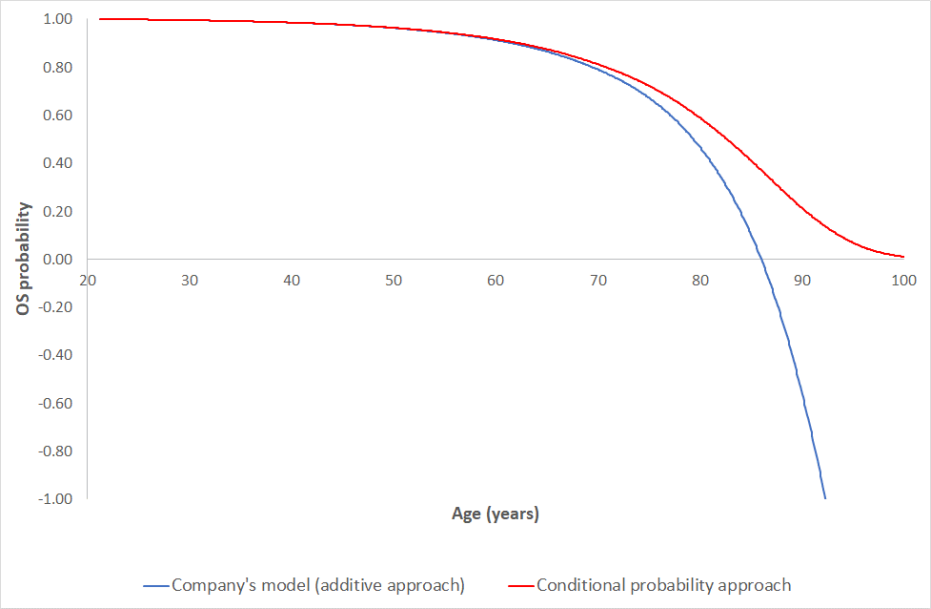
The DSU has scrutinised the company's approach to modelling mortality risk and notes the following:

- The "Raw_Mortality" model worksheet contains age-specific annual risks of death (adjusted for risk factors) from Bradt *et al.*[6] These values are used in the company's model to characterise the risk of death in people who are not functionally cured (i.e., all patients in the SoC group and the minority of exa-cel-treated patients who do not achieve functional cure). The title of Table E2 in the appendices of the report by Bradt *et al.* suggests that these values are annual probabilities of death. In the model, these values are treated as rates and are divided by 12 to convert them to reflect a monthly interval. The monthly rate is then assumed to reflect the baseline SCD mortality risk excluding any excess complication-related risks. The model trace

calculations then convert this rate to a probability, but treat it as an absolute number of new deaths which is applied in every cycle, regardless of how many patients (if any) are still alive. Because this baseline SCD mortality risk is applied repeatedly over all model cycles, the cumulative probability of being dead inevitably exceeds 1.0 when all patients have died. This occurs at Month 479 in the SoC group.

- The DSU does not understand the company's rationale for estimating deaths in an additive fashion, rather than using conditional probabilities of dying. If all complication-related excess mortality risks are removed from the model, the cumulative probability of remaining alive in a given cycle should simply reflect the probability of being alive at the end of the previous cycle multiplied by one minus the conditional probability of all-cause death in the current cycle. This approach would prevent the cumulative probability of being dead from ever exceeding 1.0. The DSU believes that the company's additive approach is mathematically incorrect and therefore reflects an error.
- This issue can be illustrated using the general population life tables applied in the exa-cel group of the company's model. The DSU has amended the company's model such that survival for the entire exa-cel group is driven exclusively by the SMR-unadjusted general population life tables for men ("qx"), assuming 100% cure, with no failures or VOCs in any patient, and excluding the =MIN() constraint. This is shown by the blue line in Figure 1. Overall survival based on these same life table risks using a conditional probability approach is shown by the red line in Figure 1. The two approaches diverge considerably. The company's approach underestimates long-term survival and produces negative probabilities which are logically impossible. The same issues will also apply to the SoC group.

Figure 1: Comparison of company's additive survival approach (blue) versus conditional survival approach (red) – exa-cel group, SMR-unadjusted life tables, men, constraint excluded



OS - overall survival

Based on the above discussion, the DSU agrees with the EAG that this aspect of the model should be revised to ensure that it is mathematically correct. This would require modification of the existing formulae, but not a full model rebuild.

Issue 2: Patients in the model can have more than one concurrent complication and can potentially "die twice"

The EAG report[1] explains that whilst it is plausible that patients can experience more than one concurrent complication in a given cycle, the company's modelling approach implies that it is also possible for patients to "die twice" in a given cycle. The EAG report further highlights that the excess risk of death is calculated based on the prevalence of each complication, but this risk is not applied to the patients with those specific complications (as described in Section 2 of this DSU report).

The DSU agrees with the EAG that the company's model only partially tracks patient history, and that the risk of complication-related death is estimated based on the frequency of specific complications, but is applied indiscriminately across the whole surviving cohort. This approach may overestimate the excess mortality associated with SCD complications and fails to properly characterise the impact of complication-dependent mortality on those patients who have these complications. The consequence of both of these issues is that the estimated probabilities of chronic complications amongst the surviving cohort is probably incorrect, which in turn, likely also influences predicted survival. The DSU considers that all of these issues appear to be fair criticisms of the company's model and that, in principle, applying a more conventional state transition modelling approach - whereby health states are defined according to combinations of SCD complications and the risks of developing complications and dying are dependent on the patient's current state - would not suffer from these computation problems.

The DSU notes that based on the range of acute and chronic complications included in the company's existing model, the development of a conventional state transition model which includes all possible combinations of complications would require 32,768 alive states (15 factors, each of which could be present or absent = 2^{15}). A dead state would also be required. This would result in a very large, unwieldy model. It is also likely that such a model would be difficult to populate with transition probabilities which properly take into account co-occurring complications and competing risks. This is neither a feasible nor proportionate solution.

Section 5.1.1 of the EAG report[1] proposes an entirely different model structure to that put forward by the company. The EAG's proposed model adopts a state transition approach, and whilst not fully clear, the description implies that the EAG would advocate the inclusion of a comparatively smaller number of mutually exclusive alive health states, including: VOCs, stroke, splenic sequestration, ACS, PE and PH, plus a dead state. The EAG proposes the inclusion of these states based on statistically significant

predictors of HRs in the analysis reported by Shah *et al.*[3] Based on the diagram of the proposed causal relationships between VOCs and other events (EAG report, Figure 22), events cannot co-occur and history of prior events is not obviously tracked. The EAG's proposed model specification also suggests the inclusion of other clinical events external to the Markov structure (i.e., as additional complications co-occuring within the states), including heart failure, infections, gallstones, leg ulcers, avascular necrosis, liver complications, neurocognitive impairment, retinopathy and VOC rates. The DSU does not consider the development of the EAG's proposed model to reflect a proportionate solution to the problems raised in the EAG report,[1] and it is very unlikely that this model could be developed and evaluated within the available timescales for this appraisal. It is also unclear whether the proposed model structure would fully mitigate against the problems regarding the overestimation of complication incidence and mortality risks identified in the company's model, whether it is reasonable to ignore history of prior events (assuming this is what the EAG intends), or whether the predictions from this model would be more reliable than those generated by the company's existing model. The DSU believes that there may be a more pragmatic way forward in modifying the company's existing model to ensure that it is suitable for informing NICE decision-making (see recommendations in Section 4).

Issue 3: Exclusion of full pre-treatment costs for exa-cel and long-term outcomes for patients in whom exa-cel treatment is planned but not delivered

The EAG report[1] highlights that the company's model assumes that all patients are successfully infused with exa-cel and that this is not consistent with the experience of the CLIMB-SCD-121 study.[2] The EAG report also states that the model does not account for the outcomes of patients who discontinue treatment between apheresis and myeloablation. The EAG suggests that an initial decision tree should be used to model the outcomes of the procedures related to the provision of exa-cel. In addition, the EAG report suggests that the proportion of patients with failed apheresis should be assigned the costs of apheresis only, whereas the proportion of patients who do not receive exa-cel (those who discontinue after manufacturing of exa-cel) should be assigned the costs of both apheresis and the costs of the exa-cel product.

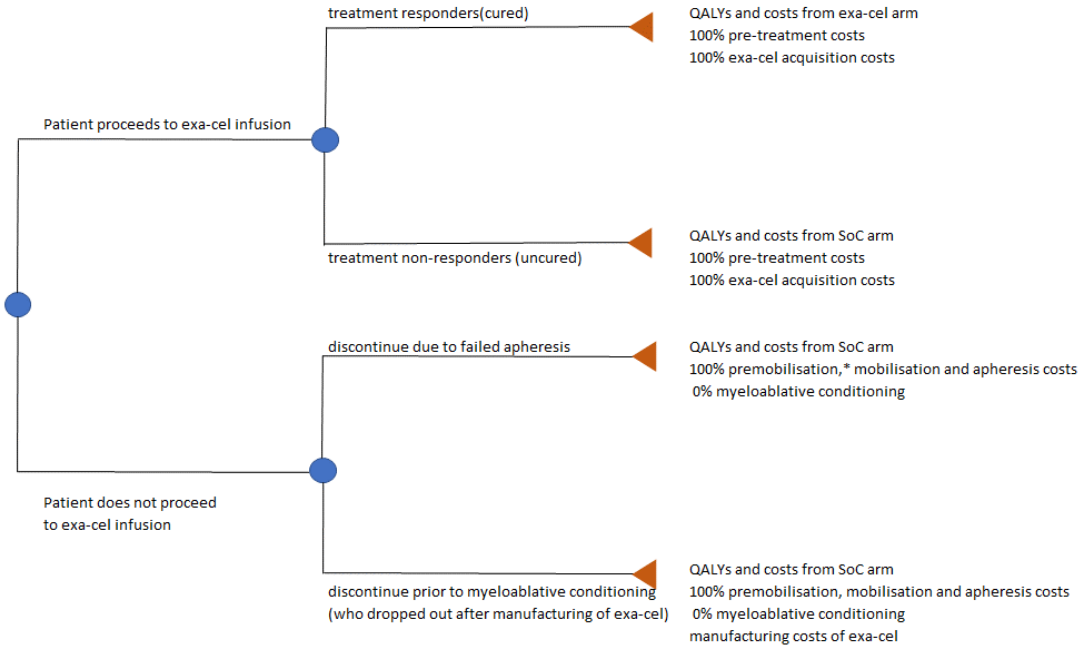
The DSU believes that the model structure should be amended take account of the following factors:

- Outcomes for people who do not receive exa-cel should be included in the model (18.96% of patients in whom exa-cel treatment is planned). These patients should not be assumed to have the same outcomes as those who do receive exa-cel; instead, they should reflect the SoC group.
- The costs of premobilisation, mobilisation and apheresis should be included in the model for all patients undergoing these pre-treatment procedures for exa-cel, regardless of whether they actually go on to receive exa-cel.
- Further clarity is required from the company around who will bear the cost of the exa-cel product in the event that the patient does not go on to receive it due to manufacturing error. If

the NHS is liable for the cost of the product in these cases, it should be included in the model for non-infused patients.

As suggested by the EAG, these factors could be captured in the company's model by adding a simple decision tree. A proposed structure for the decision tree is shown in Figure 2.

Figure 2: Proposed decision tree structure to account for outcomes and costs for patients in whom exa-cel is planned



** The cost of premobilisation for patients who do not receive exa-cel is already included in the company's model as an additional cost in the exa-cel-treated group*

4. Recommendations from the DSU

Based on the discussion above, the DSU agrees with the EAG that some modifications to the company's model are required, but considers that there may be alternative solutions which do not require a full model rebuild and which are more feasible within the available timescales of the appraisal. In the opinion of the DSU, the following amendments and assessments should be conducted using the company's existing model:

1. The probability of being alive in each cycle should be estimated based on conditional probabilities of survival, rather than using the company's additive approach. This will ensure that a maximum of 100% of patients can reach the dead state using a mathematically consistent approach, without the need to rely on constraints. This will require rewriting the formulae in the model trace worksheets. As part of this model amendment, the company should ensure that probabilities and rates, and conversions between the two, are handled appropriately and are

consistent with the original estimated parameters (e.g., from Bradt *et al.,*[6] and/or general population life tables).

2. A decision should be taken as to whether it is appropriate to include the excess mortality risks associated with SCD complications. In the opinion of the DSU and the EAG, the company's existing modelling approach may overestimate complication-related mortality risks because it assumes that these complications are independently associated with increased mortality risk, despite co-occurring in the same patients. The current model also cannot directly attribute that complication-related excess mortality risk to the patients with those complications. This has implications for the credibility of the modelled estimates of complications, survival, QALYs and costs in the SoC group. A more straightforward and transparent approach would be to remove the complication-related mortality risks altogether, and to model all-cause mortality in one step using conditional probabilities of death based on life tables and relevant SMRs. This suggested approach to handling mortality risks appears to be consistent with the model developed to inform the recent Institute for Clinical and Economic Review (ICER) evaluation of gene therapies for SCD.[10]
3. It is important to ensure that the modelled predictions of acute and chronic complications are clinically plausible (and ideally, consistent with external data) because these also drive the QALY losses and costs in the SoC group. Resolving the issues around how mortality is modelled alone (recommendations 1 and 2 above) is not enough. Clinical input and/or external data should be sought around:
    a. The plausibility of the SMR-uplifted mortality risks (applied in worksheet "Raw_Mortality" column K) and the resulting survival projections (estimated in column G in each of the model trace worksheets).
    b. The overall lifetime incidence of acute complications for the SoC group (shown in worksheet "Tx7", cells T16:Z16).
    c. The lifetime risk of ever having experienced each chronic complication in the SoC group (estimated in worksheet "Tx7", cells AT16:BA16).

    In the event that the model predictions are considered to overestimate the incidence of acute and/or chronic complications, it may be necessary to consider down-weighting these risks.
4. The costs and outcomes for patients in whom exa-cel treatment is planned but not delivered should be accounted for within the company's model structure. This could be done by adding an initial decision tree to the existing structure, as proposed in Figure 2.

5. References

1. Parsons J, Castelnuovo E, Dracup N, Connock M, Armoiry X, Grove A*, et al.* Exagamglogene autotemcel for treating sickle cell disease Warwick Evidence; 2023.
2. Clinicaltrials.gov. A safety and efficacy study evaluating CTX001 in subjects with severe sickle cell disease. Available from: https://clinicaltrials.gov/study/NCT03745287 [Date accessed 13/12/2023]. 2023.
3. Shah N, Bhor M, Xie L, Halloway R, Arcona S, Paulose J*, et al.* Evaluation of vaso-occlusive crises in United States sickle cell disease patients: A retrospective claims-based study. . *Journal of Health Eocnomics and Outcomes Research* 2019;6(3):106-17.
4. Yeruva SL, Paul Y, Oneal P, Nouraie M. Renal failure in sickle cell disease: Prevalence, predictors of disease, mortality and effect on length of hospital stay. *Hemoglobin* 2016;40(5):295-9.
5. Singh A, Minniti C. Leg ulceration in sickle cell disease: An early and visible sign of end-organ disease. In: *Sickle cell disease - pain and common chronic complications. http://dx.doi.org/10.5772/64234*; 2016.
6. Bradt P, Spackman E, Synnott PG, Chapman R, Beinfeld M, Rind DM*, et al.* Crizanlizumab, voxelotor, and L-glutamine for sickle cell disease: Effectiveness and value. Institute for Clinical and Economic Review, January 23, 2020. https://icer.org/wp-content/uploads/2020/10/ICER_SCD_Evidence-Report_031220-FOR-PUBLICATION.pdf; 2020.
7. National Institute for Health and Care Excellence. Sickle cell disease: managing acute painful episodes in hospital. NICE: London; 2012.
8. American Academy of Opthalmology. Sickle cell retinopathy. Available from: https://eyewiki.org/Sickle_Cell_Retinopathy [date accessed 13/12/2023]. 2023.
9. Gardner RV. Sickle cell diseases: Advances in treatment. *Ochsner Journal* 2018;18(4):377-89.
10. Beaudoin F, Thokala P, Nikitin D, Campbell J, Spackman E, McKenna A. Gene therapies for sickle cell disease: Effectiveness and value; Evidence report. Institute for Clinical and Economic Review, August 21, 2023. https://icer.org/assessment/sickle-cell-disease-2023/. . 2023.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

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 (see section 1.1).

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 **12 January 2024**. 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	
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 SCD, preparing the technical report, and for providing us with the opportunity to engage in the technical engagement process. Our response will address the EAG report, and will also take into consideration the recommendations made by the NICE Decision Support Unit, which provide actionable alternatives.

Our response is split into three separate parts:

1) Our response to the key issues for engagement raised by the EAG
2) Appendices: a) alternative mortality modelling, b) comparison of latest data cut with D120 data cut
3) Details of the revised company base case

With regard to point 3, the latest data cut (hereafter referred to as the ASH 2023 data cut), presented at the American Society of Hematology congress in December 2023 (1), and anticipated for publication in the *New England Journal of Medicine* in March, includes data for only one additional patient relative to the original D120 data cut (2, 3). As such, we provide a brief comparison table (Table 8), but this data does not inform the economic model.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue impacting decision making:	Description:	Does this response contain new evidence, data or analyses?	Response:
Issue 1:	Single-arm trial with short-term follow-up	No	The EAG has concerns about the sample size, duration of follow-up, and single-arm nature of CLIMB SCD-121. We note that each of these three concerns are also raised individually in issues 3-5, and as such they are addressed in response to those issues rather than here to avoid duplication. However, we note the below overarching points, which hold true for all the EAG's criticisms of the trial design. **Exa-cel is now approved by the MHRA, as well as other regulatory authorities, for the indication under review.** The evidence package supporting exa-cel has been considered sufficiently robust to support regulatory approval, not just by the MHRA but also the FDA, as well as a positive opinion from the CHMP. There are numerous instances of drugs being approved by the EMA/MHRA and rejected by the FDA, as well as vice-versa. The fact that regulatory bodies have taken a consistently positive view of the evidence package supporting exa-cel is validation of the trial's suitability to address the decision problem in this appraisal. Furthermore, the conditional marketing authorisation received from the MHRA mandates collection of additional data to support the long-term efficacy and safety of exa-cel, data that could and would be used to inform a follow-up appraisal should a managed access agreement be agreed, as proposed by Vertex. **Exa-cel is addressing a substantial unmet need, as validated by conditional approval.**

			Conditional approval of medicines by MHRA (& EMA, which MHRA follows on this in terms of eligibility) requires the fulfilment of several criteria: • the benefit-risk balance of the medicine is positive; • it is likely that the applicant will be able to provide comprehensive data post-authorisation; • the medicine fulfils an unmet medical need; • the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required. We draw particular attention to criteria #2 and #3. Exa-cel is addressing a substantial unmet need, only exacerbated by the withdrawal of crizanlizumab, and ongoing TA of voxelotor by NICE. Further, whilst we strongly defend the position that the current data package is sufficiently robust to inform decision-making, additional data collection provides confidence that any remaining uncertainties would be addressed, whilst facilitating timely access to a novel treatment that represents a paradigm shift in the management of SCD. Exa-cel was also granted an innovation passport by the MHRA, for which qualifying criteria include 'the condition is life-threatening or seriously debilitating' and 'there is a significant patient or public health need'. **CLIMB SCD-121 was designed in accordance with regulatory advice.** CLIMB SCD-121 was designed consistently with FDA advice on Gene Therapy trials that a single-arm trial may be considered if there are feasibility issues with conducting a randomised controlled trial (RCT) (4). As described in our response to subsequent clinical issues, the autologous nature of exa-cel, and lack of clinical equipoise make an RCT unfeasible. The FDA guidance also states that sponsors may consider the clinical performance of available therapies when setting the performance goal or criteria against which the product effect will be tested (4). This has been done via an Indirect Treatment Comparison (ITC) described in the submission and summarised in point 5 below. In addition, the FDA state that an endpoint based on a treatment outcome that is not expected to occur spontaneously in the natural course of the disease can facilitate the interpretability of a small trial. The likelihood of a patient with recurrent VOC becoming VOC free for 12 months fulfils this criterion (4). In summary, Vertex firmly defends the sufficiency of CLIMB SCD-121 to address the decision problem in the indication under review. Regulatory bodies including the MHRA have approved exa-cel, taking the view that the high level of unmet need means that the benefit of immediate availability outweighs any potential uncertainty relating to additional data. Furthermore, regulatory approval includes the condition that

			additional data is collected, data that would be included in a re-submission following a period of managed access, as proposed by Vertex.
Issue 2:	Generalisability of trial outcomes to NHS practice	Yes/No	The EAG notes that of the 16 study sites for CLIMB SCD-121, only 1 was in the UK, with the rest spread across the US (9 of 16 sites), Canada (1 of 16 sites) and western Europe (5 of 16 sites). As a result, the EAG has concerns over the extent to which patient characteristics and treatments received (before and after the trial) in CLIMB SCD-121 are generalisable to UK clinical practice. Whilst our main argument against this is that the vast majority of clinical trials informing the clinical efficacy evidence for NICE appraisals will only include a small proportion of patients recruited at UK centres, with others not including any UK sites (including the majority of trials guiding UK SCD practice e.g. MSH Hydroxyurea trial, STOP trial for stroke prevention and the pivotal crizanlizumab trial), there are several other points specific to SCD that support the generalisability of CLIMB SCD-121 to UK clinical practice. **Clinical practice is highly similar between the UK, Europe, and the US.** Clinical practice across the UK, Europe and US is generally the same and based on the same trial and natural history data. There are extensive collaborations between these countries in clinical practice, guideline development, natural history generation and trial development. Whilst there are no international guidelines for the comprehensive treatment of SCD, evidence for international collaboration/consistency include: • International guidelines on specific aspects of clinical care. For example, the International Collaboration for Transfusion Medicine (ICTM) produced a paper on transfusion in haemoglobinopathies in 2018 (5). The British Society of Haematology (BSH) subsequently produced a position paper confirming a consensus in the UK for the recommendations outlined in the ICTM paper (6-8). • Comprehensive US guidelines which include international authors. For example, the American Society of Hematology (ASH) (9) produced Clinical Practice Guidelines on Sickle Cell Disease in 2020/2021 on Transfusion Therapy, Cerebrovascular disease and Stem Cell transplantation which all include UK and/or European co-authors. Furthermore, the recommendations in these guidelines have been adopted in the UK. • Marked consensus between UK guidelines and those available in Europe and the US. For example, the NHLBI produced comprehensive guidelines on the management of Sickle Cell Disease in the

			UK in 2014 (Evidence-Based Management of Sickle Cell Disease: Expert Panel Report) (10). The recommendations in this guideline are replicated in the more recent UK guidelines (Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK and Sickle Cell Disease in Childhood: Standards and Recommendations for Clinical Care) (11, 12). Similarly, the recommendations in the ASH 2020 guidelines for sickle cell disease: transfusion support are broadly in agreement with those in the BSH guidelines 'Red Cell Transfusion in Sickle Cell Disease' from 2016 (7, 13, 14). • UK guidelines are primarily based on US research and reflect US practice. For example, the BSH guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease and the national guidelines on adult and paediatric sickle cell clinical care based their key recommendations from pivotal trials performed in the US (11, 12, 15). This includes the Multicenter Study of Hydroxyurea (MSH) and the BABY-HUG study which showed the efficacy of hydroxycarbamide (Hydroxyurea) in the reduction of VOC in adults and children with SCD (16, 17). These important randomised trials from the US led to guideline production and significant changes in clinical practice in the US, UK and Europe including the recommendation that hydroxycarbamide should be offered to infants aged 9-42 months with SS/SB0 regardless of clinical severity (11, 12). Treatment guidelines are centred around supportive care, with hydroxycarbamide recommended for patients experiencing multiple VOCs in a 12-month period, or experiencing VOCs that are impacting on their HRQoL, although benefits should be weighed against the challenging tolerability profile. Similarly, recommendations on use of RBC transfusions are consistent, primarily for the prevention of complications such as stroke in high-risk patients. **UK clinical experts support the generalisability of CLIMB SCD-121 to UK clinical practice.** The topic of generalisability was discussed at an advisory board convened by Vertex in support of this appraisal (18). Clinical experts noted that the genotype distribution and gender split in the trial are both in line with UK clinical practice, and that the historical annual VOC rate was similar to the rate they would expect in patients likely to be treated with exa-cel in the UK. Experts noted they would initially prioritise younger patients for treatment, and so the mean age of 21.2 years (D120, FAS) is likely to be broadly applicable (2). **Key pivotal trials in SCD did not include study sites in the UK, but their findings have been fully incorporated into UK practice.**

			Almost all the key trials in SCD over the previous 40 years have been performed in the US but the findings have been incorporated into UK clinical practice and clinical guidelines. These have been instrumental in improving care for patients with SCD in the UK and are now considered standard of care in the UK. It is therefore universally accepted within the SCD healthcare community that the results from SCD trials performed outside the UK (most commonly from the US) are generalisable to UK practice and indeed it could be postulated that lessons learnt from these trials have transformed UK practice and improved patient outcomes in the UK. Key examples are given below (this list is not exhaustive). Building on the examples described earlier on in our response to key issue 2, we note further examples here. The Stroke Prevention Trial in Sickle Cell Anaemia (STOP trial) enrolled 130 children in the US showing that regular transfusion therapy significantly reduces stroke risk in children with a raised trans-cranial doppler value (TCD). This US trial led to major changes of clinical practice in the UK with the introduction of a paediatric TCD screening service, transfusion being offered to children with SCD who have a raised TCD and a reduction in paediatric stroke rates (19). Annual TCD scanning is a key standard of care for children with SCD (12). The TCD with Transfusions Changing to Hydroxyurea trial (TWITCH) involved 121 children in the US and showed that hydroxycarbamide was as effective as transfusion therapy in primary stroke prevention. Based on this trial, UK recommendations state that children who have started regular blood transfusion for abnormal TCD can be switched to hydroxycarbamide therapy after 1 year of transfusions. This has now been embedded into UK clinical practice (15, 20). Finally, we note that crizanlizumab's pivotal trial (SUSTAIN) included 60 study sites, none of which were in the UK. Whilst this was originally flagged as an issue by the attendant EAG, it was resolved following technical engagement because of clinical expert input (21). As described above, clinical experts (n=4) participating in an advisory board agreed that the baseline characteristics in CLIMB SCD-121 are generalisable to UK clinical practice. In summary, clinical practice and treatment guidelines for SCD are consistent across countries. Whilst only 1 study site in CLIMB SCD-121 is in the UK, other countries represented (US, Canada, western Europe) are likely to treat patients in a similar way to the UK, and local clinical experts agree that the CLIMB SCD-121 study population is generalisable to UK practice.

Issue 3:	Trial sample size	Yes	The EAG has concerns with the sample size in CLIMB SCD-121, with 29 patients in the PES, and 43 patients in the FAS at the time of the D120 data cut. Further, in the EAG's view, the number of patients severely diminishes beyond about 12 months. **Patient numbers do not severely diminish beyond 12 months.** Firstly, we refute the EAG's claim that patient numbers diminish 'beyond about 12 months'. Twenty-nine (30 if including the ASH 2023 data cut) of the patients in CLIMB SCD-121 were included in the PES, defined as patients who were followed for at least 16 months after exa-cel infusion. This equates to 69% of patients having ≥16 months of follow-up, with the median VOC-free duration in the PES being 20.7 months. **CLIMB SCD-121 was sufficiently powered to demonstrate benefit of exa-cel.** CLIMB SCD-121 was designed in consultation with the FDA with a sample size of approximately 45 patients. This sample size of 45 patients was pre-specified and adequate for statistical power. 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 endpoints with 1-sided alpha of 2.5%. We note that at the most recent data cut-off, 44 patients have been dosed with exa-cel. **Exa-cel demonstrates a highly favourable benefit-risk profile at interim analysis.** At the pre-specified interim analysis in CLIMB SCD-121, exa-cel demonstrated overwhelming efficacy, with broad, transformational and clinically meaningful benefits in the indication under review. Exa-cel has demonstrated consistent, durable benefit in subjects with SCD. At D120, the overwhelming majority (28 of 29, 97%) of subjects in the PES reached the primary end-point VF12 (absence of any severe VOCs for at least 12 consecutive months after exa-cel infusion) and 100% of subjects reached HF12 (free from inpatient hospitalisation for at least 12 months after exa-cel infusion) and these benefits were sustained. Exa-cel was generally safe and well tolerated. The safety profile of exa-cel is generally consistent with busulfan conditioning and autologous HSCT. The safety profile of exa-cel has been adequately characterised with risks that are readily identified clinically or with routine laboratory monitoring and can be managed. **MHRA, FDA, and EMA (CHMP) are all in agreement that the data package is sufficient.** As described in our response to issue 1, since receipt of the EAG report, MHRA, FDA, and EMA (CHMP) have all approved, or pre-approved exa-cel, supporting the robustness of the data package. As already

			mentioned, there are several examples of drugs approved by EMA that were rejected by the FDA, that successfully achieved reimbursement in the UK. Regulators' consistently positive opinion of exa-cel is supportive of the data package. In conclusion, CLIMB SCD-121 was adequately powered to assess the efficacy of exa-cel, which is overwhelmingly demonstrated, with 28 of 29 patients in the PES achieving VF12. Of the 44 patients in the FAS, at the latest data cut (presented at ASH), 30 of these have ≥16 months of follow-up post-infusion with exa-cel (1). Finally, approvals from MHRA, FDA, and EMA (CHMP positive opinion) affirms the position that the data package for exa-cel is sufficiently robust for decision-making. Given that almost all patients achieved the primary endpoint, regardless of genotype, age, or any other characteristics, the sample size is sufficient to clearly demonstrate the effectiveness of exa-cel.
Issue 4:	Short-term follow-up of participants	No	The EAG notes that as CLIMB SCD-121 is still ongoing, there is a lack of long-term follow-up data available. On this basis, the EAG state that it is impossible to assess the efficacy of exa-cel beyond the short-term. Whilst the definition of short-term may be subjective, it is Vertex's view that ~2 years of follow-up, which does not include the 60-day RBC washout period, is a sufficient length of follow up to demonstrate a clear and considerable benefit from exa-cel that shouldn't be delayed in getting to patients. In addition, it is important to highlight two key points that are supportive of the anticipated durability of exa-cel: 1. **Overwhelming efficacy/benefit of exa-cel therapy with minimal and well understood risk.** All but one patient in CLIMB SCD-121 achieved the primary endpoint, equal to a response rate of over 96% so, in contrast to other one-time therapies where response rates are lower, there is no necessity for additional follow up and analysis to understand predictors of response & potential subgroups where the effect may be more pronounced. 2. **CRISPR gene editing provides a permanent edit**: There is no biologically plausible explanation that the introduced CRISPR/Cas9 gene edit will not be permanent in SCD. Hb concentration and allelic editing remain stable in all patients at latest follow-up, with clinical experts aligned that these stable parameters at 24 months are highly predictive of long-term durability. **Median VOC-free period in the PES was almost 2 years at latest follow-up.** In the data presented at ASH 2023, patients in the PES who achieved VF12 (29 of 30 patients) had a mean duration of 22.4 months VOC free, with a range of 14.8 – 45.5 months (1).. Whilst the definition of short-

			term may be subjective, our view is that ~2 years of follow-up, which does not include the 60-day RBC washout period, is a sufficient length of follow up to demonstrate a clear and considerable benefit from exa-cel. At baseline, patients in the PES (n=30) experienced an average (mean) of 3.9 VOCs per year, with 2.7 inpatient hospitalisations due to severe VOCs. Following exa-cel treatment, not only did 29 of 30 achieve VF12, but all 30 patients achieved HF12 (1). It may be considered that this exceptionally high bar of efficacy, with 96.7% of patients achieving the primary endpoint in itself addresses uncertainty. **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 SCD. 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 SCD-121. 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. **Clinical expert feedback supports the expected long-term benefits of exa-cel.** As part of the appraisal process, Vertex consulted clinical experts to provide feedback on a range of topics, including predictors of permanent benefit in SCD (18). Clinical consensus was that they would like to see a sustained increase in HbF levels for 2 years to be confident that exa-cel is likely to provide a long-term benefit. Clinical experts also agreed that persistence of the gene editing in bone marrow and peripheral blood (allelic editing) is a suitable proxy for long-term durability. Indeed, it could be argued that HbF and allelic editing values are more appropriate proxies for long-term durability than VOC. Even after allo-HSCT where there is no biological reason for vaso-occlusion, ongoing painful episodes are seen. One study has shown that 21% of patients experience VOC in the 12 months after allo-HSCT (22). These are likely due to ongoing chronic pain, allodynia (pain elicited by normally innocuous, low threshold stimuli) and hyperalgesia (enhanced pain response to noxious stimuli) exacerbated by chronic opiate use. Clinical experts have stated the reasons for the VOC seen after exa-cel is likely to be similar. We note that at the most recent data cut, both HbF and allelic editing levels are stable, supporting the view that exa-cel is highly likely to be associated with a durable functional cure in these patients. **Data collection through managed access is proposed to address remaining uncertainty without hindering access for patients with a considerable unmet need.**

			Vertex robustly defend the duration of follow-up in CLIMB SCD-121 as suitable for decision-making - supported by the aforementioned regulatory approvals - and note the overwhelming efficacy of exa-cel, with 29 of 30 patients in the PES achieving VF12. However, to address remaining uncertainty, Vertex has proposed a managed access agreement, which would provide additional data with a longer duration of follow-up of patients in CLIMB SCD-121 and CLIMB-131. With mean duration of follow-up of 22.4 months as of June 2023, the proposed 3 years of data in the managed access agreement would include data for most patients in CLIMB SCD-121 beyond 5 years post exa-cel infusion. In conclusion, although we acknowledge that long-term durability for any medicine will always be subject to a certain level of uncertainty at the time of HTA decision-making, the modality of exa-cel, and lack of biological plausibility for reversal of genetic edits strongly supports the anticipated durability of effects, and therefore the duration of follow-up in CLIMB SCD-121 is suitable for HTA decision making today. At the time of latest data cut, patients in the PES had almost 2 years of follow-up, and almost all (29 of 30) had achieved the primary endpoint of VF12. Clinical experts were aligned that a durable effect out to two years post-infusion is highly predictive of long-term durability. Finally, Vertex have proposed a managed access agreement to facilitate timely access for patients with a high unmet need whilst collecting data to address any remaining uncertainties.
Issue 5:	Lack of control/comparator arm	No	The EAG notes that as a single arm study, CLIMB SCD-121 includes no randomised comparator or control groups. Without this, it is the EAG's view that they are unable to determine, with a reasonable degree of certainty the true impact of exa-cel. **A single-arm trial was suitable given the modality of exa-cel, and lack of equipoise.** CLIMB SCD-121 was designed as a single-arm study because of a lack of equipoise with existing standard of care treatments. In CLIMB SCD-121, 29 of 30 patients (96.6%) in the PES achieved VOC-free for 12 months or more. In contrast data from a RWE Medicaid study has shown that in patients with 2 or more VOCs per year who are receiving standard of care treatment only approximately 10% will not have a VOC in the subsequent year and furthermore only 16.9% of patients receiving standard of care (SoC) in SUSTAIN achieved this endpoint (21, 22). Therefore, the rate of achieving the primary end point of VF12 (absence of any severe VOCs for at least 12 consecutive months after exa-cel infusion) with standard of care is only around 10-17% (22, 23). In addition randomisation would not be possible; the unique autologous procedure for exa-cel necessitates open-label treatment.

			Due to phenotypic heterogeneity in SCD, a patient's own history of VOCs is a better predictor of future VOCs than a matched control. There is marked phenotypic heterogeneity in SCD with extreme variability in VOC rate between patients. A patient's past experience of VOC has been shown to be the strongest predictor of VOC rates over time and supports an underlying 'severe disease' phenotype for SCD (9, 24). Individual patient history as a key predictor of future VOCs is supportive of a single arm trial rather than concurrent randomised methodology using matched control subjects. Furthermore, the evidence from CLIMB SCD-121 of significant reduction (and/or elimination) of VOC along a patient's own time-line following treatment with exa-cel is highly relevant. **Of the 16 NICE appraisals identified for ATMPs, in 15 of 16 cases the pivotal trial was a single-arm study.** As presented in a separate Excel file, of the 16 NICE appraisals (across STAs and HSTs) identified for ATMPs, the only RCT was for axi-cel in 2nd line diffuse large B-cell lymphoma (25). The analogues considered span an array of therapeutic areas, including haematology (transfusion-dependent thalassemia, haemophilia B, various blood cancers). As such, the design of CLIMB SCD-121 is consistent with the approach taken by other ATMPs, for reasons described above. **In the absence of a control arm, an ITC was conducted, demonstrating exa-cel's superiority to existing options.** In the absence of direct head-to-head evidence an ITC was conducted, with results summarised in the CS. The results of the MAIC support the markedly superior efficacy of exa-cel compared with SoC (26). Despite limitations relating to effective sample sizes, the median annualised VOC rate for exa-cel was 0, compared to 2.98 for SoC taken from the SUSTAIN trial, and mean annualised VOC rate was 0.06 for exa-cel compared to 2.8 in the HOPE trial. This demonstrates the potential functional cure provided by exa-cel. Had CLIMB SCD-121 included an SoC arm, it is likely the trial would have been stopped early due to overwhelming efficacy, with all patients moved over to exa-cel. Whilst we note that this is somewhat speculative, it is clear that the outcome of patients prior to treatment with exa-cel and post exa-cel is markedly different, and that the impact of exa-cel is apparent beyond reasonable doubt. In conclusion, CLIMB SCD-121 was designed as a single-arm trial due to lack of equipoise with existing standard of care treatments and because of the need for a transplant procedure to deliver exa-cel. The

			benefits provided by exa-cel are a clear departure from disease natural history, and due to the variability of SCD, a patient's own history of VOCs is a strong predictor of future VOCs. Almost all previous NICE appraisals of ATMPs have been informed by single-arm trials, and this has not stopped the majority from achieving reimbursement.
Issue 6:	The model does not have the requisites for a Markov structure	Yes	The EAG is of the view that the economic model does not follow a Markov structure, and that as a result of the model structure the rates of chronic complications and mortality calculated in the model may be biased, and ultimately may invalidate the cost-effectiveness analyses and results. **Mortality predicted by the company's model aligns with the available real-world evidence.** The most significant critique within this issue, and the one to which the ICER will be the most sensitive, is mortality. Specifically, the model attempts to incorporate individual causes of mortality within a Markov cohort structure, which is challenging to achieve. However, the most important question is whether the model predicts mortality aligned with that expected in the relevant UK SCD population. A large real-world retrospective study of UK SCD patients with similar characteristics to those considered eligible for exa-cel reported mean and median ages at death of 40.17 years and 41.00 years, respectively, for a matched severe SCD cohort of patients (27, 28). The company base case predicts mean and median age at death of 43.56 years and 44 years, respectively, which align closely with those of the retrospective UK burden of illness study, despite the complex route through which mortality has been modelled. An alternative approach proposed by the DSU, outlined below, generates less realistic predictions. **Employing an alternative approach using different data generates less realistic survival estimates.** One alternative would be to model survival based on VOC frequency alone, which avoids the issues with multiple sources of mortality. The US Institute for Clinical and Economic Review (ICER) recently published their final report on gene therapies for SCD (29), in which mortality rates for patients on SoC were estimated using standardised mortality ratios (SMRs) estimated from a large US SCD cohort. We have utilised these SMRs in order to estimate alternative mortality rates in the model (an approach also suggested by the NICE DSU). When this alternative approach is applied, the model predicts mean and median survival of 50.42 and 52.00, respectively, which is materially higher than observed in the real-world UK setting (27, 28). Furthermore, implementation of this alternative approach reduces our base case ICER from [redacted] (severity and DCEA weighted) to [redacted]. In summary, despite its limitations, our original

			approach has better external validity for current SoC than alternative, simple methods proposed by the DSU. However, due to the error identified by the NICE DSU in the calculation of cumulative mortality (see below), the original model was also underpredicting survival in the exa-cel arm, which adversely impacted the ICER. The alternative approach used is described in Appendix A: Alternative mortality modelling using ICER group SMRs, included within this response document. **Issues with respect to cumulative mortality identified by the NICE DSU have been addressed.** The NICE DSU report further identified what they considered was an error in the calculation of overall survival estimates: "*The DSU does not understand the company's rationale for estimating deaths in an additive fashion, rather than using conditional probabilities of dying. If all complication-related excess mortality risks are removed from the model, the cumulative probability of remaining alive in a given cycle should simply reflect the probability of being alive at the end of the previous cycle multiplied by one minus the conditional probability of all-cause death in the current cycle*." We were not able to reproduce Figure 1 of the DSU report in the model but have amended the Markov trace to estimate conditional probabilities of dying (activated in the model by selecting a new dropdown added to the bottom of the **EAG Functionality** sheet). This approach is also automatically implemented when the ICER group SMRs are applied. Notably, when this conditional probability approach is applied, removing excess mortality generates overall survival identical to the general population survival (minor differences likely due to half-cycle corrections), further validating this amendment. The amendment increases life years (LYs) in both the SoC and exa-cel arms.
Issue 7:	Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	No	Approximately 20% of people who initiated the exa-cel treatment journey did not receive the infusion. Some of the dropouts are due to failure of apheresis (the process used to harvest cells from the patient) whilst others fail to obtain enough exa-cel for reimplantation. The latter group undergoes apheresis, accrues the cost of manufacturing exa-cel but drops out of the process just before myeloablation. After dropping out of the process, these patients continue to receive SoC. The EAG consider that these patients should be accounted for in the economic model via a decision tree, which captures not only the costs of the withdrawing patients, but also their outcomes. We address this issue as three separate aspects below:

			1) The NHS resource use costs of treatment failures 2) The costs of exa-cel for treatment failures 3) The outcomes of treatment failures **1) The NHS resource use costs of treatment failures** The model is already structured to account for the costs of patients who do not proceed to transplantation with exa-cel within the cost effectiveness estimates. Specifically, a cost uplift equal to the proportion of patients who withdraw is applied to the following categories of pre-transplant costs in the model: • Pre-mobilisation costs • Plerixafor • Hospitalisation for the mobilisation procedure The only category missing from the cost uplift was pre-transplantation RBC transfusion costs of £13,488. Acknowledging that the latter were excluded, we have included a cost uplift to these costs to account for the patients who withdrew. This change increases our severity and DCEA-weighted base case ICER from [redacted] to [redacted]. In summary, the NHS resource costs of patients who do not proceed to transplantation with exa-cel are largely captured in the model and we have included RBC transfusions in our updated base case ICER. **2) The costs of exa-cel for treatment failures** [redacted]

			3) The outcomes of treatment failures The only economic implication of these treatment withdrawals is additional costs, which have been accounted for via a cost uplift in the model and/or via a commercial arrangement. The impact on the ICER of including the outcomes of these subjects is substantial, as the large QALY gains of exa-cel are diluted by nearly 20%. It is therefore methodologically incorrect to consider the outcomes of untransplanted patients in the economic value of such a transformative treatment, given the only difference in their pathway of care vs remaining on SoC is their mobilisation procedure, and they never actually receive the treatment. This would be synonymous with including the outcomes of patients who are genetically tested for a targeted cancer treatment but are never actually treated.
Issue 8:	Vaso-occlusive crisis (VOC) rates as a predictor in a risk equation for acute and chronic complications	No	The EAG has concerns with the way in which VOC rates are incorporated into the model. They believe that by applying the 'number of VOCs' as a significant independent variable originates from a misinterpretation of the Shah *et al* (2019) study, and that as such the number of VOCs per cycle cannot be used as an intermediate outcome in the model. **The model has reasonable external validity with respect to comorbidities.** While we understand the EAG's focus on the methods of deriving incidence of comorbidities, it is important to consider the external validity of the model and whether there is likely to be significant bias in favour of exa-cel. This is possible to a limited extent by comparing the comorbidity rates reported in a UK cohort of severe SCD patients with those in the model and aligns with the NICE DSU suggestion to compare rates with external data (27, 28). The age at index date of SCD patients in this study was 25 years and the mean follow-up of these patients was approximately 5 years. We therefore consider the proportion of patients on SoC with a given chronic comorbidity at age 30 in the economic model vs the prevalence reported in the UK severe SCD cohort. Table 1 shows that three comorbidities (chronic kidney disease, neurocognitive impairment, and post-stroke) are overpredicted by the model, but others are generally aligned. As a substantial proportion of the value in the model is contributed by life years, and mortality was shown to have external validity in Issue 6, the bias in favour of exa-cel from overprediction of these 3 comorbidities is likely to be small. With respect to acute comorbidities, the number of events predicted by the model was compared with the rate per patient-year in a UK severe SCD cohort (27, 28). It can be seen in Table 2 that other than stroke, almost all of these events are underpredicted by the model, which biases against the exa-cel arm.

Table 1: comparison of model chronic comorbidities with UK severe SCD cohort

Comorbidity	Model prevalence at age 30	Severe SCD UK prevalence
Chronic kidney disease	[redacted]	5.55%
Pulmonary hypertension	[redacted]	10.21%
Avascular necrosis	[redacted]	Not reported
Heart failure	[redacted]	6.36%
Neurocognitive impairment	[redacted]	5.46%
Post stroke	[redacted]	2.42%
Retinopathy	[redacted]	18.53%
Liver complications	[redacted]	7.79%

Table 2: comparison of model acute comorbidities with UK severe SCD cohort

Comorbidity	Model rate per patient-year	Severe SCD UK rate per patient-year
Acute chest syndrome	[redacted]	0.520
Stroke	[redacted]	0.000
Acute infection	[redacted]	0.200
Acute kidney injury/failure	[redacted]	0.130
Gallstones	[redacted]	0.290
Pulmonary embolism	[redacted]	0.060
Leg ulcers	[redacted]	Not reported

Use of the Shah paper to predict incidence of comorbidities by VOC frequency

Below, we address 3 issues raised by the EAG individually:

			1. Interpretation of the Shah paper 2. Use of Shah for deriving event incidence rate in SCD patients given frequency of VOC 3. Use of CLIMB SCD-121 VOC rates to calculate comorbidity incidence rates **1) Interpretation of the Shah paper** The Shah paper clearly demonstrated in Table 2 that VOC frequency over follow up was a predictor of comorbidities and death. Summarising extracts from the paper below: **Index date** was defined as the first clinical claim indicating SCD during the identification period. Every patient had a ≥6-month **baseline** (pre-index) and ≥1-year **follow-up** (post-index) period. **Baseline**: claims during at least 6 months *before* the index date, which included the following: • Demographics: Age, sex, race, and US geographic region • Charlson comorbidity index (CCI) • Individual comorbidities: **VOC**, pulmonary conditions such as ACS, cerebrovascular conditions (stroke), hepatic conditions (gallstones), splenic conditions (splenic sequestration), and other conditions that commonly occurred among SCD patients. • Baseline all-cause HRU (inpatient, outpatient and pharmacy visits. **Outcome measures**: events captured during the **follow-up** period: • VOC episodes (**predictor**): after the index date, VOC event rate was calculated in 100 person-years using the number of events divided by the length of the follow-up period. • Deaths: patients who died during the entire follow-up period. • Rate of complications: cerebrovascular, hepatic, pulmonary, and splenic conditions. Taking selected extracts of text below: • "Cox proportional hazards regression was used for the multivariate analysis of the time to first complication after the index date**,** concerning the relationship between **the rate of follow-up VOC and life-threatening complications requiring acute care -** including ACS, splenic sequestration, pulmonary embolism, stroke, pulmonary hypertension, and death.

- For the Cox model, **the rate of follow-up VOC events before the complication and death** were identified.
- Considering the possibility of progression of diseases with time, **follow-up VOCs were controlled in the model as time-varying variables**.
- The impact of the complications was also controlled in the model. For example, if stroke is the dependent outcome, then other complications (i.e., ACS, splenic sequestration, pulmonary embolism, pulmonary hypertension) were put in the model.
- The number of **baseline VOC** events were controlled in the model as covariates.
- Hazard ratios (23), 95% confidence intervals (CI), and p-values were examined for the **follow-up VOC** rate and all other covariates."

In summary, VOCs and comorbidities were included as both baseline (**time invariant**) and follow-up (**time-varying**) covariates for the event of interest. The reported HRs in Table 2 of the publication used the **follow-up** VOC as predictor, while controlling for **baseline** events (including VOC/pain crises) and events that happened over the follow-up period prior to development of the comorbidity of interest or death.

Table 2 of the publication describes the relationship between the **rate of follow-on VOCs (time varying)** and statistically significant comorbidities at baseline and developed during the follow-up period prior to the event. These covariates are summarised in Table 3 below, by querying the footnotes in Table 2 of the publication. All HRs for rate of **follow-up** VOCs were statistically significant (confidence intervals all above 1 in Shah Table 2), whereas **baseline** VOC/pain crisis was only significant in the models for mortality, splenic sequestration, and stroke.

Table 3: Summary of significant covariates from regressions reported in Shah Table 2

Outcome measure	Significant baseline period covariates	Significant follow-up period covariates (in addition to VOC rate)

			Time-to-Death	Age, sex, race, region, CCI, baseline neoplasms, baseline VOC, baseline use of opioids, NSAIDs, iron chelating therapy, baseline all-cause HRU,	Pulmonary embolism, stroke, and pulmonary hypertension
			Time-to-Acute Chest Syndrome	Age, sex, race, region, baseline use of iron chelating therapy, folic acid, baseline transcranial doppler ultrasonography, baseline all-cause HRU	Pulmonary embolism
			Time-to-Splenic Sequestration	Age, baseline use of hydroxyurea, and baseline pain crisis	None
			Time-to-Pulmonary Embolism	Age, sex, race, region, CCI, baseline fever, baseline use of opioids	Acute chest syndrome, stroke, and pulmonary hypertension
			Time-to-Stroke	Age, sex, race, region, CCI, baseline fever and seizures, baseline use of NSAIDs, iron chelating therapy, tricyclic antidepressants, acetaminophen, baseline blood transfusions and pneumococcal vaccine, baseline VOC	Acute chest syndrome and pulmonary hypertension
			Time-to-pulmonary hypertension	Age, CCI, baseline use of opioids, folic acid, baseline blood transfusion, baseline all-cause HRU	Pulmonary embolism, stroke, and acute chest syndrome
			2) Use of Shah in deriving event incidence rate in SCD patients given VOC vs. no VOC As explained in the previous section, the Shah paper provides the HR of developing comorbidities or death conditional on the rate per patient-year of developing VOCs over the follow-up period. Each HR can be interpreted as the additional risk of developing the comorbidity or death, conditional on having experienced one VOC a year. In order to apply these HRs in the model, a baseline risk **for SCD patients with zero VOCs** is required. The baseline risk of the outcome with no VOC over the course of a year can be calculated from the Shah paper, as the paper provides: • The rate per patient-year of the event of interest in the overall cohort (Figure 2 in Shah) • The proportion of the cohort that experienced a VOC over the follow-up (30.86% for adults in Shah) • The hazard ratio for developing the outcome conditional on experiencing a VOC		

			The baseline risk of the outcome with no VOC was therefore estimated by rearranging the following equation: Mean event rate of Shah cohort = Baseline event rate$_{(0\ VOC)}$ * % of cohort with 0 VOCs + Baseline event rate$_{(0\ VOC)}$ * HR with VOC * (1-% of cohort with 0 VOCs) The risk of the outcome for those patients experiencing a VOC within each cycle was correctly estimated by applying the HR for VOC from Shah to the calculated baseline risk of the event in absence of a VOC. **3) Use of CLIMB SCD-121 VOC rates to calculate comorbidity incidence rates** The rate per patient-year of VOCs is available from the CLIMB SCD-121 study. However, it is clearly not possible for a patient to experience a fraction of a VOC during the model cycle period of 1 month; patients either have a VOC or not. In each cycle, the model therefore assumes that patients either do or don't experience a VOC. For those who don't experience a VOC, the baseline comorbidity rate when VOC = 0 is applied (as calculated in the previous section). For the proportion that do experience a VOC, the event rate when VOC = 1 is applied.
Issue 9:	Modelling of adverse events is partial to exa-cel short list and selected events.	No	The EAG consider that "NHS costs cannot include adverse events for products not yet used in clinical practice" and that costs of AEs related to exa-cel should be costed separately. However, the EAG also states that the unit cost of hospitalisation for the transplant procedure applied in the model was appropriate. **The model correctly assumes that AE costs of exa-cel are captured within the autologous-SCT unit cost.** The unit cost applied was the 100% inpatient autologous stem cell transplant HRG, which includes costs in the 30 days preceding and 100 days post-transplant. Logically, this HRG will include inpatient management of AEs (which will be primarily due to toxicity of the mobilisation procedure and/or a weakened immune system). It is therefore unclear how the EAG can accept the autologous stem cell cost in the model while also stating that NHS costs cannot include adverse events for products not yet used in clinical practice. Any incorporation of AE costs on top of the stem cell transplant would clearly introduce double counting of healthcare resource.

			Furthermore, the same issue arose in CAR-T appraisals, during which it was agreed that all AE costs, other than ICU admission, would be included within a proposed CAR-T tariff. Specifically, a one-off cost of £41,101 was considered appropriate to cover all costs associated with the first 100 days of CAR-T delivery other than the costs of conditioning chemotherapy drugs and intravenous immunoglobulin (30, 31). Notably, this one-off cost of £41,101 is substantially lower than the revised £72.8k costs incorporated in the model (see Issue 10) to cover the pre-transplant and early post-transplant costs (including the £25k autologous-SCT HRG).
Issue 10:	Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using distribution of patients' weight.	No	The EAG believes that the cost of weight-based drugs should be calculated for all possible weights (weight distribution), which they note is a well-established practice for cost-effectiveness modelling. The EAG has consequently recalculated the NHS costs of delivering exa-cel in the model. In considering this critique we have identified two errors in the model which led to over costing of plerixafor in our submitted base case: • We had multiplied the daily weight-based dose of plerixafor by 4 days AND by 2.2 cycles. In practice, plerixafor is given for 3 days in cycle 1, up to 3 days (but on average 2) in cycle 2 and for 2 days in subsequent cycles. We have therefore amended the model to assume that plerixafor is given during 2.2 cycles for on average 2.5 days. This reduces the cost per patient of plerixafor from £31,203 in our base case to £19,502. • The unit cost of a hospitalisation for mobilisation (peripheral blood stem cell harvest inpatient) had been doubled from £5,375 to £10,749 to account for multiple cycles but was then further multiplied by another 2.2 mobilisation cycles. We removed the initial doubling of the unit cost but retained multiplying by 2.2 cycles, noting that this may still be over-costing, given that the majority of HRGs represent the cost of a spell (i.e. total patient procedure). Amending these errors reduces the total pre-transplantation cost (pre-mobilisation costs, plerixafor, hospitalisation for the mobilisation procedure, supportive RBC transfusions) from £71,000 (£84,465 after accounting for treatment withdrawals) to £47,421 (£56,415 after accounting for treatment withdrawals). These exclude the costs of the transplant procedure, which add an additional £25k to the estimated delivery costs. The above changes reduce our severity and DCEA-weighted base case ICER from [redacted] to [redacted].

			In contrast, the EAG's total mobilisation costs (~£70k) add up to more than the HRG cost of an allogeneic SCT (the most expensive type of SCT). Plerixafor makes up £44k of this cost. Firstly, plerixafor is currently only commissioned where usual treatment fails to secure the collection of sufficient cells. In an NHS plerixafor commissioning report (32), the highest incremental cost of plerixafor per successful mobilisation procedure was approximately £20-24k (in non-Hodgkin's Lymphoma). In the SMC detailed advice document, a full course of plerixafor + G-CSF was estimated to cost £10-20k per adult patient. In summary, the EAG's delivery costs result in a substantial overestimate of the likely costs to the NHS of delivering exa-cel. Even after the aforementioned cost reductions, Vertex's revised estimate of delivery costs is generous, as adding on the additional cost of the transplant itself brings the total cost per patient (before accounting for treatment withdrawals) to £72,808, which we consider a fair estimate of delivery costs to the NHS. With respect to weight-based dosing of iron chelation regimens, we note that this was not considered an issue in the ongoing TDT appraisal and that adding this additional complexity makes little difference to results.
Issue 11:	The cost of supportive blood transfusions alongside implantations of exa-cel is not included in model costs.	No	The EAG states that it is not known whether the use of supportive transfusions will become part of clinical protocols for exa-cel, and as such believe that the cost for supportive transfusions should be included in the model. **Supportive blood transfusions received by patients during delivery of exa-cel are not synonymous with transfusions received as part of SoC.** The EAG has replaced the number of supportive blood transfusions at baseline in the company base case (5) with the number of annualised blood transfusions from the CSR (11.6). This is inappropriate, because the value in the CSR represents "all cause" blood transfusions received prior to baseline, including emergency blood transfusions for treatment of VOCs and their complications, as well as those for patients requiring chronic blood transfusions as preventive treatment against VOCs. "Supportive" blood transfusions are given over 8 weeks prior to mobilisation plus 8 weeks prior to transplant (accounted for by transfusions given every 3-4 weeks, hence the 5 in the model) then additional transfusions post-myeloablation, the latter being required following all SCT procedures, not just SCD. The company has therefore already over-costed supportive blood transfusions, given:

			• The cost of chronic, preventive blood transfusions at baseline is applied during the follow-up period to those exa-cel patients who are not yet considered "cured" of their SCD (thus double-counting the 5 supportive blood transfusions assumed for all patients in the model). • Supportive blood transfusions in the 30 days prior to transplant and 100 days post- transplant would be a component of the autologous SCT HRG cost. • The HRG cost for a VOC (applied to patients experiencing VOCs during engraftment) would also include the cost of blood transfusions required as part of an admission for a VOC and associated complications. Thus, the EAG's approach of using the baseline transfusion frequency double-counts the costs of transfusions given to manage VOCs.
Issue 12:	Range of acute and chronic complications included in the model is large, but risk reduction is based on assumptions	Yes	The EAG has concerns with the extent to which parameters in the model are based on assumptions. They believe that the gaps in the evidence should be recognised, and that the extent of uncertainty should not be overwhelming, to ensure that both the logic and outputs of the model are plausible. **The model is not very sensitive to comorbidities where VOC-based incidence is based on assumptions.** As discussed in Issue 8, the rates of many comorbidities are aligned with those observed in a severe SCD cohort in the UK. However, we acknowledge that the inclusion of additional VOC-based incidence underpinned by assumptions introduces additional uncertainty. In order to explore this, we have conducted a sensitivity analysis whereby the additional complication risks arising from VOCs are removed from the model (HR set to 1) in cases where the incremental risk is underpinned by an assumption. For these comorbidities, the published cohort rates from the literature are applied, without applying additional HRs for VOCs. This has been carried out for the following comorbidities: Acute complications: • Acute infections • Gallstones • Leg ulcers Chronic complications: • Avascular necrosis • Heart failure

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>

Neurocognitive impairment
Sickle retinopathy
Liver complications

The results of this sensitivity analysis both including individual comorbidity-based mortality and using the ICER group SCD SMRs implemented in Issue 6 are provided in Table 4 below. It can be seen that in both instances, impact on the results is relatively small, with severity and DCEA-modified ICERs increasing by only 2-4%. Note that the scenario including individual comorbidities includes the fix to the error calculating cumulative mortality in Issue 6, hence the divergence from the original base case ICER of [redacted].
Table 4: ICERs with assumption-based comorbidity incidences removed
<table>
<tr><th></th><th>Including comorbidity-based mortality (base case)</th><th>SCD SMRs from ICER group (see Issue 6</th></tr>
<tr><td>Including assumption-based HRs (base case)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Excluding assumption-based HRs</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Note to EAG: This scenario can be selected via the dropdown at the bottom of the EAG Functionality sheet. The formulae have been modified in the pale orange cells in the Raw_complication_risks sheet (leading to different baseline comorbidity risk estimates) as well as in the Complication risk inputs sheet (HRs conditional on VOC set to 1).
</td>
</tr>
<tr>
<td>Issue 13:</td>
<td>Underestimation of uncertainty in modelling of overall survival in exa-cel and standard of care.</td>
<td>No</td>
<td>The EAG considers that uncertainty has been adequately accounted for in the economic model. Vertex has reviewed the document detailing parameters missing from the PSA provided by the EAG following the technical engagement call. The majority of these parameters were excluded from the PSA due to the parameter either being a zero or 100% probability or not being relevant to the base case (see Vertex comments added to the document sent by the EAG (33)). We have included additional parameters initially excluded from the PSA, including stratified probabilities of mortality of comorbidities. A re-run of the PSA</td>
</tr>
</table>

	Distributions not appropriately parameterised and some key inputs excluded from the probabilistic sensitivity analysis.		generated a severity and DCEA-modified ICER of [redacted], which remains aligned with the deterministic ICER of [redacted]. The new method of estimating SCD-based SMRs in the model applied in Issue 6 also incorporates all measures of uncertainty reported in the relevant literature (extracted from the ICER report and/or the Desai retrospective study). The uncertainty estimates are provided in columns M to P of the new inputs in the **Mortality inputs** sheet.
Issue 14:	Inclusion of severity modifier and implementation of 1.5% discount rate	No	The EAG believes that there is overlap between the conditions required to achieve the severity modifier and non-reference discount rate. Specifically, they note that the severity modifier captures the severity of the condition, which overlaps with the criterion for 1.5% discount rate 'the treatment restores people to full or near-full health when they would otherwise die or have severely impacted lives'. The EAG's view is that this may result in double-counting. **The severity modifier and non-reference discount rate are addressing different issues, and are described independently in the NICE methods manual.** In previous communications with NICE, there has been alignment that fundamentally the severity modifier and non-reference discount rate are addressing different issues. The severity modifier is a disease-specific modifier that does not consider treatment effect. In contrast, the non-reference discount rate primarily relates to treatment effect, as described below. **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 is 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 (34). **Discount rate** The 1.5% discount rate requires the 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. In summary, the severity modifier and non-reference discount rate have their own dedicated, independent sections in the NICE Methods Guide. The severity modifier is a disease-specific modifier that does not consider treatment benefit. In contrast, qualification for non-reference discount rate is driven by the technology and its benefits. As such, Vertex maintain the position that these modifiers are not mutually exclusive, and instead can be applied in combination where qualifying criteria are met.
Issue 15:	Non-reference case distributional cost-effectiveness analysis	No	The EAG considers that the DCEA should be excluded from the decision problem because it is not a part of the NICE reference-case, and that its introduction for this appraisal might result in undesirable inequity relative to previous HST assessments (*Vertex re-iterate as we did at FAC that this appraisal is proceeding along the standard STA route, not HST)*. Before getting into detail on our response, we draw attention to the recent voxelotor for SCD (GID-TA10505) appeal hearing, where one of the appeal points upheld related to the committee failing to recognise the barriers to access and/or take into account health inequalities for patients with SCD. This is a clear acknowledgement of the health inequalities experienced by patients with SCD and supports the point

			that SCD should not be treated as just another rare disease when it comes to taking account of health inequalities. **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 SCD 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). **The value for aversion to inequality is based on a survey, recommended by a single expert.** The underlying aversion value, which is derived from a survey of UK participants, was recommended to Vertex as a source to use by Prof Richard Cookson. **Health deprivation has been assumed to be an adequate proxy for ethnicity, not vice versa.** We would like to draw attention to the fact that we have, in fact, employed health deprivation in our DCEA analysis and have not used a proxy for health deprivation. However, we do assume that health deprivation by IMD group is an adequate proxy to reflect ethnicity-based health inequalities, since health inequalities are strongly correlated with health deprivation within the UK. **The DCEA provides other important metrics to consider, e.g., the Slope Index of Inequality (SII).** The DCEA provides important metrics to consider in relation to health inequalities, such as the SII. It is critical to acknowledge that there are clear inequalities within the SCD population. In addition to a reweighting of cost-effectiveness estimates based on health inequalities between deprivation quintiles, the DCEA provides a quantitative summary of health inequalities within the UK SCD population and, more importantly, the affect exa-cel is predicted to have on these health inequalities within this population, i.e., whether the product increases or decreases health inequalities within this population.

Appendix A: Alternative mortality modelling using ICER group SMRs

ICER group generated the SMRs reported below in Table 5 by comparing mortality rates between a US Medicare SCD cohort (reported by Desai et al., 2020) and those of the age and gender matched US population (35).

Table 5: Cumulative mortality and SMRs, ICER report

Age	Cumulative incidence	Mean SMR	Lower CI SMR	Upper CI SMR
Ages 13-18	15.0% (11.8-18.2%)	40.07	31	49.46
Ages 19-35	27.3% (24.9-29.6%)	24.24	21.8	26.65
Ages 35+	45.41% (41.4-49.2%)	17.48	15.47	19.5

The Desai analysis reported cumulative mortality and hazard ratios by frequency of VOCs in the baseline year (<2, 2-4 and ≥5). In the ICER report, the calculated SMRs are reported as being attributable to patients with ≥5 VOCs in the baseline year. However, the Desai manuscript does not attribute the cumulative mortality estimates used by ICER to the ≥5 VOC subgroup; we believe the figures include cumulative mortality from patients with <2 and 2-4 VOCs in the baseline year (this is evident from scrutiny of the Kaplan Meier plot, which shows that cumulative mortality for the ≥5 VOC group clearly exceeds that reported in the main body used by ICER group). Because the CLIMB SCD-121 inclusion criteria specified that patients had to have experienced ≥2 severe VOCs per year, the Desai SMRs, which included patients with <2 VOCs at

baseline, require adjusting to represent the more severe cohort eligible for exa-cel. The Desai data used for this adjustment are reported in Table 2 below:

Table 6: Data from Desai used for calculation of SMR by VOC subgroup

	Proportion of cohort		
Number of VOCs in baseline year	**<2**	**2-4**	**≥5**
Ages 13-18 (N=6,940)	55.1%	33.6%	11.3%
Ages 19-35 (N=11,064)	34.7%	33.2%	32.1%*
Ages 35+ (N=4,495)	43.5%*	32.8%	23.7%
Hazard ratio for mortality (95% Confidence interval)	1 (32)	1.26 (1.14–1.40)	1.57 (1.41–1.74)

*Note: published value increased by 0.1% to add up to 100%

As stated previously, we consider the overall SMRs calculated by ICER group to be attributable to the entire Desai cohort. They can therefore be considered as the weighted average of the SMRs for each VOC frequency subgroup, the weights being determined by both the proportion of patients in each subgroup and the hazard ratio (23) for mortality between subgroups, summarised below as:

Overall SMR =

$SMR_{(<2\ VOCs)} * HR_{(<2\ VOCs)} * \%\ cohort_{(<2\ VOCs)} +$

$SMR_{(<2\ VOCs)} * HR_{(2\text{-}4\ VOCs)} * \%\ cohort_{(2\text{-}4\ VOCs)} +$

$SMR_{(<2\ VOCs)} * HR_{(\geq 5\ VOCs)} * \%\ cohort_{(\geq 5\ VOCs)}$

Rearranging and simplifying the equation, the SMR in the <2 VOC reference group can be calculated as follows:

$SMR_{(<2\ VOCs)} =$

Overall SMR/

$(HR_{(<2\ VOCs)} * \%\ cohort_{(<2\ VOCs)} +$

$HR_{(2\text{-}4\ VOCs)}$ * % $cohort_{(2\text{-}4\ VOCs)}$ +
$HR_{(\geq 5\ VOCs)}$ * % $cohort_{(\geq 5\ VOCs)}$)

Once the SMR in the <2 VOC group is calculated, the SMRs for the 2-4 and ≥5 VOC groups can be calculated via multiplication with their respective HRs from Table 2. For the >35 age band, the whole cohort SMR calculated by ICER group is used as the Desai paper stated that mortality did not vary by baseline VOC frequency.

To calculate the risk of mortality of the CLIMB SCD-121 cohort, which excluded patients with <2 VOCs per year, the SMRs were weighted by the proportion of patients with ≥5 and 2-4 VOCs at baseline in the FAS ([redacted] and [redacted], respectively, values not available by age band). Weighting the SMRs calculated in the previous section by the proportions of patients in each VOC cohort in CLIMB SCD-121 leads to the SMRs summarised in Table 3 applied in the economic model (but using the cohort average for the >35 year cohort, as stated previously).

Table 7: SMRs by age band applied in economic model

	Proportion of cohort in CLIMB SCD-121 FAS*	
Number of VOCs in baseline year	**2-4**	**≥5**
Ages 13-18	[redacted]	[redacted]
Ages 19-35	[redacted]	[redacted]

	SMRs		**Weighted average SMR**
Number of VOCs in baseline year	**2-4**	**≥5**	**CLIMB SCD-121 cohort**
Ages 13-18	44.45	88.63	[redacted]
Ages 19-35	20.43	40.74	[redacted]
Ages 35+	17.48	17.48	17.48

*Note: values not available stratified by age band.

Vertex acknowledges the limitations in this approach, primarily that (1) hazard ratios are assumed equivalent to SMRs (2) hazard ratios were

not available stratified by age band from Desai (3) the proportion of the CLIMB SCD-121 cohort with ≥5 VOCs at baseline was not available by age band.

This approach also addresses the EAG's concerns regarding the lack of sensitivity analysis around mortality estimates (Issue 13) as all uncertainty estimates from Table 1 and Table 2 have been incorporated into the cohort SMRs.

Note to EAG:

These new calculations can be found at the bottom of the **Mortality inputs** sheet of the updated model and SMR-weighted monthly mortality rates have been added to column AB in the **Raw_Mortality** sheet.

A drop-down to select this option has been added to the bottom of the **EAG Functionality** sheet. When this option is selected, individual mortality rates or SMRs/HRs in the **Mortality inputs** sheet are set to 0 or 1, respectively, via the override cells. In all relevant Markov traces, the mortality rates in the column Base mortality – SCD rate is replaced by the new estimates. All amended cells have been highlighted in pale orange.

Appendix B: New evidence – ASH 2023 data cut vs D120

As described in the introduction, data from a further data cut (14th June, 2023) is expected to be published in *NEJM* in March 2024. This data was also presented at the American Society of Hematology 2023 congress (1). As presented in Table 8, this data cut includes only one further patient in the analysis set, and outcomes are highly similar. As such, this data has not been incorporated into the modelling.

Table 8: Comparison of D120 data cut vs ASH data

	D120	ASH 2023
Data cut-off date	16-Apr-2023	14-Jun-2023
Number in FAS	43	44
Number in PES	29	30

VF12	96.6% (28 of 29 patients)	96.7% (29 of 30 patients)
VOC-free duration; mean (range)	20.7 months (12.8, 43.6 months)	22.4 months (14.8, 45.5 months)
VOC-free through follow-up (of those to achieve VF12)	96.4% (27 of 28 patients)	96.6% (28 of 29 patients)
HF12	100% (29 of 29 patients)	100% (30 of 30 patients)

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 9: 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). Severity and DCEA weighted ICER
Issue 6: The model does not have the requisites for a Markov structure	Mortality was calculated in an additive function rather than calculating conditional probabilities of mortality.	Mortality is calculated as a conditional probability.	Original ICER: [redacted] Revised ICER: [redacted] Change from original: -£946 ([redacted])
Issue 7: Economic analyses do not account for costs and outcomes associated with treatment failures between	The cost of 5 supportive blood transfusions pre-mobilisation and myeloablation was not included in the cost uplift to	The cost of 5 supportive blood transfusions pre-mobilisation and myeloablation is now included in the cost uplift to account for treatment withdrawals.	Original ICER: [redacted] Revised ICER: [redacted] Change from original: +£36 ([redacted]%)

apheresis and myeloablation.	account for treatment withdrawals.		
Issue 10: Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using distribution of patients' weight.	The cost of plerixafor was calculated assuming 4 days of plerixafor per mobilisation cycle. The unit cost of stem cell mobilisation was pre-doubled before multiplying by the number of mobilisation cycles.	The cost of plerixafor is calculated assuming 2.5 days (2-3 days) of plerixafor per mobilisation cycle. The unit cost of stem cell mobilisation is multiplied by the number of mobilisation cycles.	Original ICER: [redacted] Revised ICER: [redacted] Change from original: -£396 ([redacted]%)
			DCEA & severity modified
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ] Unweighted: [redacted] Severity weighted: [redacted] DCEA & severity weighted: [redacted]	Incremental costs: [£££] Unweighted: [redacted] Severity weighted: [redacted] DCEA & severity weighted: [redacted]	Please provide company revised base-case ICER: [redacted]

Sensitivity analyses around revised base case

As described in Issue 6, a simplified analysis was carried out whereby an overall SMR for severe SCD was applied to uncured patients.
This analysis reduces the revised base case ICER by £1,131 to [redacted] ([redacted] decrease).

As described in Issue 8, a scenario analysis was conducted whereby hazard ratios by presence of VOC were excluded if they were based on assumptions; the reported rates per patient-year were used instead for all SCD patients.
This analysis increases the revised base case ICER by £451 to [redacted] [redacted] increase)

References

1. Frangoul H, Locatelli F, Sharma A, Bhatia M, Mapara M, et al., editors. Data on File - Exagamglogene Autotemcel for Severe Sickle Cell Disease
American Society of Hematology; 2023 06 December 2023.
2. Vertex Pharmaceuticals Inc. Data on File. Exa-cel Efficacy and Safety Update (16 April 2023). 2023.
3. Agency MHPR. Casgevy 4-13 x10^6 cells/ mL dispersion for infusion
(exagamglogene autotemcel). Vertex Pharmaceutical (Europe) Limited; 2023.
4. Services USDoHaH, Research FaDACfBEa. Human Gene Therapy for Rare Diseases 2020 January 2020.
5. Compernolle V, Chou ST, Tanael S, Savage W, Howard J, Josephson CD, et al. Red blood cell specifications for patients with hemoglobinopathies: a systematic review and guideline. Transfusion. 2018;58(6):1555-66.
6. Trompeter S, Massey E, Robinson S, Transfusion Task Force of the British Society of Haematology Guidelines C. Position paper on International Collaboration for Transfusion Medicine (ICTM) Guideline 'Red blood cell specifications for patients with hemoglobinopathies: a systematic review and guideline'. Br J Haematol. 2020;189(3):424-7.
7. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Advances. 2020;4(2):327-55.
8. DeBaun MR, Jordan LC, King AA, Schatz J, Vichinsky E, Fox CK, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv. 2020;4(8):1554-88.
9. Zakaria O, Buhalim RA, Almulhim F, Al Jabr FA, Alrashid A, Almutairi M. Clinical and Laboratory Predictors of Painful Vaso-Occlusive Crisis Among Sickle Cell Disease Patients: A Single-Center Study in Saudi Arabia. Cureus. 2021;13(5):e14980.
10. National Heart Lung and Blood Institute. Evidence-Based Management of Sickle Cell Disease. Available at https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf 2014 [
11. Sickle Cell Society. Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK 2018 [Available from: https://www.sicklecellsociety.org/wp-content/uploads/2018/05/Standards-for-the-Clinical-Care-of-Adults-with-Sickle-Cell-in-the-UK-2018.pdf.
12. Society SC. Sickle Cell Disease in Childhood Standards and Recommendations for Clinical Care. Available at https://www.sicklecellsociety.org/wp-content/uploads/2019/11/SCD-in-Childhood_Final-version-1.pdf 2019 [
13. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N, et al. Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. British Journal of Haematology. 2017;176(2):179-91.

14. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N, et al. Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion. British Journal of Haematology. 2017;176(2):192-209.
15. Qureshi A, Kaya B, Pancham S, Keenan R, Anderson J, Akanni M, et al. Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. Br J Haematol. 2018;181(4):460-75.
16. Charache S, , Terrin ML, , Moore RD, , Dover GJ, , Barton FB, , Eckert SV, , et al. Effect of hydroxyurea on the frequency of painful crises in Sickle cell anemia. New England Journal of Medicine. 1995;332:1317–22.
17. Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). Lancet. 2011;377(9778):1663-72.
18. Vertex Pharmaceuticals Inc. Data on file. Exa-cel UK HTA Advisory Board. 2022.
19. Adams RJ, , McKie VC, , Hsu L, , Files B, , Vichinsky E, , Pegelow C, , et al. Prevention of a first stroke by transfusions in children with sickle cell anemia & abnormal results on transcranial Doppler ultrasonography. New England Journal of Medicine. 1998;339:5-11.
20. Ware RE, Davis BR, Schultz WH, Brown RC, Aygun B, Sarnaik S, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. Lancet. 2016;387(10019):661-70.
21. National Institute for Health and Care Excellence. Crizanlizumab for preventing sickle cell crises in sickle cell disease. Committee Papers 2021 [Available from: https://www.nice.org.uk/guidance/ta743/documents/committee-papers.
22. Mahesri M, Lee BS, Levin R, Imren S, Zhang L, Beukelman T, et al. PATIENTS WITH SEVERE SICKLE CELL DISEASE ON STANDARD OF CARE TREATMENT ARE VERY UNLIKELY TO BECOME VOC FREE FOR ONE YEAR: A COHORT STUDY OF MEDICAID ENROLLEES. European Hematology Association (EHA)2022. p. 2597-8.
23. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017;376(5):429-39.
24. Panepinto JA, Bonner M. Health-related quality of life in sickle cell disease: past, present, and future. Pediatr Blood Cancer. 2012;59(2):377-85.
25. Vertex Pharmaceuticals Inc. Data on file. ATMP analogue analysis. 2024.
26. Vertex Pharmaceuticals Inc. Data on File. Exagamglogene Autotemcel (exa-cel) for the Treatment of Sickle Cell Disease: Indirect treatment comparison. 2023.
27. Udeze C, Ly, N. F., Ingleby, C. et al. Mortality and clinical complications among patients with sickle cell disease with recurrent VOCs in England. British Journal of Haematology. 2023.

28. Vertex Pharmaceuticals Inc. Data on file. Sickle Cell Disease with recurrent VOCs and Transfusion-dependent β-thalassaemia: Economic and Clinical Burden of Disease in England. 2023.
29. Beaudoin F, Thokala P, Nikitin D, Campbell J, Spackman E, McKenna A, et al. Gene Therapies for Sickle Cell Disease: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review; 2023 13 July 2023.
30. Excellence NIfHaC. Axicabtagene ciloleucel for treating relapsed or refractory diffuse large Bcell lymphoma after first-line chemoimmunotherapy 2023.
31. Excellence NIfHaC. Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over 2023.
32. Transplantation NECRGfBaM. Clinical Commissioning Policy: Use of Plerixafor for Stem Cell Mobilisation (update). 2015.
33. Parsons J, Castelnuovo E, Dracup N, Connock M, Armoiry X, Grove A, et al. Data on file. Exagamglogene autotemcel for treating sickle cell disease- parameters to be considered in probabilistic sensitivity analysis 2024.
34. Buchanan V, Madani O, Soboil J. HTA53 Will NICE's New Severity Weighting Criteria Be Capable of Identifying Severe Conditions? Value in Health. 2022;25(12):S306.
35. Desai RJ, Mahesri M, Globe D, Mutebi A, Bohn R, Achebe M, et al. Clinical outcomes and healthcare utilization in patients with sickle cell disease: a nationwide cohort study of Medicaid beneficiaries. Ann Hematol. 2020;99(11):2497-505.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

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 (see section 1.1).

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 **12 January 2024**. 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] **and** [redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Anthony Nolan and The Sickle Cell 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.	Anthony Nolan has not received any funding from Vertex Pharmaceuticals Inc, nor any associated subsidiary entities. The Sickle Cell Society has received the following grant funding and financial support from Vertex Pharmaceuticals Inc, between January 2023 and January 2024. The purpose of this support has been to enable the Society's work in creating educational resources for families and individuals impacted by sickle cell disease.: [Details to be confirmed directly to Public Involvement team]
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

Key issue	Does this response contain new evidence, data or analyses?	Response
Single-arm trial with short-term follow-up	No	• With regards to there being no comparator technologies within the CLIMB SCD-121 clinical trial, it is important this is set into the context of available treatments. This is the first gene therapy that offers a functional cure for patients with Sickle Cell. This is the nature of new technologies which are truly innovative.
Generalisability of trial outcomes to NHS practice	No	• The EAG's concerns over the number of UK trial participants could be addressed through a managed access arrangement, providing real-world data. • It is not feasible to expect large numbers of UK patients in clinical trials for a gene therapy of this nature given the context and history of sickle cell in the UK, and the complexity of decision-making for patients and families considering trialling a treatment of this nature. • The Sickle Cell patient community, many of whom are from a Black or minority ethnic background, have experienced years of delay in technological progress to improve their outcomes and quality of life. • It is important that NICE and decision makers consider this context and remain open-minded in how access can be widened and enable the collection of further outcomes data.

Trial sample size	N/a	No comment
Short-term follow-up of participants	N/a	No comment
Lack of control/comparator arm	N/a	No comment
The model does not have the requisites for a Markov structure	N/a	No comment
Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	N/a	No comment
Vaso-occlusive crisis (VOC) rates as a predictor in a risk equation for acute and chronic complications	N/a	No comment
Modelling of adverse events is partial to exa-cel short list and selected events.	N/a	No comment
Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using distribution of patients' weight.	N/a	No comment
The cost of supportive blood transfusions alongside implantations of exa-cel is not included in model costs.	N/a	No comment

Range of acute and chronic complications included in the model is large, but risk reduction is based on assumptions	N/a	No comment
Underestimation of uncertainty in modelling of overall survival in exa-cel and standard of care. Distributions not appropriately parameterised and some key inputs excluded from the probabilistic sensitivity analysis.	N/a	No comment
Inclusion of severity modifier and implementation of 1.5% discount rate	N/a	No comment
Non-reference case distributional cost-effectiveness analysis	N/a	No comment
Additional issues	Yes	• It is acknowledged by the EAG that many of the fundamental outstanding technical issues are a result of a lack of historic innovation in the field of Sickle Cell (lack of comparators) and the complexity of recruiting larger sample sizes from a relatively small patient population in the UK). • Alongside our Patient Organisation Submission, Anthony Nolan and the Sickle Cell Society have also surveyed Sickle Cell patients in the UK (n=60). • The advantages and disadvantages of current treatments and the overall impact on patients' quality of life, we hope the Committee will consider with appropriate weight, and make best possible endeavours to widening access to potentially life-changing and life-saving technologies. This community has been particularly underserved the healthcare system and a positive change can now be made.

		Key patient survey findings (n=60) • In the last two years (since November 2021), 45.45% of patients we heard from have experienced over 8 crises in the last two years. For patients with severe SCD (defined in the CLIMB SCD-121 trial as a history of >2 VOCs per year in the previous 2 years), there is clear unmet need in the UK. • The 3 most common symptoms experienced during a crisis reported to us were: o Pain in more than one place in your body (78.79%) o Extreme tiredness (72.73%) o Intense localised pain at crisis site (69.70%) • The potential for VOC-free outcomes would result in a significant increase in the quality of life for patients, and the prospect of this, we feel, should be strongly considered by the committee. • 66% of patient respondents needed emergency care and support due to a crisis at least 2-3 times in the last two years. In resolving or heavily reducing the number of VOCs, the reduced demand for emergency medicine should also be considered in the cost-effectiveness of this technology. • Similarly, the number of related bed days, with 24% of patients spending 1-2 weeks as an in-patient in the last two years. The costs of SOC should be factored into all relevant economic modelling, and to note this for the average patients' life expectancy. • With respect to the disadvantages of current treatments, patients commented on the impact of regular blood transfusions to their work and social lives. One patient said, "I couldn't plan things around the weekend of my transfusion as I know I would be exhausted and wasn't sure if it would lead to hospitalisation."

		• Others commented about the need to take time out of school and the detrimental impact this had on their education. • Side effects related to SOC-related medicines included drowsiness and extreme tiredness which limited patients' ability to do housework and socialise. • The overall effectiveness of existing treatments was a strong theme for many respondents. A representative comment stated that "I worry about the overall effectiveness of the current treatment. Although it may help slightly, the reality is that my son continues to have sickle cell complications." • In managing the symptoms of Sickle Cell Disease, nearly a third of patients (29.63%) said existing treatments did not manage their disease very well. • Understandably, patients and their families want to see technologies capable of delivering cures made available. They are aware of the emerging availability of gene therapies in other international jurisdictions and want to see effective treatments made available to them in the UK as well.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

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 (see section 1.1).

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 **12 January 2024**. 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] and [redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Royal College of Pathologists and British Society for 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.	Both [redacted] and [redacted] work at King's College Hospital NHS Foundation Trust, which is one of the centres which has successfully bid to perform gene therapy in those with sickle cell disease if NHS funding is commissioned.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**No**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

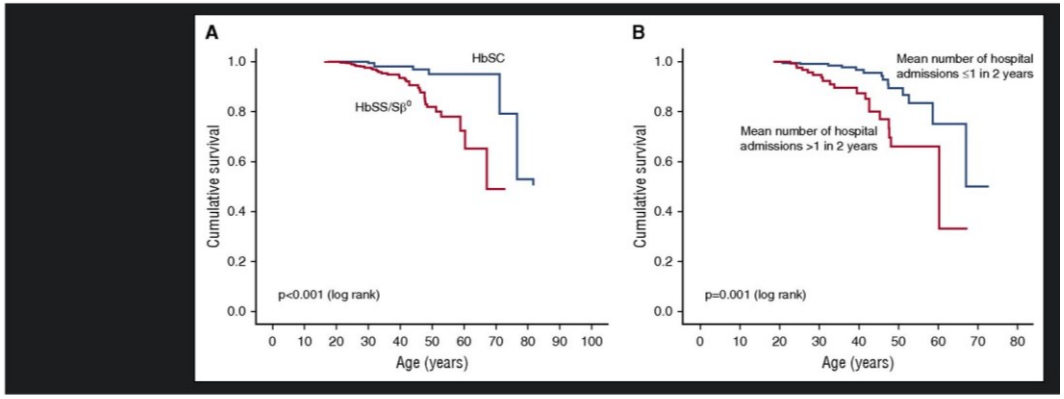
Key issue	Does this response contain new evidence, data or analyses?	Response
Single-arm trial with short-term follow-up	Yes	The CLIMB-121 study [the pivotal Phase 3 trial of exa-cel in participants with severe sickle cell disease (SCD)] has now reported on 44 adolescent and adult patients who have undergone treatment with exa-cel. Although this is a single arm study, the efficacy of the product far exceeds what is seen in conventional therapy such as hydroxyurea. The safety profile is also significantly better than the more conventional curative approaches such as allogeneic transplantation, in which there are high risks of transplant rejection and graft versus host disease. Recent data submitted to the American Society for Haematology meeting (December 2023) indicate that 96.7% patients (29 out of 30 patients in the Primary Efficacy Study) met the primary efficacy endpoint of the trial (defined as proportion of patients free of severe VOCs for ≥12 consecutive months after treatment with exa-cel). Additionally, patients experienced a mean of 22.4 months (range 14.8-44.5) of vaso-occlusive crisis (VOC)- free duration following treatment. All patients (30 out of 30 patients in the Primary Efficacy Study) met the secondary efficacy endpoint (defined as free from in-patient hospitalization for severe VOCs for ≥12 consecutive months). Adverse events mostly occurred in the first three months of the study and reduced over time. The study also demonstrated a durable bone

		marrow and peripheral blood allelic editing through follow-up indicating long-term meaningful benefit after exa-cel. We agree that the follow-up is short, however the outcomes are excellent and unprecedented in this disease group, and established regulatory requirements for patients receiving this type of treatment (cell and gene therapy) are mandated to 15 years' so this information will become available with time. The ASH data confirms good long-term follow up of 30 patients in the primary efficacy set for more than 12 months, of which have 29/30 have reached the primary endpoint of absence of VOC for 12 months. The median VOC duration is 20.7 months for these 29 patients. If the consensus view is that there is insufficient evidence to recommend NHS funded gene therapy currently, then our view is that a pilot of gene therapy in SCD cases is NHS funded so that more evidence can be accrued, or that a managed access scheme is considered, so that the data is constantly accrued and monitored.
Generalisability of trial outcomes to NHS practice	Yes	Centres chosen by NHS England to provide exa-cel treatment have expertise in delivering specialised sickle cell care and cellular therapies, including stem cell transplant. Patient selection, approval, work up, stem cell mobilisation, myeloablation, care during myelosuppression and post infusion patient care can be provided in the NHS as standard of care due to existing expertise. Thus it is expected that trial outcomes can be generalised to NHS practice. In addition haemoglobinopathy networks in England have been established to ensure equitable care for patients with haemoglobin disorders; standard of care is the expectation for all patients in the NHS.

		Although not all patients in this published series were from the UK, there is no evidence that their sickle disease is genetically or phenotypically different to that of the UK SCD population – it is the same genetic disease and clinical practice is similar. We already base much of our current UK sickle clinical practice on trials carried out in the US and other developed health care settings e.g. the BABY HUG study (The Lancet, 2011) of children between the ages of one and three years with sickle cell anaemia receiving hydroxycarbamide, the positive results of which have led directly to the widespread use of hydroxycarbamide in infancy, and the Multicenter Study of Hydroxyurea (JAMA 2003) which led to widening of the criteria for starting hydroxycarbamide in sickle cell disease, and directly resulted in changes to UK practice which is reflected in the British Society for Haematology guidelines (Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease, 2018) to direct our management in the UK.
Trial sample size	Yes	Latest information indicate that 44 patients have participated in the CLIMB 121 study, of which 12 participants were between 12 and 18 years of age and the rest between 18 to 35 years. Our opinion is that these numbers are sufficient to understand immediate safely and efficacy signals and recommend this treatment for eligible NHS patients. We acknowledge the small sample size, however given the high efficacy this shows adequate evidence of a true effect size in this population (not findings which could have occurred by chance) and this a complex new likely curative treatment of a historically underinvested, marginalised and stigmatised patient group which is highly deserving of further NHS investment.
Short-term follow-up of participants	Yes	Although follow up period for patients is relatively short, 17 patients have completed the 24 month follow up (as of June 2023) in the CLIMB 121 study (and have enrolled in the 13- year follow up study CLIMB 131). These patients have all

		demonstrated high efficacy of treatment- including being VOC free and not needing hospitalisation up to this time point and longer term data will ensue. See above, as this is a new treatment, there is currently insufficient long term follow up possible, but NHS and UK cell and gene regulatory frameworks are in place to detect any long term issues, including long-term efficacy (engraftment) and side effects. The recently available ASH data provides a mean of 20.7 months follow up for the 29 patients who achieved the primary endpoint of no VOC for > 12 months, and their haemoglobins remained normal and stable and the inserted allele levels were sustained at 12 months, and at 24 months where available.
Lack of control/comparator arm	Yes	This is an open label, single arm, non- comparator Phase 3 study of safety and efficacy of exa-cel in SCD. The efficacy rates (both primary and secondary endpoints) are extremely high (>96% VOC free survival and 100% hospitalisation-free survival) would make any comparator arm unethical to continue. The safety signals compare well with historical data from allogeneic transplantation data and with no graft versus host disease. We acknowledge it was a single arm trial, however for this cohort (severe sickle cell disease with no available fully matched sibling) there is no alternative therapy to provide a comparator arm. The only other newly available therapies (voxelotor and crizanlizumab) that could be considered as a comparator, where not suitable because of their lack of demonstrable benefit. The standard of care is so ineffective that it is not a fair comparison. There is a graph in the ASH paper which sows the patients own VOC histories as their own controls which clearly illustrates prior frequent VOCs that then stop.

		Because of the phenotypic variability between patients, using patients as their own controls regarding VOC frequency before and after treatment is a better control, and negates the need for a comparator arm.
The model does not have the requisites for a Markov structure	No	No comment.
Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	Yes	It is likely that there will be patients whose stem cells will fail the process of gene editing, and hence these patients will revert to standard of care (SoC). Nonetheless, the cost of patient selection, work up and apheresis cycle(s) will still be accrued by the NHS. However, although the likelihood of this is minimal, it should be factored into the costing. Agreed – the funding of the 20% of patients who have insufficient product for use, will need to be recognised in the funding model.
Vaso-occlusive crisis (VOC) rates as a predictor in a risk equation for acute and chronic complications	Yes	The EAG analysis cited a paper by the company (Shah et al 2019) and mentions that that a significantly higher hazard for death for people with VOCs (1.56) results from a contrast between people with (any) VOCs and those with no VOCs, therefore a contrast between people with or without VOCs, not a quantification of the relationship between number of VOCs and death. The increased hazard for time to splenic sequestration (HR=43.99) was associated with “baseline pain crisis” not otherwise specified. We interpret this hazard to be applicable to the contrast “people with any pain crisis (whether it is a VOC or other). It is not clear what the EAG report authors mean by ‘any pain crisis, whether VOC or other’- in this instance and in most cited literature, the terms ‘VOC’ and ‘pain crisis’ are used interchangeably, and there are not instances where a pain crisis is clinically disparate from a VOC

		A better comparator might be annualised VOC events and measures of end organ damage/function but this data takes longer to accumulate and is difficult to measure. Published data on survival in adults with sickle cell disease in a high-income setting (King's College Hospital, UK) by Kate Gardner in Blood in 2016 clearly illustrated that those with more frequent admission, the majority of which were related to VOC events, had a demonstrably higher risk of death, and that individuals with severe phenotype sickle cell disease have a significantly reduced life expectancy with the mean age at death of 41 years.  **Kaplan-Meier survival curves.** (A) Survival curve by sickle genotype. (B) Survival curve for HbSS/Sβ⁰, by hospitalization frequency.
Modelling of adverse events is partial to exa-cel short list and selected events.	No	Adverse events after exa-cel treatment are exceedingly rare
Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be	Yes	It is unlikely to result in significant differences due to the low incidence of overweight and obesity in this group of patients Agree, perhaps a range of weight would give more accurate costings.

modelled using distribution of patients' weight.		
The cost of supportive blood transfusions alongside implantations of exa-cel is not included in model costs.	Yes	This should be included in the model The use of supportive blood transfusions alongside implantations of exa-cel is short term, and is relatively negligible in the context of the need for long-term red ell exchange transfusions (using 8-10 units per 4-8 weeks) for patients with ongoing severe sickle cell disease.
Range of acute and chronic complications included in the model is large, but risk reduction is based on assumptions	Yes No	Lack of SoC arm and short follow up duration has resulted in defining risk reductions based on assumptions. However, significant reduction in VOC rates soon after the procedure, persistent editing of stem cells resulting in high concentration of HbF in cells is very likely to result in significantly low rates of acute complications based on our knowledge on patients with naturally high HbF concentrations, such as those with compound heterozygosity of sickle haemoglobin and hereditary persistence of fetal haemoglobin and those with high F QTLs and high F haplotypes. We agree that there is some uncertainty in the VOC based model of risk reduction assumption, and this clinical uncertainly is an every day reality.
Underestimation of uncertainty in modelling of overall survival in exa-cel and standard of care. Distributions not appropriately parameterised and some key inputs excluded from the probabilistic sensitivity analysis.	Yes	Prospective long term data on survival and cost of care in SoC and exa- cel are lacking however we could extrapolate data from other autologous transplants and graft survival.
Inclusion of severity modifier and implementation of 1.5% discount rate	Yes	The decision to use the higher discount rate is based on two factors – 1) Costs and 2) Health outcomes. Medicines which improve health over a long period of time (as we would expect to be the case in this situation) are disadvantaged due to inflation. We would expect that sickle cell being a life limiting and indeed often fatal disorder would meet criteria for 1.5% discount rate.

		The use of the 1.5% discount rate is suitable as the following criteria **<u>are</u>** fully met in the scenario of exa-cel therapy in sickle cell disease: 1. Restores people to full or near-full health when they would otherwise die or have severely impaired lives 2. Is likely to restore them to full or near full health 3. Benefits are likely to be sustained over a very long period – based on current data this is the expected outcome , although we acknowledge that because of a lack of availability of long-term follow up data for this novel treatment Sickle cell disease is a severe and distressing lifelong disease, from childhood in which individuals suffer enormously and have a severely impaired quality of life and the likelihood of early death. We currently have very limited treatment options.
Non-reference case distributional cost-effectiveness analysis	Unable to comment	Whilst we cannot comment on this specifically, we would like to emphasise the point that this specific population have experience decades of inequality and deprivation, stigmatisation and poor access to novel or effective treatments.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

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 (see section 1.1).

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 **12 January 2024**. 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]
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 by the forum and provided by a number of pharmaceutical companies including Vertex, 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	**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

Key issue	Does this response contain new evidence, data or analyses?	Response
Single-arm trial with short-term follow-up	Yes	Single arm studies are a standard and accepted approach for gene therapy clinical trials in haematopoietic disease, of note this approach has also been used for gene therapy trials in haemophilia and other indications. The MHRA, FDA and EMA have approved gene therapies using evidence from trials with similar design. The most similar example is the FDA's approval of both exa-cel and lovo-cel in December 2023 based on similar data for lovo-cel 36 patients in a phase 1 / 2 trial and the exact same data for exa-cel as is being considered here, we also make note of the MHRA's approval of exa-cel in November 2023. Although gene therapy with autologous haematopoietic stem cells has been in use in medicine for more than 2 decades (to treat immunodeficiency conditions), the longest follow up with regard to Sickle Cell Disease (SCD), is in the first successfully treated sickle patient, a 13 year old male patient who received treatment in 2014 and is now some 9 years post treatment (ref: Ribeil et al – paper included in submission). Since then there have been numerous studies as well as a rapid evolution in this therapy area. Gene therapy in the treatment of sickle cell disease is a relatively novel treatment, and very few of the reported studies have multiple years of patient follow up. This

		has to be balanced against the undeniable fact that sickle cell disease is a chronic, debilitating lifelong condition with reduced life expectancy, poor quality of life and few curative options. In the UK the only option for a cure at present, is a matched sibling donor stem cell transplant, which is not an option for greater than 85% of the patient population who will not have a matched sibling donor. Sibling allogeneic transplant also carries additional risks of graft versus host disease and a higher risk of draft rejection. Gene therapy using autologous stem cells, offers the proportion of patients who meet specific severity criteria, but who do not have a matched sibling donor, a chance at cure.
Generalisability of trial outcomes to NHS practice	Yes	Sickle cell disease originated from a single mutation in Africa, but is found in all regions endemic with malaria including, Africa, The middle east and Mediterranean regions as well as India. Sickle cell is thought to give a survival advantage in the heterozygote state to falciparum infection on a population level. In Europe and the Americas' the sickle disease population is heterogeneous as it results from migration and immigration from these endemic areas (including forced migration due to slavery). These cohorts of SCD patients have representation from a wide variety of ethnic groups including most of Africa, India and the Middle east all. The populations in Europe, America, and the UK are hence more heterogenous, than those that would be found in, for example, Nigeria or Angola. While studies have shown differences in healthcare organisation impact healthcare utilisation in SCD cohorts between different countries (ref: Strunk C et al paper included in submission), the biology of the condition has not been shown to differ between the Americas, Europe and the UK. There are well recognised disease modifiers which are found more commonly in some ethnic groups and may impact overall prognosis and various haplotypes may also have some impact severity (ref David Rees et al 2022 paper included with submission). However, in comparing the generalisability of the outcome this study which was performed in 16 high to middle income countries, none of which has an endemic sickle population, similar to the UK, and all of which have a heterogenous population from which study participants were recruited, then we would not expect

		there to be any material differences in outcomes of these patients compared to the cohort managed in the NHS. Studies looking at health related quality of life has shown multiple similarities between patient cohorts in the UK, France and the US. Finally the trial entry criteria reflects a cohort of patients with SCD, managed within the UK and we would expect similar outcomes in the group.
Trial sample size	Yes	Data presented at the American society of haematology conference in December 2023 shows there now now 30 patients in the primary efficacy set of whom 29 meet the primary endpoint and with a mean VOC duration of 22.4 months. This is a fairly large patient number with reference to studies in gene therapy in SCD. A search for interventional studies involving gene therapy in sickle disease on clinical trials.Gov confirms almost all trials with gene therapy as an intervention for sickle cell disease have small recruitment targets, of the studies registered the numbers ranged from 5 – 25 patients.. The sample sizes for these trials likely reflect the complexity of the procedure. The sample size in this trial is one of the larger sample sizes reported in the literature.
Short-term follow-up of participants	Yes	Although gene therapy with autologous haematopoietic stem cells has been in use in medicine for more than 2 decades (to treat immunodeficiency conditions), the individual with the longest duration of follow up is the first successfully treated sickle patient, then a 13 year old male patient who received treatment in 2014 and is now 9 years post treatment (Ribeil JA et al 2017 paper included with submission). Since then there have been numerous studies and a rapid evolution in this therapy area however gene therapy for the treatment of sickle is still relatively novel, and very few reported studies have multiple years of patient follow. With allogeneic stem cell transplant absence of VOCs for > 12 months is expected to predict long-term efficacy among patients with SCD who have undergone HSCT in the clinical setting (Mahesri M et al 2021 https://doi.org/10.1111/ejh.13546). This can be extrapolated to gene therapy interventions given the stability shown in patients with successful engraftment after 6months. The autologous product also reduces the risk of some significant late effects found in allogeneic transplant for example graft vs host disease which is a debilitating and chronic condition in itself.

		Sickle cell disease is a chronic, debilitating lifelong condition with reduced life expectancy, poor quality of life and few curative options. In the UK the only option for a cure at present, is a matched sibling donor stem cell transplant, however this is not an option for the 85% of patients will not have a donor.
Lack of control/comparator arm	Yes	Clinical trials involving gene therapy as noted above usually have small sample sizes the only other product that is entering the clinic has 26 patients (Kanter J et al 2023) in the final optimised arm. None of these trials can be blinded due to the nature of the intervention. There is however large trove of natural history data, both prospective and retrospective on the prognosis and outcomes of individuals with SCD, including HES data in the UK, prospective data from the cooperative study in the USA, all of which the trial participant outcomes can be compared to.
The model does not have the requisites for a Markov structure	Yes	The only comment to make here is with regards to the statement in the EAR regarding “Exclusion of relapse rate” and its effect on the Markhov structure. Gene therapy unlike allogeneic stem cell transplant involves recipient receiving their own modified stem cell after conditioning therapy. Unlike allogeneic transplantation where a state of tolerance needs to be achieved and hence there may be a risk of late graft rejection, as the recipient is immunologically identical this risk will not be present leading to late relapses.
Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	Yes/No	Agree it EAR findings that it is reasonable to include the cost for patients who undergo apheresis but do not proceed with gene therapy.
Vaso-occlusive crisis (VOC) rates as a predictor in a risk equation for acute and chronic complications		Multiple publications have VOC/Pain crises when associated with admission to be an independent predictor of prognosis in SCD and it is identified as an independent predictor of morbidity and early mortality by a number of publications (2 references included with submission Gardner et al 2016 and Piel at al 2021). Additionally, VOCs impact on health related quality of life measures significantly, with one study showing 40% of adults with SCD (from United States, the United Kingdom, France, Germany, and Italy) experienced a recent VOC which had

		significant negative impacts on their HRQoL and functional status including their ability to work. Hence an effective therapy such as exa-cel which can impactfully reduce VOC would have benefits for the patient group over and above reduction in morbidity. The EAR report also repeatedly notes splenic infarction as a complication that is not considered in the structure. In sickle cell patients with SS (homozygous) sickle many authors have shown hypospenia and asplenia to occur early in life (by age 6) and even in patients with a spleen visible on imagining there are usually features on the blood morphology to indicate hyposplenia. Hyposplenisim is presumed in all patients with sickle cell disease and appropriate measures including penicillin prophylaxis is commenced at 3 months of age and vaccinations against encapsulated organisms through life. This is the purpose of the inclusion of sickle cell disease in the perinatal screening programme.
Modelling of adverse events is partial to exa-cel short list and selected events.		It is reasonable to exclude the side effects directly attributable to Busulphan as standard NHS costs already incorporates the adverse events associated.
Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using distribution of patients' weight.		We are not able to comment on the EAR's request that the costs for drugs and relative procedures be recalculated to include costs by cycle
The cost of supportive blood transfusions alongside implantations of exa-cel is not included in model costs.		The EAR seems to contradict itself on this point by noting that it is not normal to include trial-driven costs in the economic model, the same authors then go on to request this exact action be undertaken to cover off a possibility they are not confident is required. We would content that due process be followed. Transfusion is part of standard care for patients with SCD, it is used to rescue patients in the acute clinical situation, manage disease complications and prophylactically to prevent severe complications.
Range of acute and chronic complications included in the		The haemolysis and vaso-occlusion associated with the sickle condition underly all the complications associated with the condition. As noted by the EAR report "the

model is large, but risk reduction is based on assumptions		evidence suggests strong effectiveness of exa-cel" albeit for a short follow up duration, however follow up is planned for 15 years for all study participants..
Underestimation of uncertainty in modelling of overall survival in exa-cel and standard of care. Distributions not appropriately parameterised and some key inputs excluded from the probabilistic sensitivity analysis.		Unable to comment
Inclusion of severity modifier and implementation of 1.5% discount rate		In section 1.3.8 in discussing the EAR report seems to equate the significant inequity experienced by patients with SCD when utilizing healthcare similar to other rare conditions they note "same could be said of most orphan conditions". Which we would like to strongly refute, SCD is a condition affecting people from predominantly BAME groups, the most common presentation is acute and severe pain episodes which are unpredictable, have no pathognomic features and often may not even have abnormal clinical findings on review. Multiple patient surveys across many different health settings including the APPG report published in November 2021 in the UK, have all demonstrated the gaps in care, and the effect that both overt and institutionalised racism has on the care patients receive. This is unique to SCD and is not replicated in any other rare condition. Without recognition of this then the premise on which the EAR adjudicates on the weighting of inequality is biased.
Non-reference case distributional cost-effectiveness analysis		Unable to comment

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

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 (see section 1.1).

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 **12 January 2024**. 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]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Clinical Reference Group, Haemoglobinopathy, 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.	**No**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**No**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Single-arm trial with short-term follow-up	Yes	The CLIMB-121 study [the pivotal Phase 3 trial of exa-cel in participants with severe sickle cell disease (SCD)] has now reported on 44 adolescent and adult patients who have undergone treatment with exa-cel. Although this is a single arm study, the efficacy of the product far exceeds what is seen in conventional therapy such as hydroxyurea. The safety profile is also significantly better than the more conventional curative approaches such as allogeneic transplantation, where there are high risks of transplant rejection and graft versus host disease. Data submitted to the American Society for Haematology meeting in San Diego in December 2023 indicate that 96.7% patients (29 out of 30 patients in the Primary Efficacy Study) met the primary efficacy endpoint of the trial (defined as proportion of patients free of severe VOCs for ≥12 consecutive months after treatment with exa-cel). Additionally, patients experienced a mean of 22.4 months (range 14.8-44.5) of vaso-occlusive crisis (VOC)- free duration following treatment. All patients (30 out of 30 patients in the Primary Efficacy Study) met the secondary efficacy endpoint (defined as free from in-patient hospitalization for severe VOCs for ≥12 consecutive months). Adverse events mostly occurred in the first three months of the study and reduced over time. The study also demonstrated a durable bone

		marrow and peripheral blood allelic editing through follow-up indicating long-term meaningful benefit after exa-cel.
Generalisability of trial outcomes to NHS practice	Yes	Centres chosen by NHS England to provide exa-cel treatment have expertise in delivering specialised sickle cell care and cellular therapies, including stem cell transplant. Patient selection, approval, work up, stem cell mobilisation, myeloablation, care during myelosuppression and post infusion patient care can be provided in the NHS as standard of care due to existing expertise. Thus it is expected that trial outcomes can be generalised to NHS practice.
Trial sample size	Yes	Latest information indicate that 44 patients have participated in the CLIMB 121 study, of which 12 participants were between 12 and 18 years of age and the rest between 18 to 35 years. Our opinion is that these numbers are sufficient to understand immediate safely and efficacy signals and recommend this treatment for eligible NHS patients.
Short-term follow-up of participants	Yes	Although follow up period for patients is relatively short, 17 patients have completed the 24 month follow up (as of June 2023) in the CLIMB 121 study (and have enrolled in the 13- year follow up study CLIMB 131). All these patients have demonstrated high efficacy of treatment- including being VOC free and not needing hospitalisation.
Lack of control/comparator arm	Yes	This is an open label, single arm, non- comparator Phase 3 study of safety and efficacy of exa-cel in SCD. The efficacy rates (both primary and secondary endpoints) are extremely high (>96% VOC free survival and 100% hospitalisation-free survival) and would make any comparator arm unethical to continue. The safety signals compare well with historical data from allogeneic transplantation data and with no graft versus host disease.
The model does not have the requisites for a Markov structure	Yes/No	Unable to comment

Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	Yes	It is likely that there will be patients whose stem cells will fail the process of gene editing, and hence these patients will revert to standard of care (SoC). Nonetheless, the cost of patient selection, work up and apheresis cycle(s) will still be accrued by the NHS. However, although the likelihood of this is minimal, it should be factored into the costing.
Vaso-occlusive crisis (VOC) rates as a predictor in a risk equation for acute and chronic complications		The EAG report analyses a paper cited by the company (Shah et al 2019) and mentions that that a significantly higher hazard for death for people with VOCs (1.56) results from a contrast between people with (any) VOCs and those with no VOCs, therefore a contrast between people with or without VOCs, not a quantification of the relationship between number of VOCs and death. The increased hazard for time to splenic sequestration (HR=43.99) was associated with “baseline pain crisis” not otherwise specified. We interpret this hazard to be applicable to the contrast “people with any pain crisis (whether it is a VOC or other). It is not clear what the EAG report authors mean by ‘any pain crisis, whether VOC or other’- in this instance and in most cited literature, the terms ‘VOC’ and ‘pain crisis’ are used interchangeably, and there are not instances where a pain crisis is clinically disparate from a VOC
Modelling of adverse events is partial to exa-cel short list and selected events.	No	Adverse events after exa-cel treatment are exceedingly rare
Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using distribution of patients’ weight.	Yes	It is unlikely to result in significant differences due to the low incidence of overweight and obesity in this group of patients
The cost of supportive blood transfusions alongside implantations of exa-cel is not included in model costs.	Yes	This should be included in the model

Range of acute and chronic complications included in the model is large, but risk reduction is based on assumptions	Yes	Lack of SoC arm and short follow up duration has resulted in defining risk reductions based on assumptions. However, significant reduction in VOC rates soon after the procedure, persistent editing of stem cells resulting in high concentration of HbF in cells is very likely to result in significantly low rates of acute complications based on our knowledge of patients with naturally high HbF concentrations, such as those with compound heterozygosity of sickle haemoglobin and hereditary persistence of fetal haemoglobin and those with high F QTLs and high F haplotypes.
Underestimation of uncertainty in modelling of overall survival in exa-cel and standard of care. Distributions not appropriately parameterised and some key inputs excluded from the probabilistic sensitivity analysis.	Yes	Prospective long term data on survival and cost of care in SoC and exa- cel are lacking however we could extrapolate data from other autologous transplants and graft survival.
Inclusion of severity modifier and implementation of 1.5% discount rate	Unable to comment	Medicines which improve health over a long period of time (as we would expect to be the case in this situation) are disadvantaged due to inflation. We would consider sickle cell to be a life limiting and indeed often fatal disorder.
Non-reference case distributional cost-effectiveness analysis	Unable to comment	

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

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 (see section 1.1).

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 **12 January 2024**. 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 SCD, preparing the technical report, and for providing us with the opportunity to engage in the technical engagement process. Our response will address the EAG report, and will also take into consideration the recommendations made by the NICE Decision Support Unit, which provide actionable alternatives.

Our response is split into three separate parts:

1) Our response to the key issues for engagement raised by the EAG
2) Appendices: a) alternative mortality modelling, b) comparison of latest data cut with D120 data cut
3) Details of the revised company base case

With regard to point 3, the latest data cut (hereafter referred to as the ASH 2023 data cut), presented at the American Society of Hematology congress in December 2023 (1), and anticipated for publication in the *New England Journal of Medicine* in March, includes data for only one additional patient relative to the original D120 data cut (2, 3). As such, we provide a brief comparison table (Table 8), but this data does not inform the economic model.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue impacting decision making:	Description:	Does this response contain new evidence, data or analyses?	Response:	EAG response
Issue 1:	Single-arm trial with short-term follow-up	No	The EAG has concerns about the sample size, duration of follow-up, and single-arm nature of CLIMB SCD-121. We note that each of these three concerns are also raised individually in issues 3-5, and as such they are addressed in response to those issues rather than here to avoid duplication. However, we note the below overarching points, which hold true for all the EAG's criticisms of the trial design. **Exa-cel is now approved by the MHRA, as well as other regulatory authorities, for the indication under review.** The evidence package supporting exa-cel has been considered sufficiently robust to support regulatory approval, not just by the MHRA but also the FDA, as well as a positive opinion from the	The EAG considers this issue not resolved. The EAG acknowledges that the MHRA and the FDA have now approved exa-cel, who have reached a regulatory conclusion, and that Vertex is mandated to collect post-marketing data. The EAG considers that the FDA and the MHRA have given a "conditional" approval, they have in fact taken a position similar to

			CHMP. There are numerous instances of drugs being approved by the EMA/MHRA and rejected by the FDA, as well as vice-versa. The fact that regulatory bodies have taken a consistently positive view of the evidence package supporting exa-cel is validation of the trial's suitability to address the decision problem in this appraisal. Furthermore, the conditional marketing authorisation received from the MHRA mandates collection of additional data to support the long-term efficacy and safety of exa-cel, data that could and would be used to inform a follow-up appraisal should a managed access agreement be agreed, as proposed by Vertex. **Exa-cel is addressing a substantial unmet need, as validated by conditional approval.** Conditional approval of medicines by MHRA (& EMA, which MHRA follows on this in terms of eligibility) requires the fulfilment of several criteria: • the benefit-risk balance of the medicine is positive; • it is likely that the applicant will be able to provide comprehensive data post-authorisation; • the medicine fulfils an unmet medical need; • the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.	ours, in the sense that the data must be integrated with further evidence. The EAG acknowledges that exa-cel has the potential to address unmet need, however it is also very well known – and there is consensus about – the fact that addressing an unmet need is not the objective of NICE evaluations; the objective of the NICE assessment is whether the drug has the capability – and not just the potential – to fulfil the unmet need. The trial data are subject to substantial uncertainty in this respect and with regards to this objective. **It is likely that the applicant will be able to provide comprehensive data post-authorisation;** suggests to the EAG that the current data packages provided is not sufficient.

			We draw particular attention to criteria #2 and #3. Exa-cel is addressing a substantial unmet need, only exacerbated by the withdrawal of crizanlizumab, and ongoing TA of voxelotor by NICE. Further, whilst we strongly defend the position that the current data package is sufficiently robust to inform decision-making, additional data collection provides confidence that any remaining uncertainties would be addressed, whilst facilitating timely access to a novel treatment that represents a paradigm shift in the management of SCD. Exa-cel was also granted an innovation passport by the MHRA, for which qualifying criteria include 'the condition is life-threatening or seriously debilitating' and 'there is a significant patient or public health need'. **CLIMB SCD-121 was designed in accordance with regulatory advice.** CLIMB SCD-121 was designed consistently with FDA advice on Gene Therapy trials that a single-arm trial may be considered if there are feasibility issues with conducting a randomised controlled trial (RCT) (4). As described in our response to subsequent clinical issues, the autologous nature of exa-cel, and lack of clinical equipoise make an RCT unfeasible. The FDA guidance also states that sponsors may consider the clinical performance of available therapies when setting the performance goal or criteria against which the product effect will be tested (4). This has been	**the medicine fulfils an unmet medical need;** as discussed above this is not the criteria for reimbursement for NICE. Operational details of (i) "***the collection of additional data to support the long-term efficacy and safety of exa-cel***" and how this might relate to (ii) a possible "***managed access agreement*** " are currently unclear to EAG. Examples are considerations that do not seem to be addressed yet**:** 1. Will only UK patients be involved in (i) and (ii) or will one or other of (i) or (ii) require data from non-UK patients? 2. The EAG queries the delivery of a MAA in the NHS that is understaffed and strained with long wating lists. 3. Vertex Submission Doc B (Table 56, market uptake) estimates it will take [redacted] UK patients to have received exa-cel. Although this increases the current status of patient numbers and duration of follow- up- patients the EAG is concerned about the operational details that underpin this exercise.

			done via an Indirect Treatment Comparison (ITC) described in the submission and summarised in point 5 below. In addition, the FDA state that an endpoint based on a treatment outcome that is not expected to occur spontaneously in the natural course of the disease can facilitate the interpretability of a small trial. The likelihood of a patient with recurrent VOC becoming VOC free for 12 months fulfils this criterion (4). In summary, Vertex firmly defends the sufficiency of CLIMB SCD-121 to address the decision problem in the indication under review. Regulatory bodies including the MHRA have approved exa-cel, taking the view that the high level of unmet need means that the benefit of immediate availability outweighs any potential uncertainty relating to additional data. Furthermore, regulatory approval includes the condition that additional data is collected, data that would be included in a re-submission following a period of managed access, as proposed by Vertex.	The EAG opinion remains that the data presented in submission Doc B (+appendices) had a small number of patients followed for insufficient time to allow robust an estimate of the lifetime effectiveness of exa-cel. The EAG agrees that additional data may allow a far more robust estimate and that in the short-term exa-cel is shown to be strongly effective for a small number of patients.
Issue 2:	Generalisability of trial outcomes to NHS practice	Yes/No	The EAG notes that of the 16 study sites for CLIMB SCD-121, only 1 was in the UK, with the rest spread across the US (9 of 16 sites), Canada (1 of 16 sites) and western Europe (5 of 16 sites). As a result, the EAG has concerns over the extent to which patient characteristics and treatments received (before and after the trial) in CLIMB SCD-121 are generalisable to UK clinical practice. Whilst our main argument against this is that the vast majority of clinical trials informing the clinical	The EAG considers this issue partially resolved. **Generalisability of trial outcomes based on small sample of UK patients** The EAG acknowledges the information provided about the similarities in clinical practice between the UK, Europe and the US, and the historic process of UK guidelines and

			efficacy evidence for NICE appraisals will only include a small proportion of patients recruited at UK centres, with others not including any UK sites (including the majority of trials guiding UK SCD practice e.g. MSH Hydroxyurea trial, STOP trial for stroke prevention and the pivotal crizanlizumab trial), there are several other points specific to SCD that support the generalisability of CLIMB SCD-121 to UK clinical practice. **Clinical practice is highly similar between the UK, Europe, and the US.** Clinical practice across the UK, Europe and US is generally the same and based on the same trial and natural history data. There are extensive collaborations between these countries in clinical practice, guideline development, natural history generation and trial development. Whilst there are no international guidelines for the comprehensive treatment of SCD, evidence for international collaboration/consistency include: • International guidelines on specific aspects of clinical care. For example, the International Collaboration for Transfusion Medicine (ICTM) produced a paper on transfusion in haemoglobinopathies in 2018 (5). The British Society of Haematology (BSH) subsequently produced a position paper confirming a consensus in the UK for the	practice being informed by studies conducted in the US and Europe. However, the EAG has the following concerns about generalisability: **Generalisability of CLIMB findings to wider populations than recruited to CLIMB and to a life-time horizon.** The EAG notes there is no evidence to support the inference that effectiveness measures obtained from CLIMB SCD-121 can be extended to a lifetime horizon for the SCD population. This company inference is based solely on clinical opinion. In particular, the EAG has concern: 1. That a more than 20-fold extrapolation of effect size from that seen over about 2 years to a lifetime median of about 55 years is speculative. 2. The population in CLIMB SCD-121, and in its study centres, may not be generalisable to individuals that may subsequently be eligible for exa-cel should it be adopted. The EAG observes:

			recommendations outlined in the ICTM paper (6-8). • Comprehensive US guidelines which include international authors. For example, the American Society of Hematology (ASH) (9) produced Clinical Practice Guidelines on Sickle Cell Disease in 2020/2021 on Transfusion Therapy, Cerebrovascular disease and Stem Cell transplantation which all include UK and/or European co-authors. Furthermore, the recommendations in these guidelines have been adopted in the UK. • Marked consensus between UK guidelines and those available in Europe and the US. For example, the NHLBI produced comprehensive guidelines on the management of Sickle Cell Disease in the UK in 2014 (Evidence-Based Management of Sickle Cell Disease: Expert Panel Report) (10). The recommendations in this guideline are replicated in the more recent UK guidelines (Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK and Sickle Cell Disease in Childhood: Standards and Recommendations for Clinical Care) (11, 12). Similarly, the recommendations in the ASH 2020 guidelines for sickle cell disease: transfusion support are broadly in agreement with those in the BSH	The submission states that vast majority of UK SCD is in people of African or Caribbean ethnicity, as also were patients in CLIMB SCD-121. Genetic variability amongst indigenous Africans is, and has been, far greater than across the rest of the world's population and will be reflected in the wider population eligible for exa-cel. Historical forced transportation of African people and the more recent migration of African or Caribbean people means that this is a highly heterogeneous group that may not be well represented in the sub-sample selected for inclusion in CLIMB SCD-121 and the study centres (particularly those centres (e.g., in UK) with very few patients recruited). Responses to treatments are influenced by background genetic make-up. Because "*people of African or Caribbean ethnicity*" are a genetically heterogeneous group (Campbell et al., 2008) in EAG opinion it has yet to be demonstrated that CLIMB SCD-121 responses are generalisable to lifetime for a wider SCD population. EAG is unaware of any evidence relating to potential effects of long-term circulation of foetal Hb at levels seen after exa-cel.

			guidelines 'Red Cell Transfusion in Sickle Cell Disease' from 2016 (7, 13, 14). • UK guidelines are primarily based on US research and reflect US practice. For example, the BSH guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease and the national guidelines on adult and paediatric sickle cell clinical care based their key recommendations from pivotal trials performed in the US (11, 12, 15). This includes the Multicenter Study of Hydroxyurea (MSH) and the BABY-HUG study which showed the efficacy of hydroxycarbamide (Hydroxyurea) in the reduction of VOC in adults and children with SCD (16, 17). These important randomised trials from the US led to guideline production and significant changes in clinical practice in the US, UK and Europe including the recommendation that hydroxycarbamide should be offered to infants aged 9-42 months with SS/SB0 regardless of clinical severity (11, 12). Treatment guidelines are centred around supportive care, with hydroxycarbamide recommended for patients experiencing multiple VOCs in a 12-month period, or experiencing VOCs that are impacting on their HRQoL, although benefits should be weighed against the challenging tolerability profile. Similarly,	In summary: generalisability is threatened by narrow CLIMB SCD-121 population and its short duration requiring speculative extrapolation to a lifetime horizon. *Campbell MC, Tishkoff SA. African genetic diversity: implications for human demographic history, modern human origins, and complex disease mapping. Annu Rev Genomics Hum Genet. 2008;9:403-33.*

			recommendations on use of RBC transfusions are consistent, primarily for the prevention of complications such as stroke in high-risk patients. **UK clinical experts support the generalisability of CLIMB SCD-121 to UK clinical practice.** The topic of generalisability was discussed at an advisory board convened by Vertex in support of this appraisal (18). Clinical experts noted that the genotype distribution and gender split in the trial are both in line with UK clinical practice, and that the historical annual VOC rate was similar to the rate they would expect in patients likely to be treated with exa-cel in the UK. Experts noted they would initially prioritise younger patients for treatment, and so the mean age of 21.2 years (D120, FAS) is likely to be broadly applicable (2). **Key pivotal trials in SCD did not include study sites in the UK, but their findings have been fully incorporated into UK practice.** Almost all the key trials in SCD over the previous 40 years have been performed in the US but the findings have been incorporated into UK clinical practice and clinical guidelines. These have been instrumental in improving care for patients with SCD in the UK and are now considered standard of care in the UK. It is therefore universally accepted within the SCD healthcare community that the results from SCD trials performed outside the UK (most commonly from the US) are generalisable to UK practice and indeed it could	

			be postulated that lessons learnt from these trials have transformed UK practice and improved patient outcomes in the UK. Key examples are given below (this list is not exhaustive). Building on the examples described earlier on in our response to key issue 2, we note further examples here. The Stroke Prevention Trial in Sickle Cell Anaemia (STOP trial) enrolled 130 children in the US showing that regular transfusion therapy significantly reduces stroke risk in children with a raised trans-cranial doppler value (TCD). This US trial led to major changes of clinical practice in the UK with the introduction of a paediatric TCD screening service, transfusion being offered to children with SCD who have a raised TCD and a reduction in paediatric stroke rates (19). Annual TCD scanning is a key standard of care for children with SCD (12). The TCD with Transfusions Changing to Hydroxyurea trial (TWITCH) involved 121 children in the US and showed that hydroxycarbamide was as effective as transfusion therapy in primary stroke prevention. Based on this trial, UK recommendations state that children who have started regular blood transfusion for abnormal TCD can be switched to hydroxycarbamide therapy after 1 year of transfusions. This has now been embedded into UK clinical practice (15, 20). Finally, we note that crizanlizumab's pivotal trial (SUSTAIN) included 60 study sites, none of which were in the UK. Whilst this was originally flagged	

			as an issue by the attendant EAG, it was resolved following technical engagement because of clinical expert input (21). As described above, clinical experts (n=4) participating in an advisory board agreed that the baseline characteristics in CLIMB SCD-121 are generalisable to UK clinical practice. In summary, clinical practice and treatment guidelines for SCD are consistent across countries. Whilst only 1 study site in CLIMB SCD-121 is in the UK, other countries represented (US, Canada, western Europe) are likely to treat patients in a similar way to the UK, and local clinical experts agree that the CLIMB SCD-121 study population is generalisable to UK practice.	
Issue 3:	Trial sample size	Yes	The EAG has concerns with the sample size in CLIMB SCD-121, with 29 patients in the PES, and 43 patients in the FAS at the time of the D120 data cut. Further, in the EAG's view, the number of patients severely diminishes beyond about 12 months. **Patient numbers do not severely diminish beyond 12 months.** Firstly, we refute the EAG's claim that patient numbers diminish 'beyond about 12 months'. Twenty-nine (30 if including the ASH 2023 data cut) of the patients in CLIMB SCD-121 were included in the PES, defined as patients who were followed for at least 16 months after exa-cel infusion. This equates to 69% of patients having	The EAG considers this issue not resolved. **Patient numbers do not severely diminish beyond 12 months.** The EAG concedes that this generalisation is too strongly worded. Most EAG text refers to post 15 months rather than 12 months. However, the EAG reiterates that for most of the outcomes reported the number of patients at risk diminishes considerably at later time points and that end of follow up data is often

			≥16 months of follow-up, with the median VOC-free duration in the PES being 20.7 months. **CLIMB SCD-121 was sufficiently powered to demonstrate benefit of exa-cel.** CLIMB SCD-121 was designed in consultation with the FDA with a sample size of approximately 45 patients. This sample size of 45 patients was pre-specified and adequate for statistical power. 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 endpoints with 1-sided alpha of 2.5%. We note that at the most recent data cut-off, 44 patients have been dosed with exa-cel. **Exa-cel demonstrates a highly favourable benefit-risk profile at interim analysis.** At the pre-specified interim analysis in CLIMB SCD-121, exa-cel demonstrated overwhelming efficacy, with broad, transformational and clinically meaningful benefits in the indication under review. Exa-cel has demonstrated consistent, durable benefit in subjects with SCD. At D120, the overwhelming majority (28 of 29, 97%) of subjects in the PES reached the primary end-point VF12 (absence of any severe VOCs for at least 12 consecutive months after exa-cel infusion) and 100% of subjects reached HF12 (free from inpatient hospitalisation for at least 12 months after exa-cel infusion) and these benefits were sustained. Exa-cel was generally safe and well	based only one or two patients remaining at risk. The EAG acknowledges that at the most recent data cut-off, 44 patients have been dosed with exa-cel, however not all of these were included in the PES. Only 29 patients were included in the PES, equivalent to less than two thirds of this number.

			tolerated. The safety profile of exa-cel is generally consistent with busulfan conditioning and autologous HSCT. The safety profile of exa-cel has been adequately characterised with risks that are readily identified clinically or with routine laboratory monitoring and can be managed. **MHRA, FDA, and EMA (CHMP) are all in agreement that the data package is sufficient.** As described in our response to issue 1, since receipt of the EAG report, MHRA, FDA, and EMA (CHMP) have all approved, or pre-approved exa-cel, supporting the robustness of the data package. As already mentioned, there are several examples of drugs approved by EMA that were rejected by the FDA, that successfully achieved reimbursement in the UK. Regulators' consistently positive opinion of exa-cel is supportive of the data package. In conclusion, CLIMB SCD-121 was adequately powered to assess the efficacy of exa-cel, which is overwhelmingly demonstrated, with 28 of 29 patients in the PES achieving VF12. Of the 44 patients in the FAS, at the latest data cut (presented at ASH), 30 of these have ≥16 months of follow-up post-infusion with exa-cel (1). Finally, approvals from MHRA, FDA, and EMA (CHMP positive opinion) affirms the position that the data package for exa-cel is sufficiently robust for decision-making. Given that almost all patients achieved the primary endpoint, regardless of genotype, age, or any other characteristics, the	

			sample size is sufficient to clearly demonstrate the effectiveness of exa-cel.	
Issue 4:	Short-term follow-up of participants	No	The EAG notes that as CLIMB SCD-121 is still ongoing, there is a lack of long-term follow-up data available. On this basis, the EAG state that it is impossible to assess the efficacy of exa-cel beyond the short-term. Whilst the definition of short-term may be subjective, it is Vertex's view that ~2 years of follow-up, which does not include the 60-day RBC washout period, is a sufficient length of follow up to demonstrate a clear and considerable benefit from exa-cel that shouldn't be delayed in getting to patients. In addition, it is important to highlight two key points that are supportive of the anticipated durability of exa-cel: 1. **Overwhelming efficacy/benefit of exa-cel therapy with minimal and well understood risk.** All but one patient in CLIMB SCD-121 achieved the primary endpoint, equal to a response rate of over 96% so, in contrast to other one-time therapies where response rates are lower, there is no necessity for additional follow up and analysis to understand predictors of response & potential subgroups where the effect may be more pronounced. 2. **CRISPR gene editing provides a permanent edit**: There is no biologically plausible explanation that the introduced	**The EAG considers this issue partially resolved** The EAG agrees that designating CLIMB SCD-121 as "*short term*" is a subjective adjectivisation. Nevertheless, the EAG suggests that: 1. In terms of robust analysis, the longer the follow-up and the more the patients the better. 2. The patient numbers and follow-up time in CLIMB SCD-121 are both modest.

			CRISPR/Cas9 gene edit will not be permanent in SCD. Hb concentration and allelic editing remain stable in all patients at latest follow-up, with clinical experts aligned that these stable parameters at 24 months are highly predictive of long-term durability. **Median VOC-free period in the PES was almost 2 years at latest follow-up.** In the data presented at ASH 2023, patients in the PES who achieved VF12 (29 of 30 patients) had a mean duration of 22.4 months VOC free, with a range of 14.8 – 45.5 months (1).. Whilst the definition of short-term may be subjective, our view is that ~2 years of follow-up, which does not include the 60-day RBC washout period, is a sufficient length of follow up to demonstrate a clear and considerable benefit from exa-cel. At baseline, patients in the PES (n=30) experienced an average (mean) of 3.9 VOCs per year, with 2.7 inpatient hospitalisations due to severe VOCs. Following exa-cel treatment, not only did 29 of 30 achieve VF12, but all 30 patients achieved HF12 (1). It may be considered that this exceptionally high bar of efficacy, with 96.7% of patients achieving the primary endpoint in itself addresses uncertainty. **There is no biological plausibility that the exa-cel genetic edit is reversible.**	The EAG has not identified a mechanism by which the CRISPR/Cas9 modification can be reversed.

			Biologically there is no reason the introduced CRISPR/Cas9 gene edit will not be permanent in SCD. 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 SCD-121. 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. **Clinical expert feedback supports the expected long-term benefits of exa-cel.** As part of the appraisal process, Vertex consulted clinical experts to provide feedback on a range of topics, including predictors of permanent benefit in SCD (18). Clinical consensus was that they would like to see a sustained increase in HbF levels for 2 years to be confident that exa-cel is likely to provide a long-term benefit. Clinical experts also agreed that persistence of the gene editing in bone marrow and peripheral blood (allelic editing) is a suitable proxy for long-term durability. Indeed, it could be argued that HbF and allelic editing values are more appropriate proxies for long-term durability than VOC. Even after allo-HSCT where there is no biological reason for vaso-occlusion, ongoing painful episodes are seen. One study has shown that 21% of patients experience VOC in	However, robust evidence of effectiveness beyond a few years has yet to be collected and lifetime horizon effectiveness is currently based only on clinical opinion. The EAG notes that rates of VOCs before study entry were not adjudicated; the company present a composite definition of VOCs as any of the following: – Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] nonsteroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions. – Acute chest syndrome – Priapism lasting > 2 hours and requiring a visit to a medical facility. – Splenic sequestration (CS Doc B p12) So any reason for the patient to refer to services (pain episodes or other events) is classified as VOCs for the purposes of CLIMB SCD-121. Yet, after exa-cel, the term VOC is

			the 12 months after allo-HSCT (22). These are likely due to ongoing chronic pain, allodynia (pain elicited by normally innocuous, low threshold stimuli) and hyperalgesia (enhanced pain response to noxious stimuli) exacerbated by chronic opiate use. Clinical experts have stated the reasons for the VOC seen after exa-cel is likely to be similar. We note that at the most recent data cut, both HbF and allelic editing levels are stable, supporting the view that exa-cel is highly likely to be associated with a durable functional cure in these patients. **Data collection through managed access is proposed to address remaining uncertainty without hindering access for patients with a considerable unmet need.** Vertex robustly defend the duration of follow-up in CLIMB SCD-121 as suitable for decision-making - supported by the aforementioned regulatory approvals - and note the overwhelming efficacy of exa-cel, with 29 of 30 patients in the PES achieving VF12. However, to address remaining uncertainty, Vertex has proposed a managed access agreement, which would provide additional data with a longer duration of follow-up of patients in CLIMB SCD-121 and CLIMB-131. With mean duration of follow-up of 22.4 months as of June 2023, the proposed 3 years of data in the managed access agreement would include data	not used anymore, and events are interpreted as “pain episodes” despite the adjudication in the trial. 1. Events before entry were not adjudicated – hence VOC rates overestimated; 2. Events after the trial were adjudicated, so they are not painful episodes, there are VOCs. The company argues that calling the events post-exa-cel “VOC2s is misinterpretation. Those events were adjudicated by trialists, hence there is no space for misinterpretation. If the trial has to be believed, the adjudication of events cannot be contested. Furthermore, the same event definition has to be used for events that occur before exa-cel and those that occur after exa-cel. The submission runs with the overarching hypothesis that “absence of VOCs” is equal to functional cure. During study follow-up, three participants (10% of study population) reported adjudicated VOCs – hence they did not remain functionally cured according to the definition of the company. Neither it helps to argue “functional cure” is within 2 years. There are only 4 participants with >24 months follow up – so CLIMB SCD-121 at this time only supports a functional cure

			for most patients in CLIMB SCD-121 beyond 5 years post exa-cel infusion. In conclusion, although we acknowledge that long-term durability for any medicine will always be subject to a certain level of uncertainty at the time of HTA decision-making, the modality of exa-cel, and lack of biological plausibility for reversal of genetic edits strongly supports the anticipated durability of effects, and therefore the duration of follow-up in CLIMB SCD-121 is suitable for HTA decision making today. At the time of latest data cut, patients in the PES had almost 2 years of follow-up, and almost all (29 of 30) had achieved the primary endpoint of VF12. Clinical experts were aligned that a durable effect out to two years post-infusion is highly predictive of long-term durability. Finally, Vertex have proposed a managed access agreement to facilitate timely access for patients with a high unmet need whilst collecting data to address any remaining uncertainties.	rate of 10% (provisional of course and not addressing the further point that even if functionally cured, these patients do not have baseline health as the normal population) There is an inherent contradiction in the way VOCs are classified before and after the receipt of exa-cel. The EAG argues that definitions have to be kept consistent. 1. Shah used hospitalisations only – hence the baseline rate used by the company has to be halved; 2. Post-exa-cel, there was one patient with one hospitalisation VOC and four non-hospitalised VOCs. So – 1. Either the terminology “functional cure” is removed; 2. Or it has to be recognised that at least one patient fails the definition of “functional cure” after exa-cel. Or 3. the application of the Shah coefficients is invalid. With regard to: “**Data *collection through managed access is proposed to address remaining uncertainty without hindering access for patients with a considerable unmet need.”***

				The EAG agrees that collection of further data is highly desirable and that given sufficient patient numbers and length of follow-up this has the potential capacity to substantiate the expressed clinical opinion based on less complete data.
Issue 5:	Lack of control/comparator arm	No	The EAG notes that as a single arm study, CLIMB SCD-121 includes no randomised comparator or control groups. Without this, it is the EAG's view that they are unable to determine, with a reasonable degree of certainty the true impact of exa-cel. **A single-arm trial was suitable given the modality of exa-cel, and lack of equipoise.** CLIMB SCD-121 was designed as a single-arm study because of a lack of equipoise with existing standard of care treatments. In CLIMB SCD-121, 29 of 30 patients (96.6%) in the PES achieved VOC-free for 12 months or more. In contrast data from a RWE Medicaid study has shown that in patients with 2 or more VOCs per year who are receiving standard of care treatment only approximately 10% will not have a VOC in the subsequent year and furthermore only 16.9% of patients receiving standard of care (SoC) in SUSTAIN achieved this endpoint (21, 22). Therefore, the rate of achieving the primary end point of VF12 (absence of any severe VOCs for at least 12 consecutive months after exa-cel infusion) with standard of care is only around 10-	The EAG considers this issue resolved. **In addition randomisation would not be possible; the unique autologous procedure for exa-cel necessitates open-label treatment** The EAG considers that it would be possible to conduct an RCT (and many RCTs are open-label) but acknowledge it might not be ethical or easily feasible in the light of early results from exa-cel. The EAG acknowledges that an RCT comparing exa-cel to SoC would have likely

			17% (22, 23). In addition randomisation would not be possible; the unique autologous procedure for exa-cel necessitates open-label treatment. **Due to phenotypic heterogeneity in SCD, a patient's own history of VOCs is a better predictor of future VOCs than a matched control.** There is marked phenotypic heterogeneity in SCD with extreme variability in VOC rate between patients. A patient's past experience of VOC has been shown to be the strongest predictor of VOC rates over time and supports an underlying 'severe disease' phenotype for SCD (9, 24). Individual patient history as a key predictor of future VOCs is supportive of a single arm trial rather than concurrent randomised methodology using matched control subjects. Furthermore, the evidence from CLIMB SCD-121 of significant reduction (and/or elimination) of VOC along a patient's own time-line following treatment with exa-cel is highly relevant. **Of the 16 NICE appraisals identified for ATMPs, in 15 of 16 cases the pivotal trial was a single-arm study.** As presented in a separate Excel file, of the 16 NICE appraisals (across STAs and HSTs) identified for ATMPs, the only RCT was for axi-cel in 2nd line diffuse large B-cell lymphoma (25). The analogues considered span an array of therapeutic areas, including haematology	failed to recruit patients, especially given the promising Phase I results. **Due to phenotypic heterogeneity in SCD, a patient's own history of VOCs is a better predictor of future VOCs than a matched control.** The EAG is not persuaded that the patients recruited to CLIMB SCD-121 fully reflect the heterogeneity of the eligible population (i.e., is not necessarily generalisable). **Of the 16 NICE appraisals identified for ATMPs, in 15 of 16 cases the pivotal trial was a single-arm study.** The EAG concedes that the company submission based on a single trial arm is not unusual.

			(transfusion-dependent thalassemia, haemophilia B, various blood cancers). As such, the design of CLIMB SCD-121 is consistent with the approach taken by other ATMPs, for reasons described above. **In the absence of a control arm, an ITC was conducted, demonstrating exa-cel's superiority to existing options.** In the absence of direct head-to-head evidence an ITC was conducted, with results summarised in the CS. The results of the MAIC support the markedly superior efficacy of exa-cel compared with SoC (26). Despite limitations relating to effective sample sizes, the median annualised VOC rate for exa-cel was 0, compared to 2.98 for SoC taken from the SUSTAIN trial, and mean annualised VOC rate was 0.06 for exa-cel compared to 2.8 in the HOPE trial. This demonstrates the potential functional cure provided by exa-cel. Had CLIMB SCD-121 included an SoC arm, it is likely the trial would have been stopped early due to overwhelming efficacy, with all patients moved over to exa-cel. Whilst we note that this is somewhat speculative, it is clear that the outcome of patients prior to treatment with exa-cel and post exa-cel is markedly different, and that the impact of exa-cel is apparent beyond reasonable doubt. In conclusion, CLIMB SCD-121 was designed as a single-arm trial due to lack of equipoise with existing standard of care treatments and because	**In the absence of a control arm, an ITC was conducted, demonstrating exa-cel's superiority to existing options.** The EAG notes that treatments for SCD include gene-therapy using a lenti-viral vector. Although not listed as a comparator by NICE, data from such studies may have allowed a more meaningful ITC to be undertaken.

			of the need for a transplant procedure to deliver exa-cel. The benefits provided by exa-cel are a clear departure from disease natural history, and due to the variability of SCD, a patient's own history of VOCs is a strong predictor of future VOCs. Almost all previous NICE appraisals of ATMPs have been informed by single-arm trials, and this has not stopped the majority from achieving reimbursement.	
Issue 6:	The model does not have the requisites for a Markov structure	Yes	The EAG is of the view that the economic model does not follow a Markov structure, and that as a result of the model structure the rates of chronic complications and mortality calculated in the model may be biased, and ultimately may invalidate the cost-effectiveness analyses and results.	The model has been reviewed by the DSU, specifically focussing on the model structure and the way mortality is incorporated. Similarly, to the EAG, the DSU found that the method used to incorporate mortality generates inadmissible death rates (negative probabilities). The DSU also stated that complication rates should be modelled conditionally. Both the EAG and the DSU convene that the method used to estimate mortality should be changed for the model to be considered valid. The EAG believes that the original structure, reiterated as the choice of the Company for the base case, is invalid. The Markov structure does not respect the conventions of modelling with regards to Markov structures. The Company implemented a change to the model structure to estimate mortality independently, i.e., not determined within the

				model applying relevant death rates to complications and general mortality to the cohort. The company used general mortality rates, inflated by a set of SMRs for SCD. The EAG believe that the method has been implemented correctly and therefore that the model structure with "unconditional mortality" should be the base-case. The ICER is not most sensitive to mortality, in fact, the model is most sensitive to the discount rate, followed by choice of complication rates. Mortality ranks third in the order of importance (see EAG response to TE addendum).
			Mortality predicted by the company's model aligns with the available real-world evidence. The most significant critique within this issue, and the one to which the ICER will be the most sensitive, is mortality. Specifically, the model attempts to incorporate individual causes of mortality within a Markov cohort structure, which is challenging to achieve. However, the most important question is whether the model predicts mortality aligned with that expected in the relevant UK SCD population. A large real-world retrospective study of UK SCD patients with similar characteristics to those considered eligible for exa-cel reported mean and median ages at death of 40.17 years and 41.00 years, respectively, for a matched severe SCD cohort of	The company did not conduct model validation with respect to prediction of mean age for the SOC cohort using external estimated of survival for a population with SCD eligible for exa-cel. The burden of disease study submitted as part of ID4016 includes 1117 patients followed up for an average of 4.2 years. This is an unpublished study; the population in this study is sufficiently large but not too large. The EAG conducted a rapid search for literature to identify mortality estimates in the SCD population. Although the literature review is crude, the EAG was able to locate a

			patients (27, 28). The company base case predicts mean and median age at death of 43.56 years and 44 years, respectively, which align closely with those of the retrospective UK burden of illness study, despite the complex route through which mortality has been modelled. An alternative approach proposed by the DSU, outlined below, generates less realistic predictions.	reasonable number of studies including large cohorts of SCD patients with similar inclusion criteria to the burden of disease conducted by the Company. Please see EAG response addendum document for details.
			Employing an alternative approach using different data generates less realistic survival estimates. One alternative would be to model survival based on VOC frequency alone, which avoids the issues with multiple sources of mortality. The US Institute for Clinical and Economic Review (ICER) recently published their final report on gene therapies for SCD (29), in which mortality rates for patients on SoC were estimated using standardised mortality ratios (SMRs) estimated from a large US SCD cohort. We have utilised these SMRs in order to estimate alternative mortality rates in the model (an approach also suggested by the NICE DSU). When this alternative approach is applied, the model predicts mean and median survival of 50.42 and 52.00, respectively, which is materially higher than observed in the real-world UK setting (27, 28). Furthermore, implementation of this alternative approach reduces our base case ICER from [redacted] severity and DCEA weighted) to [redacted]. In summary, despite its limitations, our	First, the presentation of the ICER is misleading: the base-case ICER incorporating the change to the model structure is [redacted] (down from the ICER with the company's mortality methodology of [redacted]). The company's estimates presented here are not the base-case, but scenario analyses based on a non-reference case using a non-validated approach (DCEA) and assuming the applicability of severity modifiers. The acceptability of these assumptions/scenarios is the decision of the Appraisal Committee and therefore cannot be presented or anticipated as the ICER estimate. All ICERs presented by the company in this document are therefore misleading. The EAG will present the appropriate corresponding base-case ICERs.

			original approach has better external validity for current SoC than alternative, simple methods proposed by the DSU. However, due to the error identified by the NICE DSU in the calculation of cumulative mortality (see below), the original model was also underpredicting survival in the exa-cel arm, which adversely impacted the ICER. The alternative approach used is described in Appendix A: Alternative mortality modelling using ICER group SMRs, included within this response document.	With regards to model structure, there is consensus, based on the logic, that when an instrument is shown to be flawed, it should not be trusted under any circumstance, because it does not support extrapolation or prediction. The justification of a model structure cannot be done based on the results it generates, both a priori, and by logic of the results being flawed. The correct approach is to use a correctly designed model to generate appropriate (validated) outputs. The resolution of structural validity issues for the mortality estimates generated in the model is necessary, but not sufficient. Structural issues in the model are crucial to be able to assess the remaining issues: importantly, an inadmissible model structure does not allow to validate rates of acute and chronic complication, a fundamental driver of the cost-effectiveness, for reasons that are explained in the initial EAG report. Once structural issues are resolved, validation of the estimation of clinical event rates can be conducted. Furthermore, structural flows are one of the many issues that the EAG identified for the model the EAG has already described how the model relies extensively on many assumptions,

				none of which has been justified from both a modelling and an evidence base viewpoint.
			Issues with respect to cumulative mortality identified by the NICE DSU have been addressed. The NICE DSU report further identified what they considered was an error in the calculation of overall survival estimates: "*The DSU does not understand the company's rationale for estimating deaths in an additive fashion, rather than using conditional probabilities of dying. If all complication-related excess mortality risks are removed from the model, the cumulative probability of remaining alive in a given cycle should simply reflect the probability of being alive at the end of the previous cycle multiplied by one minus the conditional probability of all-cause death in the current cycle*." We were not able to reproduce Figure 1 of the DSU report in the model but have amended the Markov trace to estimate conditional probabilities of dying (activated in the model by selecting a new dropdown added to the bottom of the **EAG Functionality** sheet). This approach is also automatically implemented when the ICER group SMRs are applied. Notably, when this conditional probability approach is applied, removing excess mortality generates overall survival identical to the general population survival (minor differences likely due to half-cycle corrections), further	The EAG considers the "unconditional mortality" approach the only valid approach therefore the base-case, not a sensitivity. The EAG is satisfied with respect to the factual implementation of the approach in the model (as the company explains). However, this does not resolve the assessment of which SMRs are most appropriate for the cost-effectiveness.

			validating this amendment. The amendment increases life years (LYs) in both the SoC and exa-cel arms.	
Issue 7:	Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	No	Approximately 20% of people who initiated the exa-cel treatment journey did not receive the infusion. Some of the dropouts are due to failure of apheresis (the process used to harvest cells from the patient) whilst others fail to obtain enough exa-cel for reimplantation. The latter group undergoes apheresis, accrues the cost of manufacturing exa-cel but drops out of the process just before myeloablation. After dropping out of the process, these patients continue to receive SoC. The EAG consider that these patients should be accounted for in the economic model via a decision tree, which captures not only the costs of the withdrawing patients, but also their outcomes. We address this issue as three separate aspects below: 1) The NHS resource use costs of treatment failures 2) The costs of exa-cel for treatment failures 3) The outcomes of treatment failures **1) The NHS resource use costs of treatment failures** The model is already structured to account for the costs of patients who do not proceed to transplantation with exa-cel within the cost	Point 1: The EAG welcomes the appropriate incorporation of blood transfusion costs. The corresponding ICER for this scenario is [redacted]. Point 2: [redacted] Point 3: The outcomes of treatment failures. Apheresis is not part of standard practice; it adds the risk of adverse events and a small risk of death. Hence the outcomes of anyone who receives apheresis (regardless of the outcomes) are part of the decision problem because the only ethical reason to ask patients to undergo such procedure is that they then will receive exa-cel with the associated benefits.

			effectiveness estimates. Specifically, a cost uplift equal to the proportion of patients who withdraw is applied to the following categories of pre-transplant costs in the model: • Pre-mobilisation costs • Plerixafor • Hospitalisation for the mobilisation procedure The only category missing from the cost uplift was pre-transplantation RBC transfusion costs of £13,488. Acknowledging that the latter were excluded, we have included a cost uplift to these costs to account for the patients who withdrew. This change increases our severity and DCEA-weighted base case ICER from [redacted] to [redacted]. In summary, the NHS resource costs of patients who do not proceed to transplantation with exa-cel are largely captured in the model and we have included RBC transfusions in our updated base case ICER. **2) The costs of exa-cel for treatment failures** [redacted]	Second, when designing the cost-effectiveness of a diagnostic test, the outcomes of those that fail to receive treatment because of misclassification (false negatives) are indeed incorporated in the outcomes. However, the fundamental difference between a diagnostic test and apheresis is that there is a choice to be made in the case of a test, whilst apheresis is a condition sine qua non exa-cel cannot be received. A test is not compulsory. For example, treatment for women with BRAF mutations can still be given to BRAF- women. The cost-effectiveness for the diagnostic would have two arms: A. Test and treat BRAF + vs B. Treat everyone (and no test). So, the two arms differ by outcomes for false negative and false positives with test, and cost for negatives for the no test arm. Apheresis is not a test done to determine which patients should receive treatment and which should not: apheresis is necessary to obtain biological material; a patient cannot be given exa-cel without apheresis but also, in the case of low exa-cel yield, exa-cel cannot be redeployed to another patient. The example of a test for a cancer mutation is not an appropriate precedent; more appropriate precedents are the appraisals of CAR-Ts. All

			[redacted] **3) The outcomes of treatment failures** The only economic implication of these treatment withdrawals is additional costs, which have been accounted for via a cost uplift in the model and/or via a commercial arrangement. The impact on the ICER of including the outcomes of these subjects is substantial, as the large QALY gains of exa-cel are diluted by nearly 20%. It is therefore methodologically incorrect to consider the outcomes of untransplanted patients in the economic value of such a transformative treatment, given the only difference in their pathway of care vs remaining on SoC is their mobilisation procedure, and they never actually receive the treatment. This would be synonymous with including the outcomes of patients who are genetically tested for a targeted cancer treatment but are never actually treated.	models of CAR-Ts include outcomes for treatment failures. In addition, the NHS supports the costs of exa-cel for these recipients (because of no commercial agreement) therefore the outcomes must be accounted for. The use of the term “dilution” is also inappropriate. After apheresis, the patient supports an extent of “chance”, consisting the risk of adverse events, weighted against the chance to be transplanted or not, not the choice to be transplanted or not; whilst the genetically tested patient has the choice to still receive treatment or not, it is not a chance, and the NHS accrues no costs if a patient decides to walk away. Therefore, the term “risk” is more appropriate than dilution when conceptualising the options open to the NHS. The counterfactual of receiving exa-cel without undergoing apheresis is the only scenario where the outcomes of not receiving exa-cel should not be included in the decision problem; but it is an inadmissible scenario.
Issue 8:	Vaso-occlusive crisis (VOC) rates as a predictor in a risk equation for	No	The EAG has concerns with the way in which VOC rates are incorporated into the model. They believe that by applying the ‘number of VOCs’ as a significant independent variable originates from a misinterpretation of the Shah *et al* (2019) study,	The company did not conduct validation of the model outcomes with external literature based on alternative data than the company’s study.

	acute and chronic complications		and that as such the number of VOCs per cycle cannot be used as an intermediate outcome in the model. **The model has reasonable external validity with respect to comorbidities.** While we understand the EAG's focus on the methods of deriving incidence of comorbidities, it is important to consider the external validity of the model and whether there is likely to be significant bias in favour of exa-cel. This is possible to a limited extent by comparing the comorbidity rates reported in a UK cohort of severe SCD patients with those in the model and aligns with the NICE DSU suggestion to compare rates with external data (27, 28). The age at index date of SCD patients in this study was 25 years and the mean follow-up of these patients was approximately 5 years. We therefore consider the proportion of patients on SoC with a given chronic comorbidity at age 30 in the economic model vs the prevalence reported in the UK severe SCD cohort. Table 1 shows that three comorbidities (chronic kidney disease, neurocognitive impairment, and post-stroke) are overpredicted by the model, but others are generally aligned. As a substantial proportion of the value in the model is contributed by life years, and mortality was shown to have external validity in Issue 6, the bias in favour of exa-cel from overprediction of these 3 comorbidities is likely to be small.	The EAG presented a breakdown of event rates for acute and chronic complications in the Addendum. The EAG used the outcomes from a French claims database (Brousse et al., 2023) to assess the impact of complication rates in the model. Please see EAG response to TE addendum document for details. The addendum provides a very detailed characterisation of the complication rates used in the model, the overall model rates, and model outcomes. The EAG has chosen to model rates in the SOC arm only; given the large number of assumptions used in the exa-cel arm, and no corresponding evidence, the EAG has decided to focus on the "best case" scenario for exa-cel assuming that all the benefits hoped for will be realised. The company used the Vertex BOD study as the only source of validation; nonetheless a very rapid and top-level search on Medline provided additional references of large European studies that the company has not considered; the EAG has explored the impact

With respect to acute comorbidities, the number of events predicted by the model was compared with the rate per patient-year in a UK severe SCD cohort (27, 28). It can be seen in Table 2 that other than stroke, almost all of these events are underpredicted by the model, which biases against the exa-cel arm.

Table 1: comparison of model chronic comorbidities with UK severe SCD cohort

Comorbidity	Model prevalence at age 30	Severe SCD UK prevalence
Chronic kidney disease	[redacted]	5.55%
Pulmonary hypertension	[redacted]	10.21%
Avascular necrosis	[redacted]	Not reported
Heart failure	[redacted]	6.36%
Neurocognitive impairment	[redacted]	5.46%
Post stroke	[redacted]	2.42%
Retinopathy	[redacted]	18.53%
Liver complications	[redacted]	7.79%

of these alternative estimates on model outcomes.

The EAG has also used the Vertex BOD estimates in the model.

The validation exercise showed that the model is most sensitive to rates of chronic complications, whilst the impact of acute complications is limited, perhaps due to the one-off nature of the acute events.

The data presented by the company show that the model overestimates chronic comorbidities more, compared with the acute. Please see Technical Engagement Addendum document for details.

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>
Table 2: comparison of model acute comorbidities with UK severe SCD cohort
<table>
<tr><th>Comorbidity</th><th>Model rate per patient-year</th><th>Severe SCD UK rate per patient-year</th></tr>
<tr><td>Acute chest syndrome</td><td>[redacted]</td><td>0.520</td></tr>
<tr><td>Stroke</td><td>[redacted]</td><td>0.000</td></tr>
<tr><td>Acute infection</td><td>[redacted]</td><td>0.200</td></tr>
<tr><td>Acute kidney injury/failure</td><td>[redacted]</td><td>0.130</td></tr>
<tr><td>Gallstones</td><td>[redacted]</td><td>0.290</td></tr>
<tr><td>Pulmonary embolism</td><td>[redacted]</td><td>0.060</td></tr>
<tr><td>Leg ulcers</td><td>[redacted]</td><td>Not reported</td></tr>
</table>
Use of the Shah paper to predict incidence of comorbidities by VOC frequency
Below, we address 3 issues raised by the EAG individually:

Interpretation of the Shah paper
Use of Shah for deriving event incidence rate in SCD patients given frequency of VOC
Use of CLIMB SCD-121 VOC rates to calculate comorbidity incidence rates

</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><u>1.) Interpretation of the Shah paper</u></td>
<td>The EAG’s point was about</td>
</tr>
</table>

			The Shah paper clearly demonstrated in Table 2 that VOC frequency over follow up was a predictor of comorbidities and death. Summarising extracts from the paper below: **Index date** was defined as the first clinical claim indicating SCD during the identification period. Every patient had a ≥6-month **baseline** (pre-index) and ≥1-year **follow-up** (post-index) period. **Baseline**: claims during at least 6 months *before* the index date, which included the following: • Demographics: Age, sex, race, and US geographic region • Charlson comorbidity index (CCI) • Individual comorbidities: **VOC**, pulmonary conditions such as ACS, cerebrovascular conditions (stroke), hepatic conditions (gallstones), splenic conditions (splenic sequestration), and other conditions that commonly occurred among SCD patients. • Baseline all-cause HRU (inpatient, outpatient and pharmacy visits. **Outcome measures**: events captured during the **follow-up** period: • VOC episodes (**predictor**): after the index date, VOC event rate was calculated in 100 person-years using the number of events divided by the length of the follow-up period.	1. the method of estimation of those equations: Shah et al use both pre-index date VOCs and post-index data VOCs. Unless there was an intervention at index date, pre and post VOC rates are expected to be correlated, in which case, the solutions to the regression equations would be non-identified. The Shah paper does not address the issue, so presumably (as the regression was "stepwise") one of the two was dropped from the regression; 2. the clarity in the definition of which VOC measure was used as independent variable – The use of post-index date VOCs rate presupposes a unit of time; the company suggests that the rate was expressed as 100/persons-year over the duration of follow-up (as here on the left in the Company's response (Outcome measures); therefore, it is not clear how it would also be "time-varying". As acknowledged during TE discussions with the company, the Shah paper presents several methods shortcomings, also owing to poor reporting. In light of point 3. Below, application of VOC rates in the model, the discussion whether it was a rate or a stratifier is actually a low priority.

			• Deaths: patients who died during the entire follow-up period. • Rate of complications: cerebrovascular, hepatic, pulmonary, and splenic conditions. Taking selected extracts of text below: • "Cox proportional hazards regression was used for the multivariate analysis of the time to first complication after the index date**,** concerning the relationship between **the rate of follow-up VOC and life-threatening complications requiring acute care -** including ACS, splenic sequestration, pulmonary embolism, stroke, pulmonary hypertension, and death. • For the Cox model, **the rate of follow-up VOC events before the complication and death** were identified. • Considering the possibility of progression of diseases with time, **follow-up VOCs were controlled in the model as time-varying variables**. • The impact of the complications was also controlled in the model. For example, if stroke is the dependent outcome, then other complications (i.e., ACS, splenic sequestration, pulmonary embolism,	3. The interpretation of the results, specifically the difference between a significant model and significant predictors. The Shah paper, in Table 2, clearly acknowledges that when VOC is used as a predictor in the equation, the predictor coefficient is non-significant, although the model is significant. Because Shah used a stepwise regression approach, this means that VOCs baseline rates were dropped from the model; it also means that if follow-on rates were correlated with baseline VOCs, follow-on VOCs rates were also dropped from the regressions. Here below is the Table where the results from Shah are reported. Highlighted are the regressions where VOCs are retained as predictors, and the corresponding endpoints in which VOCs figure as predictors. The Company's table also states the same information (The EAG has highlighted the wording in light blue). There is no doubt that VOCs were included as the company says, but also there is no doubt that the VOC variable was dropped from the regressions, as a result of failing the stepwise significance coefficient.

			pulmonary hypertension) were put in the model. • The number of **baseline VOC** events were controlled in the model as covariates. • Hazard ratios (23), 95% confidence intervals (CI), and p-values were examined for the **follow-up VOC** rate and all other covariates." In summary, VOCs and comorbidities were included as both baseline (**time invariant**) and follow-up (**time-varying**) covariates for the event of interest. The reported HRs in Table 2 of the publication used the **follow-up** VOC as predictor, while controlling for **baseline** events (including VOC/pain crises) and events that happened over the follow-up period prior to development of the comorbidity of interest or death. Table 2 of the publication describes the relationship between the **rate of follow-on VOCs (time varying)** and statistically significant comorbidities at baseline and developed during the follow-up period prior to the event. These covariates are summarised in Table 3 below, by querying the footnotes in Table 2 of the publication. All HRs for rate of **follow-up** VOCs were statistically significant (confidence intervals all above 1 in Shah Table 2), whereas **baseline**	This means that VOCs should not be used in an equation, not that VOCs are not a relevant endpoint. The EAG remains of the opinion that VOCs should be incorporated in the model in the same way as all other acute and chronic complications, as a rate in its own right. Ultimately, the EAG scenarios based on complication rates derived from the literature are implemented independently from the VOC rates, effectively overriding the company's functionality (VOCs as regressors). **Table 2. Cox Model to Examine the Relationship between VOC and Complications** Outcomes among Sickle Cell patients (N=20,909) — Results from Cox Model for Follow-up VOC HR — 95% CI — p-value Time-to-Death[a]: 1.56 — 1.19 — 2.05 — 0.0014 Time-to-Acute Chest Syndrome[b]: 58.67 — 50.21 — 68.55 — <0.0001 Time-to-Splenic Sequestration[c]: 43.99 — 30.65 — 63.13 — <0.0001 Time-to-Pulmonary Embolism[d]: 2.82 — 2.21 — 3.58 — <0.0001 Time-to-Stroke[e]: 2.26 — 1.94 — 2.63 — <0.0001 Time-to-Pulmonary hypertension[f]: 4.12 — 3.14 — 5.41 — <0.0001 *Significant covariates after the stepwise model selection for each endpoint model include – [a] age, sex, race, region, CCI, baseline neoplasms, baseline VOC, baseline use of opioids, NSAIDs, iron chelating therapy, baseline all-cause HRU, follow-up pulmonary embolism, stroke, and pulmonary hypertension; [b] age, sex, race, region, baseline use of iron chelating therapy, folic acid, baseline transcranial doppler ultrasonography, baseline all-cause HRU, and follow-up pulmonary embolism; [c] age, baseline use of hydroxyurea, and baseline pain crisis; [d] age, sex, race, region, CCI, baseline fever, baseline use of opioids, follow-up acute chest syndrome, stroke, and pulmonary hypertension; [e] age, sex, race, region, CCI, baseline fever and seizures, baseline use of NSAIDs, iron chelating therapy, tricyclic antidepressants, acetaminophen, baseline blood transfusions and pneumococcal vaccine, baseline VOC, follow-up acute chest syndrome and pulmonary hypertension; [f] age, CCI, baseline use of opioids, folic acid, baseline blood transfusion, baseline all-cause HRU, follow-up pulmonary embolism, stroke, and acute chest syndrome

VOC/pain crisis was only significant in the models for mortality, splenic sequestration, and stroke.

Table 3: Summary of significant covariates from regressions reported in Shah Table 2

Outcome measure	Significant baseline period covariates	Significant follow-up period covariates (in addition to VOC rate)
Time-to-Death	Age, sex, race, region, CCI, baseline neoplasms, baseline VOC, baseline use of opioids, NSAIDs, iron chelating therapy, baseline all-cause HRU,	Pulmonary embolism, stroke, and pulmonary hypertension
Time-to-Acute Chest Syndrome	Age, sex, race, region, baseline use of iron chelating therapy, folic acid, baseline	Pulmonary embolism

				transcranial doppler ultrasonography, baseline all-cause HRU		
			Time-to-Splenic Sequestration	Age, baseline use of hydroxyurea, and baseline pain crisis	None	
			Time-to-Pulmonary Embolism	Age, sex, race, region, CCI, baseline fever, baseline use of opioids	Acute chest syndrome, stroke, and pulmonary hypertension	
			Time-to-Stroke	Age, sex, race, region, CCI, baseline fever and seizures, baseline use of NSAIDs, iron chelating therapy, tricyclic antidepressants, acetaminophen, baseline blood transfusions and pneumococcal vaccine, baseline VOC	Acute chest syndrome and pulmonary hypertension	

			Time-to-pulmonary hypertension | Age, CCI, baseline use of opioids, folic acid, baseline blood transfusion, baseline all-cause HRU | Pulmonary embolism, stroke, and acute chest syndrome	
			2) Use of Shah in deriving event incidence rate in SCD patients given VOC vs. no VOC As explained in the previous section, the Shah paper provides the HR of developing comorbidities or death conditional on the rate per patient-year of developing VOCs over the follow-up period. Each HR can be interpreted as the additional risk of developing the comorbidity or death, conditional on having experienced one VOC a year. In order to apply these HRs in the model, a baseline risk **for SCD patients with zero VOCs** is required. The baseline risk of the outcome with no VOC over the course of a year can be calculated from the Shah paper, as the paper provides: • The rate per patient-year of the event of interest in the overall cohort (Figure 2 in Shah)	This point is rather surprising in the light of the discussion above. The use of annualised rate per 100 persons means that the coefficient of a particular regressor applies to the rate, not to the single occurrence; the rate is a continuous variable. The interpretation of a regression coefficient implies that for a variable like VOC, the rate for zero VOCs is the intercept of the regression (bar coefficients for predictors other than VOC). We acknowledge that Shah does not present the actual regression coefficients but only the HRs. Nonetheless, the company also argues that a zero rate of VOC implies functional cure and therefore no SCD-related complications. This is one of the major assumptions in the model. Therefore, it is unclear why a baseline rate for zero VOC is needed. There are no subgroups in the model that have complication rates despite also having zero VOCs. The model tool has one

			• The proportion of the cohort that experienced a VOC over the follow-up (30.86% for adults in Shah) • The hazard ratio for developing the outcome conditional on experiencing a VOC The baseline risk of the outcome with no VOC was therefore estimated by rearranging the following equation: Mean event rate of Shah cohort = Baseline event rate$_{(0\ VOC)}$ * % of cohort with 0 VOCs + Baseline event rate$_{(0\ VOC)}$ * HR with VOC * (1-% of cohort with 0 VOCs) The risk of the outcome for those patients experiencing a VOC within each cycle was correctly estimated by applying the HR for VOC from Shah to the calculated baseline risk of the event in absence of a VOC.	parameter for people who have no VOCs and no benefit however there is no material use for that cohort in this appraisal, because it is unclear how this is applied. Nonetheless, what is even more surprising in the light of the discussion above is that eventually the VOC rate is implemented in the model as a probability (see point 3 below).
			3) Use of CLIMB SCD-121 VOC rates to calculate comorbidity incidence rates The rate per patient-year of VOCs is available from the CLIMB SCD-121 study. However, it is clearly not possible for a patient to experience a fraction of a VOC during the model cycle period of 1 month; patients either have a VOC or not. In each cycle, the model therefore assumes that patients either do or don't experience a VOC. For those who don't experience a VOC, the baseline comorbidity rate when VOC = 0 is applied (as	This comment presents a basic confusion between first order uncertainty (variation between people in a sample) and second order uncertainty, variation of the mean across samples. The model is not a simulation, so the values for VOCs in the model are not 0 or 1. The EAG has implemented a function to override this confusion.

			calculated in the previous section). For the proportion that do experience a VOC, the event rate when VOC = 1 is applied.	
Issue 9:	Modelling of adverse events is partial to exa-cel short list and selected events.	No	The EAG consider that "NHS costs cannot include adverse events for products not yet used in clinical practice" and that costs of AEs related to exa-cel should be costed separately. However, the EAG also states that the unit cost of hospitalisation for the transplant procedure applied in the model was appropriate. **The model correctly assumes that AE costs of exa-cel are captured within the autologous-SCT unit cost.** The unit cost applied was the 100% inpatient autologous stem cell transplant HRG, which includes costs in the 30 days preceding and 100 days post-transplant. Logically, this HRG will include inpatient management of AEs (which will be primarily due to toxicity of the mobilisation procedure and/or a weakened immune system). It is therefore unclear how the EAG can accept the autologous stem cell cost in the model while also stating that NHS costs cannot include adverse events for products not yet used in clinical practice. Any incorporation of AE costs on top of the stem cell transplant would clearly introduce double counting of healthcare resource. Furthermore, the same issue arose in CAR-T appraisals, during which it was agreed that all AE costs, other than ICU admission, would be included within a proposed CAR-T tariff.	The EAG has accepted the validity of the cost obtained from standard source for the UK (Reference costs) for the HRG 'autologous transplant' etc. The EAG also underlined how that cost, determined given current practice for the procedure, which uses busulphan, certainly does not include adverse events added by the transfusion with exa-cel. Indeed, the CLIMB-121 CSR clearly states that of adverse events reported, some can be attributed to busulphan only, some attributed to exa-cel only and some attributed to the both of them. See Table 12-5 from the CLIMB-121 CSR, page 131. These events must be explicitly included to be able to run them in the PSA. With regards to the reference to the CAR-T tariff, there is no such agreement in place for exa-cel. The CAR-T – type tariff therefore is not a suitable reference for cost-comparisons in this appraisal, where the cost of transplant must be calculated from all the inputs and accounting for variability across the reference patient group (see cost of drug by weight below).

			Specifically, a one-off cost of £41,101 was considered appropriate to cover all costs associated with the first 100 days of CAR-T delivery other than the costs of conditioning chemotherapy drugs and intravenous immunoglobulin (30, 31). Notably, this one-off cost of £41,101 is substantially lower than the revised £72.8k costs incorporated in the model (see Issue 10) to cover the pre-transplant and early post-transplant costs (including the £25k autologous-SCT HRG).	[redacted]
Issue 10:	Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using distribution of patients' weight.	No	The EAG believes that the cost of weight-based drugs should be calculated for all possible weights (weight distribution), which they note is a well-established practice for cost-effectiveness modelling. The EAG has consequently recalculated the NHS costs of delivering exa-cel in the model. In considering this critique we have identified two errors in the model which led to over costing of plerixafor in our submitted base case: • We had multiplied the daily weight-based dose of plerixafor by 4 days AND by 2.2 cycles. In practice, plerixafor is given for 3 days in cycle 1, up to 3 days (but on average 2) in cycle 2 and for 2 days in subsequent cycles. We have therefore amended the model to assume that plerixafor is given during 2.2 cycles for on average 2.5 days. This reduces the cost	The EAG accepts the company's position, and this issue is resolved. The costing using Reference costs has been long based on HRGs – where one forfeit is calculated based on the total costs of services, apportioned by patients, rather than the (laborious) costing using bottom-up methods. HRGs are based on compensation across patients with the costs of patients that require longer or shorter stays / more or less intensive care being averaged out. This approach removes the risk of "cream-skimming", i.e., treating only the patients who require less resources. As such, the HRG approach does not constitute underestimate – it is an average, applied uniformly across the model.

			per patient of plerixafor from £31,203 in our base case to £19,502. • The unit cost of a hospitalisation for mobilisation (peripheral blood stem cell harvest inpatient) had been doubled from £5,375 to £10,749 to account for multiple cycles but was then further multiplied by another 2.2 mobilisation cycles. We removed the initial doubling of the unit cost but retained multiplying by 2.2 cycles, noting that this may still be over-costing, given that the majority of HRGs represent the cost of a spell (i.e. total patient procedure). Amending these errors reduces the total pre-transplantation cost (pre-mobilisation costs, plerixafor, hospitalisation for the mobilisation procedure, supportive RBC transfusions) from £71,000 (£84,465 after accounting for treatment withdrawals) to £47,421 (£56,415 after accounting for treatment withdrawals). These exclude the costs of the transplant procedure, which add an additional £25k to the estimated delivery costs. The above changes reduce our severity and DCEA-weighted base case ICER from [redacted] to [redacted]. In contrast, the EAG's total mobilisation costs (~£70k) add up to more than the HRG cost of an	The cost of drugs by weight is a drastic simplification as it allows one cost calculation instead than repeating the calculation in all the traces in the model (5) over the course of the model (short of 1000 cycles) and ensures consistency with other Appraisals. With respect to the costs involved by exa-cel, the cost of chelation is minimal and has little impact, but the correct implementation of costs ensures the predictive validity of the model under alternative scenarios, i.e., that the model remains reactive even in the scenarios where the costs of other treatments in the model may be such that these costs do make a difference. Yet for simplicity accepts these changes and considers these issues resolved.

			allogeneic SCT (the most expensive type of SCT). Plerixafor makes up £44k of this cost. Firstly, plerixafor is currently only commissioned where usual treatment fails to secure the collection of sufficient cells. In an NHS plerixafor commissioning report (32), the highest incremental cost of plerixafor per successful mobilisation procedure was approximately £20-24k (in non-Hodgkin's Lymphoma). In the SMC detailed advice document, a full course of plerixafor + G-CSF was estimated to cost £10-20k per adult patient. In summary, the EAG's delivery costs result in a substantial overestimate of the likely costs to the NHS of delivering exa-cel. Even after the aforementioned cost reductions, Vertex's revised estimate of delivery costs is generous, as adding on the additional cost of the transplant itself brings the total cost per patient (before accounting for treatment withdrawals) to £72,808, which we consider a fair estimate of delivery costs to the NHS. With respect to weight-based dosing of iron chelation regimens, we note that this was not considered an issue in the ongoing TDT appraisal and that adding this additional complexity makes little difference to results.	
Issue 11:	The cost of supportive blood transfusions	No	The EAG states that it is not known whether the use of supportive transfusions will become part of clinical protocols for exa-cel, and as such believe	The EAG accepts the company's position, and this issue is resolved.

	alongside implantations of exa-cel is not included in model costs.		that the cost for supportive transfusions should be included in the model. **Supportive blood transfusions received by patients during delivery of exa-cel are not synonymous with transfusions received as part of SoC.** The EAG has replaced the number of supportive blood transfusions at baseline in the company base case (5) with the number of annualised blood transfusions from the CSR (11.6). This is inappropriate, because the value in the CSR represents "all cause" blood transfusions received prior to baseline, including emergency blood transfusions for treatment of VOCs and their complications, as well as those for patients requiring chronic blood transfusions as preventive treatment against VOCs. "Supportive" blood transfusions are given over 8 weeks prior to mobilisation plus 8 weeks prior to transplant (accounted for by transfusions given every 3-4 weeks, hence the 5 in the model) then additional transfusions post-myeloablation, the latter being required following all SCT procedures, not just SCD. The company has therefore already over-costed supportive blood transfusions, given: • The cost of chronic, preventive blood transfusions at baseline is applied during the follow-up period to those exa-cel patients who are not yet considered "cured" of their SCD (thus double-counting	

			the 5 supportive blood transfusions assumed for <u>all</u> patients in the model). • Supportive blood transfusions in the 30 days prior to transplant and 100 days post-transplant would be a component of the autologous SCT HRG cost. • The HRG cost for a VOC (applied to patients experiencing VOCs during engraftment) would also include the cost of blood transfusions required as part of an admission for a VOC and associated complications. Thus, the EAG's approach of using the baseline transfusion frequency double-counts the costs of transfusions given to manage VOCs.	
Issue 12:	Range of acute and chronic complications included in the model is large, but risk reduction is based on assumptions	Yes	The EAG has concerns with the extent to which parameters in the model are based on assumptions. They believe that the gaps in the evidence should be recognised, and that the extent of uncertainty should not be overwhelming, to ensure that both the logic and outputs of the model are plausible. **The model is not very sensitive to comorbidities where VOC-based incidence is based on assumptions.** As discussed in Issue 8, the rates of many comorbidities are aligned with those observed in a severe SCD cohort in the UK. However, we acknowledge that the inclusion of additional VOC-based incidence underpinned by assumptions introduces additional uncertainty. In order to	The EAG tested the impact of assumptions regarding the estimation of complications using the VOC equation and have found that the model is very sensitive to the approach on how complications are modelled. Please see addendum for further details. The EAG considers that this issue has not been resolved.

			explore this, we have conducted a sensitivity analysis whereby the additional complication risks arising from VOCs are removed from the model (HR set to 1) in cases where the incremental risk is underpinned by an assumption. For these comorbidities, the published cohort rates from the literature are applied, without applying additional HRs for VOCs. This has been carried out for the following comorbidities: Acute complications: • Acute infections • Gallstones • Leg ulcers Chronic complications: • Avascular necrosis • Heart failure • Neurocognitive impairment • Sickle retinopathy • Liver complications The results of this sensitivity analysis both including individual comorbidity-based mortality and using the ICER group SCD SMRs implemented in Issue 6 are provided in Table 4 below. It can be seen that in both instances, impact on the results is relatively small, with severity and DCEA-modified ICERs increasing by only 2-4%. Note that the scenario including individual comorbidities includes the fix to the	

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>error calculating cumulative mortality in Issue 6, hence the divergence from the original base case ICER of [redacted].

Table 4: ICERs with assumption-based comorbidity incidences removed
<table>
<tr><th></th><th>Including comorbidity-based mortality (base case)</th><th>SCD SMRs from ICER group (see Issue 6</th></tr>
<tr><td>Including assumption-based HRs (base case)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Excluding assumption-based HRs</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>

Note to EAG: This scenario can be selected via the dropdown at the bottom of the EAG Functionality sheet. The formulae have been modified in the pale orange cells in the Raw_complication_risks sheet (leading to different baseline comorbidity risk estimates) as well as in the Complication risk inputs sheet (HRs conditional on VOC set to 1).</td>
<td></td>
</tr>
<tr>
<td>Issue 13:</td>
<td>Underestimation of uncertainty in</td>
<td>No</td>
<td>The EAG considers that uncertainty has been adequately accounted for in the economic model.</td>
<td>The parameters set to 0 or 1 are chance parameters, having hit an observation of the</td>
</tr>
</table>

	modelling of overall survival in exa-cel and standard of care. Distributions not appropriately parameterised and some key inputs excluded from the probabilistic sensitivity analysis.		Vertex has reviewed the document detailing parameters missing from the PSA provided by the EAG following the technical engagement call. The majority of these parameters were excluded from the PSA due to the parameter either being a zero or 100% probability or not being relevant to the base case (see Vertex comments added to the document sent by the EAG (33)). We have included additional parameters initially excluded from the PSA, including stratified probabilities of mortality of comorbidities. A re-run of the PSA generated a severity and DCEA-modified ICER of [redacted] which remains aligned with the deterministic ICER of [redacted]. The new method of estimating SCD-based SMRs in the model applied in Issue 6 also incorporates all measures of uncertainty reported in the relevant literature (extracted from the ICER report and/or the Desai retrospective study). The uncertainty estimates are provided in columns M to P of the new inputs in the **Mortality inputs** sheet.	extremes at 0 or 1 from one clinical trial does not make these parameters a certainty, therefore they should be included in the PSA based on a more realistic value that may be observed over the long run. The ICER reported here are invalid because they are sub-scenario analyses that the Appraisal Committee must deliberate about. This issue is considered not resolved.
Issue 14:	Inclusion of severity modifier and implementation of 1.5% discount rate	No	The EAG believes that there is overlap between the conditions required to achieve the severity modifier and non-reference discount rate. Specifically, they note that the severity modifier captures the severity of the condition, which overlaps with the criterion for 1.5% discount rate 'the treatment restores people to full or near-full health when they would otherwise die or have	Discount rate: Apart from perhaps condition 1, condition 2 and 3 are not demonstrated, either with direct or with indirect evidence. The EAG has calculated the quality adjusted life expectancy shortfall of the SCD population and has concluded that no severity modifier weight that should be applied.

			severely impacted lives'. The EAG's view is that this may result in double-counting. **The severity modifier and non-reference discount rate are addressing different issues, and are described independently in the NICE methods manual.** In previous communications with NICE, there has been alignment that fundamentally the severity modifier and non-reference discount rate are addressing different issues. The severity modifier is a disease-specific modifier that does not consider treatment effect. In contrast, the non-reference discount rate primarily relates to treatment effect, as described below. **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	The EAG confirms that the severity modifier and non-reference discount rate are addressing different issues and are described independently in the NICE methods manual.

			for a modifier is by decreasing the QALY discount rate. It is 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 (34). **Discount rate** The 1.5% discount rate requires the 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. In summary, the severity modifier and non-reference discount rate have their own dedicated, independent sections in the NICE Methods Guide. The severity modifier is a disease-specific modifier that does not consider treatment benefit. In contrast, qualification for non-reference discount rate is driven by the technology and its benefits. As such, Vertex maintain the position that these modifiers are not mutually exclusive, and instead can be applied in combination where qualifying criteria are met.	
Issue 15:	Non-reference case distributional cost-effectiveness analysis	No	The EAG considers that the DCEA should be excluded from the decision problem because it is not a part of the NICE reference-case, and that its introduction for this appraisal might result in undesirable inequity relative to previous HST assessments (*Vertex re-iterate as we did at FAC that this appraisal is proceeding along the standard STA route, not HST)*. Before getting into detail on our response, we draw attention to the recent voxelotor for SCD (GID- TA10505) appeal hearing, where one of the appeal points upheld related to the committee failing to recognise the barriers to access and/or take into account health inequalities for patients with SCD. This is a clear acknowledgement of the health inequalities experienced by patients with SCD and supports the point that SCD should not	The EAG considers this non-reference case scenario, which should not be used to adjust the ICERs for this decision problem.

			be treated as just another rare disease when it comes to taking account of health inequalities. **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 SCD 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). **The value for aversion to inequality is based on a survey, recommended by a single expert.** The underlying aversion value, which is derived from a survey of UK participants, was recommended to Vertex as a source to use by Prof Richard Cookson. **Health deprivation has been assumed to be an adequate proxy for ethnicity, not vice versa.** We would like to draw attention to the fact that we have, in fact, employed health deprivation in our DCEA analysis and have not used a	

			proxy for health deprivation. However, we do assume that health deprivation by IMD group is an adequate proxy to reflect ethnicity-based health inequalities, since health inequalities are strongly correlated with health deprivation within the UK. **The DCEA provides other important metrics to consider, e.g., the Slope Index of Inequality (SII).** The DCEA provides important metrics to consider in relation to health inequalities, such as the SII. It is critical to acknowledge that there are clear inequalities within the SCD population. In addition to a reweighting of cost-effectiveness estimates based on health inequalities between deprivation quintiles, the DCEA provides a quantitative summary of health inequalities within the UK SCD population and, more importantly, the affect exa-cel is predicted to have on these health inequalities within this population, i.e., whether the product increases or decreases health inequalities within this population.	

Appendix A: Alternative mortality modelling using ICER group SMRs

ICER group generated the SMRs reported below in Table 5 by comparing mortality rates between a US Medicare SCD cohort (reported by Desai et al., 2020) and those of the age and gender matched US population (35).

Table 5: Cumulative mortality and SMRs, ICER report

Age	Cumulative incidence	Mean SMR	Lower CI SMR	Upper CI SMR
Ages 13-18	15.0% (11.8-18.2%)	40.07	31	49.46
Ages 19-35	27.3% (24.9-29.6%)	24.24	21.8	26.65
Ages 35+	45.41% (41.4-49.2%)	17.48	15.47	19.5

The Desai analysis reported cumulative mortality and hazard ratios by frequency of VOCs in the baseline year (<2, 2-4 and ≥5). In the ICER report, the calculated SMRs are reported as being attributable to patients with ≥5 VOCs in the baseline year. However, the Desai manuscript does not attribute the cumulative mortality estimates used by ICER to the ≥5 VOC subgroup; we believe the figures include cumulative mortality from patients with <2 and 2-4 VOCs in the baseline year (this is evident from scrutiny of the Kaplan Meier plot, which shows that cumulative mortality for the ≥5 VOC group clearly exceeds that reported in the main body used by ICER group). Because the CLIMB SCD-121 inclusion criteria specified that patients had to have experienced ≥2 severe VOCs per year, the Desai SMRs, which included patients with <2 VOCs at

baseline, require adjusting to represent the more severe cohort eligible for exa-cel. The Desai data used for this adjustment are reported in Table 6 below:

Table 6: Data from Desai used for calculation of SMR by VOC subgroup

	Proportion of cohort		
Number of VOCs in baseline year	**<2**	**2-4**	**≥5**
Ages 13-18 (N=6,940)	55.1%	33.6%	11.3%
Ages 19-35 (N=11,064)	34.7%	33.2%	32.1%*
Ages 35+ (N=4,495)	43.5%*	32.8%	23.7%
Hazard ratio for mortality (95% Confidence interval)	1 (32)	1.26 (1.14–1.40)	1.57 (1.41–1.74)

*Note: published value increased by 0.1% to add up to 100%

As stated previously, we consider the overall SMRs calculated by ICER group to be attributable to the entire Desai cohort. They can therefore be considered as the weighted average of the SMRs for each VOC frequency subgroup, the weights being determined by both the proportion of patients in each subgroup and the hazard ratio (23) for mortality between subgroups, summarised below as:

Overall SMR =

$SMR_{(<2\ VOCs)} * HR_{(<2\ VOCs)} * \%\ cohort_{(<2\ VOCs)} +$

$SMR_{(<2\ VOCs)} * HR_{(2\text{-}4\ VOCs)} * \%\ cohort_{(2\text{-}4\ VOCs)} +$

$SMR_{(<2\ VOCs)} * HR_{(\geq 5\ VOCs)} * \%\ cohort_{(\geq 5\ VOCs)}$

Rearranging and simplifying the equation, the SMR in the <2 VOC reference group can be calculated as follows:

$SMR_{(<2\ VOCs)} =$

Overall SMR/

$(HR_{(<2\ VOCs)} * \%\ cohort_{(<2\ VOCs)} +$

$HR_{(2\text{-}4\ VOCs)}$ * % $cohort_{(2\text{-}4\ VOCs)}$ +
$HR_{(\geq 5\ VOCs)}$ * % $cohort_{(\geq 5\ VOCs)}$)

Once the SMR in the <2 VOC group is calculated, the SMRs for the 2-4 and ≥5 VOC groups can be calculated via multiplication with their respective HRs from Table 6. For the >35 age band, the whole cohort SMR calculated by ICER group is used as the Desai paper stated that mortality did not vary by baseline VOC frequency.

To calculate the risk of mortality of the CLIMB SCD-121 cohort, which excluded patients with <2 VOCs per year, the SMRs were weighted by the proportion of patients with ≥5 and 2-4 VOCs at baseline in the FAS ([redacted] and [redacted] respectively, values not available by age band). Weighting the SMRs calculated in the previous section by the proportions of patients in each VOC cohort in CLIMB SCD-121 leads to the SMRs summarised in Table 7 applied in the economic model (but using the cohort average for the >35 year cohort, as stated previously).

Table 7: SMRs by age band applied in economic model

	Proportion of cohort in CLIMB SCD-121 FAS*		
Number of VOCs in baseline year	**2-4**	**≥5**	
Ages 13-18	[redacted]	[redacted]	
Ages 19-35	[redacted]	[redacted]	
	SMRs		**Weighted average SMR**
Number of VOCs in baseline year	**2-4**	**≥5**	**CLIMB SCD-121 cohort**
Ages 13-18	44.45	88.63	[redacted]
Ages 19-35	20.43	40.74	[redacted]
Ages 35+	17.48	17.48	17.48

*Note: values not available stratified by age band.

Vertex acknowledges the limitations in this approach, primarily that (1) hazard ratios are assumed equivalent to SMRs (2) hazard ratios were

not available stratified by age band from Desai (3) the proportion of the CLIMB SCD-121 cohort with ≥5 VOCs at baseline was not available by age band.

This approach also addresses the EAG's concerns regarding the lack of sensitivity analysis around mortality estimates (Issue 13) as all uncertainty estimates from Table 5 and Table 6 have been incorporated into the cohort SMRs.

Note to EAG:

These new calculations can be found at the bottom of the **Mortality inputs** sheet of the updated model and SMR-weighted monthly mortality rates have been added to column AB in the **Raw_Mortality** sheet.

A drop-down to select this option has been added to the bottom of the **EAG Functionality** sheet. When this option is selected, individual mortality rates or SMRs/HRs in the **Mortality inputs** sheet are set to 0 or 1, respectively, via the override cells. In all relevant Markov traces, the mortality rates in the column Base mortality – SCD rate is replaced by the new estimates. All amended cells have been highlighted in pale orange.

Appendix B: New evidence – ASH 2023 data cut vs D120

As described in the introduction, data from a further data cut (14th June, 2023) is expected to be published in *NEJM* in March 2024. This data was also presented at the American Society of Hematology 2023 congress (1). As presented in Table 8, this data cut includes only one further patient in the analysis set, and outcomes are highly similar. As such, this data has not been incorporated into the modelling.

Table 8: Comparison of D120 data cut vs ASH data

	D120	ASH 2023
Data cut-off date	16-Apr-2023	14-Jun-2023
Number in FAS	43	44
Number in PES	29	30

VF12	96.6% (28 of 29 patients)	96.7% (29 of 30 patients)
VOC-free duration; mean (range)	20.7 months (12.8, 43.6 months)	22.4 months (14.8, 45.5 months)
VOC-free through follow-up (of those to achieve VF12)	96.4% (27 of 28 patients)	96.6% (28 of 29 patients)
HF12	100% (29 of 29 patients)	100% (30 of 30 patients)

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 9: 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). Severity and DCEA weighted ICER
Issue 6: The model does not have the requisites for a Markov structure	Mortality was calculated in an additive function rather than calculating conditional probabilities of mortality.	Mortality is calculated as a conditional probability.	Original ICER: [redacted] Revised ICER: [redacted] Change from original: -£946 [redacted]
Issue 7: Economic analyses do not account for costs and outcomes associated with treatment failures between	The cost of 5 supportive blood transfusions pre-mobilisation and myeloablation was not included in the cost uplift to	The cost of 5 supportive blood transfusions pre-mobilisation and myeloablation is now included in the cost uplift to account for treatment withdrawals.	Original ICER: [redacted] Revised ICER: [redacted] Change from original: +£36 [redacted]%)

apheresis and myeloablation.	account for treatment withdrawals.		
Issue 10: Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using distribution of patients' weight.	The cost of plerixafor was calculated assuming 4 days of plerixafor per mobilisation cycle. The unit cost of stem cell mobilisation was pre-doubled before multiplying by the number of mobilisation cycles.	The cost of plerixafor is calculated assuming 2.5 days (2-3 days) of plerixafor per mobilisation cycle. The unit cost of stem cell mobilisation is multiplied by the number of mobilisation cycles.	Original ICER: [redacted] Revised ICER: [redacted] Change from original: -£396 ([redacted]%)
			DCEA & severity modified
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ] Unweighted: [redacted] Severity weighted: [redacted] DCEA & severity weighted: [redacted]	Incremental costs: [£££] Unweighted: [redacted] Severity weighted: [redacted] DCEA & severity weighted: [redacted]	Please provide company revised base-case ICER: [redacted]

Sensitivity analyses around revised base case

As described in Issue 6, a simplified analysis was carried out whereby an overall SMR for severe SCD was applied to uncured patients.
This analysis reduces the revised base case ICER by £1,131 to [redacted] ([redacted]decrease).

As described in Issue 8, a scenario analysis was conducted whereby hazard ratios by presence of VOC were excluded if they were based on assumptions; the reported rates per patient-year were used instead for all SCD patients.
This analysis increases the revised base case ICER by £451 to [redacted] ([redacted]increase)

References

1. Frangoul H, Locatelli F, Sharma A, Bhatia M, Mapara M, et al., editors. Data on File - Exagamglogene Autotemcel for Severe Sickle Cell Disease
American Society of Hematology; 2023 06 December 2023.
2. Vertex Pharmaceuticals Inc. Data on File. Exa-cel Efficacy and Safety Update (16 April 2023). 2023.
3. Agency MHPR. Casgevy 4-13 x10^6 cells/ mL dispersion for infusion
(exagamglogene autotemcel). Vertex Pharmaceutical (Europe) Limited; 2023.
4. Services USDoHaH, Research FaDACfBEa. Human Gene Therapy for Rare Diseases 2020 January 2020.
5. Compernolle V, Chou ST, Tanael S, Savage W, Howard J, Josephson CD, et al. Red blood cell specifications for patients with hemoglobinopathies: a systematic review and guideline. Transfusion. 2018;58(6):1555-66.
6. Trompeter S, Massey E, Robinson S, Transfusion Task Force of the British Society of Haematology Guidelines C. Position paper on International Collaboration for Transfusion Medicine (ICTM) Guideline 'Red blood cell specifications for patients with hemoglobinopathies: a systematic review and guideline'. Br J Haematol. 2020;189(3):424-7.
7. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Advances. 2020;4(2):327-55.
8. DeBaun MR, Jordan LC, King AA, Schatz J, Vichinsky E, Fox CK, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv. 2020;4(8):1554-88.
9. Zakaria O, Buhalim RA, Almulhim F, Al Jabr FA, Alrashid A, Almutairi M. Clinical and Laboratory Predictors of Painful Vaso-Occlusive Crisis Among Sickle Cell Disease Patients: A Single-Center Study in Saudi Arabia. Cureus. 2021;13(5):e14980.
10. National Heart Lung and Blood Institute. Evidence-Based Management of Sickle Cell Disease. Available at https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf 2014 [
11. Sickle Cell Society. Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK 2018 [Available from: https://www.sicklecellsociety.org/wp-content/uploads/2018/05/Standards-for-the-Clinical-Care-of-Adults-with-Sickle-Cell-in-the-UK-2018.pdf.
12. Society SC. Sickle Cell Disease in Childhood Standards and Recommendations for Clinical Care. Available at https://www.sicklecellsociety.org/wp-content/uploads/2019/11/SCD-in-Childhood_Final-version-1.pdf 2019 [
13. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N, et al. Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. British Journal of Haematology. 2017;176(2):179-91.

14. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N, et al. Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion. British Journal of Haematology. 2017;176(2):192-209.
15. Qureshi A, Kaya B, Pancham S, Keenan R, Anderson J, Akanni M, et al. Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. Br J Haematol. 2018;181(4):460-75.
16. Charache S, , Terrin ML, , Moore RD, , Dover GJ, , Barton FB, , Eckert SV, , et al. Effect of hydroxyurea on the frequency of painful crises in Sickle cell anemia. New England Journal of Medicine. 1995;332:1317–22.
17. Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). Lancet. 2011;377(9778):1663-72.
18. Vertex Pharmaceuticals Inc. Data on file. Exa-cel UK HTA Advisory Board. 2022.
19. Adams RJ, , McKie VC, , Hsu L, , Files B, , Vichinsky E, , Pegelow C, , et al. Prevention of a first stroke by transfusions in children with sickle cell anemia & abnormal results on transcranial Doppler ultrasonography. New England Journal of Medicine. 1998;339:5-11.
20. Ware RE, Davis BR, Schultz WH, Brown RC, Aygun B, Sarnaik S, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. Lancet. 2016;387(10019):661-70.
21. National Institute for Health and Care Excellence. Crizanlizumab for preventing sickle cell crises in sickle cell disease. Committee Papers 2021 [Available from: https://www.nice.org.uk/guidance/ta743/documents/committee-papers.
22. Mahesri M, Lee BS, Levin R, Imren S, Zhang L, Beukelman T, et al. PATIENTS WITH SEVERE SICKLE CELL DISEASE ON STANDARD OF CARE TREATMENT ARE VERY UNLIKELY TO BECOME VOC FREE FOR ONE YEAR: A COHORT STUDY OF MEDICAID ENROLLEES. European Hematology Association (EHA)2022. p. 2597-8.
23. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017;376(5):429-39.
24. Panepinto JA, Bonner M. Health-related quality of life in sickle cell disease: past, present, and future. Pediatr Blood Cancer. 2012;59(2):377-85.
25. Vertex Pharmaceuticals Inc. Data on file. ATMP analogue analysis. 2024.
26. Vertex Pharmaceuticals Inc. Data on File. Exagamglogene Autotemcel (exa-cel) for the Treatment of Sickle Cell Disease: Indirect treatment comparison. 2023.
27. Udeze C, Ly, N. F., Ingleby, C. et al. Mortality and clinical complications among patients with sickle cell disease with recurrent VOCs in England. British Journal of Haematology. 2023.

28. Vertex Pharmaceuticals Inc. Data on file. Sickle Cell Disease with recurrent VOCs and Transfusion-dependent β-thalassaemia: Economic and Clinical Burden of Disease in England. 2023.
29. Beaudoin F, Thokala P, Nikitin D, Campbell J, Spackman E, McKenna A, et al. Gene Therapies for Sickle Cell Disease: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review; 2023 13 July 2023.
30. Excellence NIfHaC. Axicabtagene ciloleucel for treating relapsed or refractory diffuse large Bcell lymphoma after first-line chemoimmunotherapy 2023.
31. Excellence NIfHaC. Brexucabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over 2023.
32. Transplantation NECRGfBaM. Clinical Commissioning Policy: Use of Plerixafor for Stem Cell Mobilisation (update). 2015.
33. Parsons J, Castelnuovo E, Dracup N, Connock M, Armoiry X, Grove A, et al. Data on file. Exagamglogene autotemcel for treating sickle cell disease- parameters to be considered in probabilistic sensitivity analysis 2024.
34. Buchanan V, Madani O, Soboil J. HTA53 Will NICE's New Severity Weighting Criteria Be Capable of Identifying Severe Conditions? Value in Health. 2022;25(12):S306.
35. Desai RJ, Mahesri M, Globe D, Mutebi A, Bohn R, Achebe M, et al. Clinical outcomes and healthcare utilization in patients with sickle cell disease: a nationwide cohort study of Medicaid beneficiaries. Ann Hematol. 2020;99(11):2497-505.

Title: Exagamglogene autotemcel for treating sickle cell disease- addendum of EAG response to company's technical engagement response form

Produced by Warwick Evidence

Authors

Jo Parsons, Assistant Professor[1]
Emanuela Castelnuovo, Senior Health Economist[1]
Naila Dracup, Information Specialist[1]
Martin Connock, Honorary Senior Research Fellow[1]
Xavier Armoiry, Honorary Senior Research Fellow and Professor of Pharmacy[1,2,3]
Amy Grove, Professor of Health Technology Assessment and Implementation Science[1]
Peter Auguste, Assistant Professor in Health Economics & Decision Modelling[1]

[1]Warwick Evidence, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, CV4 7AL
[2]Claude Bernard University Lyon, Villeurbanne 69100, France
[3]Lyon University Hospitals- Hôpital Edouard Herriot Pharmacy department, 69003 Lyon, France

Correspondence to

Mr Peter Auguste
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry, CV4 7AL.

Date completed 09/02/2024

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/60/84.

Declared competing interests of the authors

Description of any pecuniary relationship with sponsors, both personal and of the TAR Centre. If there are none, please state 'none'.

Acknowledgements

We would like to thank Professor Baba PD Inusa, consultant paediatric haematologist, King's College, London and Dr Elizabeth Rhodes, consultant haematologist, St. George's University Hospitals NHS Foundation Trust who provided clinical support. Emeritus Professor Aileen Clarke, Professor of Public Health, and Health Services research, University of Warwick who quality assessed the EAG report.

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.

This report should be referenced as follows:

Parsons J, Castelnuovo E, Dracup N, Connock M, Armoiry X, Auguste P. Exagamglogene autotemcel for treating sickle cell disease, Warwick Evidence, 2023: A Single Technology Appraisal.

Contributions of authors

Jo Parsons (Assistant Professor), Martin Connock (Honorary Senior Research Fellow), Xavier Armoiry (Honorary Senior Research Fellow and Professor) and Amy Grove (Professor) reviewed and critiqued the clinical effectiveness evidence. Martin Connock reviewed and critiqued the statistics and undertook any additional statistical analyses. Xavier Armoiry reviewed and critiqued the mixed treatment comparisons. Naila Dracup (Information Specialist) critiqued the company's searches and undertook additional searches. Emanuela Castelnuovo reviewed and critiqued the cost-effectiveness evidence and undertook additional economic analyses. Baba Inusa (Paediatric Haematologist) and Elizabeth Rhodes provided expert clinical advice. Peter Auguste (Assistant Professor) reviewed the cost-effectiveness evidence and co-ordinated the project and the report.

Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

Table of Contents

Table of Tables

Table of Figures

Content of this addendum

In this addendum, we undertook several scenario analyses, then an EAG's base-case analysis. The structure of this addendum is as follows:

- Calculation errors
- Mortality estimation- correction of Markov structure
- Complication rates
- Discount rates and severity modifiers
- EAG's base-case

1 Calculation errors

The company used the cycle mortality probability previously calculated by the EAG (Sheet Raw_Mortality, column Y), applied a conversion formula to obtain the rate and then apply the SMR. The conversion formula was applied to the weighted cycle probability, by gender, whilst it should have been applied to the (separate) cycle probabilities for males and females – and then apply the cohort weights by gender. The EAG has corrected this error. The impact is almost null, the EAG has replaced the formula.

Errors were also found in the calculation of overall complication rates [rows AB18:AI18 sheet SOC and AA16:AH16 in the EXA-CEL sheet]. These are cells where summary calculations are obtained from the trace; as such, they are not affecting the ICER but just noted here.

Finally, the cumulative chronic complication rates at each cycle (time t) were calculated using the cycle proportion of alive people but at cycle t+1, the occupancy of state t was added without taking into account cycle t+1 mortality of complications at time t. This omission had no impact on mortality (calculated unconditionally) but only on the cumulative rates of complications.

The ICER that is generated is approximately [redacted] per QALY. This ICER is an update of [redacted] presented in the EAG appraisal in 2023, updated for Issues 10 and 11, which we considered resolved.

It is important to consider that these ICERs correspond to non-reference case discount rate of 1.5% per annum that the company considers is a given in the base-case.

In addition, the company included a severity modifier for this decision problem, based on a calculation using an online tool, which takes total model outputs only, rather than more appropriately, using the specific age/gender distribution for quality-adjusted life expectancy calculated in the model. Finally, the company applied a distributional cost-effectiveness

adjustment, obtained using a methodology that is not part of the reference case. According to the company, such adjustments would decrease the ICER to [redacted].

The EAG considers that the reference case discount rate of 3.5% applies to this decision problem, whilst the correct calculation of severity modifier shortfalls shows that severity modifiers do not apply. Furthermore, the DCEA is a subscenario, therefore it cannot be used to adjust the reference case ICER; it is worth noting that the use of those adjustments in other appraisals are the result of decisions taken by the Appraisal Committee which should not be anticipated as a given. The removal of these three adjustments gives an ICER of approximately [redacted] per QALY that the EAG considers the appropriate company's base case.

2 Mortality estimation- correction of Markov structure

Summarising, in the original submission, deaths were calculated at each cycle, applying a state-specific death rate to the (large) number of acute and chronic complications states, for which state occupancy was calculated independently (i.e., non-conditionally) as a proportion of the people alive. Death rates were then assigned to each state (independently from one another) and summed across all states (or multiplied, but this is not a key issue); the total was subtracted from people alive in the previous cycle. This methodology estimates event rates independently from one another, i.e., complications are not mutually exclusive; with this method, it is possible that the sum of events calculated is larger than the total size of the cohort. Whilst for complications this is not an unrealistic assumption (although it probably leads to overestimation), it is not an admissible solution for the calculation of deaths, because the same individual cannot "die twice" in the same cycle. As a result, the model estimated 1. The total number of deaths above 100%, that also 2. Resulted in negative probabilities for events in the model as time passed. These features are violation of the fundamental methodological requirements for a Markov state-transition model. To resolve this issue, the company imposed a constraint on deaths such that the sum of alive and dead would remain equal to 100% thorough the model. Nonetheless, the constraint could not resolve the misestimation of all events in the model, which yielded persistently flawed estimates for all events included, and as a consequence, for the ICER overall and each of its component.

Because of the non-mutually exclusive character of event rates so estimated, the model also resulted in overestimation of complication rates in SOC, losses in quality of life, as well as inflated costs, for the SOC arm. The model construct was therefore considered structurally flawed and could not be used to provide a base case. The EAG judgement regarding the

model structure was confirmed by further model structure appraisal by the Decision Support Unit (DSU). Because death rates were so fundamental to determine event rates, their assessment under the previous structure was not deemed appropriate. The EAG deferred the assessment of complication rates to the time when an acceptable model structure would be implemented.

During technical engagement, the company implemented structural changes in the model in this respect, as suggested by the DSU, applying an SCD specific death rate to the cohort, independent from acute and chronic events in the model. The EAG's starting point therefore relies on the updated model structure. This is the only structure that does not pose challenges to the validity of the appraisal, at a minimum. Nevertheless, the company's base-case remains that of the original model, incorporating the structural flaws described above. This choice relies on the argument that the correct model structure generates estimates that are invalid and not consistent with real life data, specifically survival. The company did not provide any validation of mortality and life expectancy generated in the model to justify such position.

Of course, the validity of a model involves an approximate, yet realistic, estimate of survival for the SOC arm. This is because the cost-effectiveness case relies on the marginal difference between exa-cel and SOC.

First, there is general consensus that when an instrument is shown to be flawed, it should not be trusted under any circumstance, because it does not support extrapolation or prediction; in fact, the EAG found confirmation of this statement: when decreasing complication rates in the model, the company's model's life expectancy with SOC increases to almost 62 years, as a result of negative death probabilities being much reduced. Such reactivity clearly makes the company's approach to mortality implausible.
Second, the justification of a model structure cannot be done based on the results it generates. Finally, the resolution of structural validity issues for the mortality estimates generated in the model is necessary, but not sufficient. Indeed, the validation of complication rates conducted by the EAG, in the absence of one conducted by the company, showed that this approach led to implausible model outputs. Model structure was one of the many issues that the EAG identified for the model. The EAG has already described how the model relies extensively on a large number of assumptions, none of which has been justified from both a modelling and an evidence base viewpoint.

In the exa-cel model, event rates are not estimated conditionally, i.e., using a mutually exclusive structure of events over the course of lifetime. In truth, the incorporation of a structure of conditional events seems hardly feasible in the model as is and would require extensive model rebuild. The model event rates are also not determined as competing events, and importantly, the model does not include variance-covariance matrix for acute and chronic events and deaths. As a result, event rates are constrained by mortality only, therefore the mortality rate drives the estimation of the overall burden of events in the model, not the reverse as it should be. The company's preferred approach involves the estimation of the overall death rate per cycle adding all cause specific death rates, estimated with independent death rates (i.e., noncompeting events rates) leading to an inflated death rate applied in the model in the early years, until the calculated death rate becomes negative. The impact of the calculated death rate on event rates is impossible to determine (other than looking at estimates of event rates).

It is important to underline that failing to estimate model rates conditionally, and regardless of the method used to estimate deaths, either using the incorrect company rates or the correct overall SMR-based death rate, biases the estimates of acute and chronic events, with a possible overestimation of the rates of most severe events (those with the highest event-specific death rate), because in a model that uses conditional events, the death rate applied to such events is probably higher that the average survival of the overall SCD population. Using stroke as an example, the model applies the average death rate to people that report a stroke and to those that do not, allowing survival of people with ACS in the model longer than it should be.

Therefore, the EAG has reappraised the case starting from the model structure with the overall all cause death rate, hereafter termed "unconditional mortality" model".

The EAG also validated complication event rates. Because the model is so locked into its own logic, the only way for the EAG to implement such analyses was to override the calculation of rates based on VOCs. Unlike most models which calculate cycle probabilities before propagating these in the model, this model takes input parameters and implements all calculations in the trace formulae, including calculation of rates based on baseline rate and hazard and the transformation of rates into probabilities. This makes it impossible for the EAG to test values, determined in other ways than with a hazard, using the user defined functionality.

For this reason, the validation of complication rates could not be done in any other way than overriding the implementation based on VOC rates. State occupancy for VOCs however remains in the model as independent event and as the base for all company's estimates.

2.1.1 SMR estimates calculated by the company

This section provides an overview of the model estimates for mortality generated by the model.

The new estimates of overall death rates applied in the model are explained in this section, together with resulting life expectancy modelled and ICER for the company preferred approach to modelling deaths and for the DSU recommended approach.

From a study (Desai et al) (1) the company calculates the weighted HR for death by frequency of VOCs (a)x(b) using data from adolescents, a factor of 1.46.

Table 1: Weighted HR for death by frequency of VOCs (company's SMR parameterisation)

No. of VOCs	Death HR by baseline frequency of VOCs (Desai et al.,) (a)	% patients with no. VOCs aged 13-18 (b)	% patients with no. of VOCs aged 19-35
<2	1.00	55%	35%
2-4	1.62	34%	33%
>=5	3.23	11%	32%

The SCD-specific SMR from Baudoin (ICER report) for ages 13-18, 40.07, is then divided by the factor 1.46 obtained above to obtain the distribution by number of VOCs (see Table 2) giving the SMR by age for VOCs<2. The value for age>35 years is not corrected. Finally, the HRs from Desai are applied to the distribution by age of SMR for VOCs<2.

Table 2: Distribution by age of SMR for VOCs <2 (company's assumptions)

Overall cohort SMRs		SMR for VOCs<2	2-4	≥5	Applied in the model
Ages 13-18	40.07	27.44	44.45	88.63	[redacted]
Ages 19-35	24.24	12.61	20.43	40.74	[redacted]
Ages 35+	17.48	17.48	17.48	17.48	17.48

The computation of the age>35 SMR consistent with the methodology used for other age groups would give 9.1 correspondent to a minimal shift in the ICER, therefore not implemented.

The company does not explain why the data from Baudoin are adjusted, given that the comparator in Baudoin et al is the same as in this appraisal; logically, it is thought that data from Baudoin would already have undergone an adjustment by age distribution.

2.1.2 Prediction of the unconditional mortality model

The company argues that the version of the model that uses a negative rate of mortality is preferred because it provides an appropriate estimation of mortality. Yet the company did not provide any information regarding what the appropriate estimated mortality should be.

Further details of the EAG's critique are reported in the Appendix Table 6.

The EAG conducted a very rapid, non-systematic search for studies that reported overall mortality for the SCD population. The intent was to identify suitable external evidence for model comparison, to obtain at least reasonable estimates for a representative population for this decision problem, to be able to:

1. Compare the overall survival estimated in the model with estimates from the literature in a comparable population.
2. Compare the distribution, or percentage survival at specific time points, of overall survival for people with SCD who did not receive transplant.

Despite the difficulties of obtaining a cohort that precisely represents the definition of the appraisal population, the EAG identified recent studies that appear robust, based on large cohorts of people. Mortality rates presented in these studies were similar, varying in a range between 43 years and (Brousse et al (2)) and 55 years (Jiao et al (3)) , and others). The following studies were identified:

2.1.2.1 Jiao et al

Jiao et al (2023)(3) conducted a claims data study using the Medicaid Analytic eXtract files and Medicare Part A and B Fee-for-Service claims, covering enrolees from 2008 to 2016. This study was restricted to individuals who received "common care", i.e., all-comers who either received no treatment or who received hydroxyurea or transfusions, but that did not receive HSCT. The authors state that this cohort was selected to "serve as a control group for individuals who would be eligible for novel disease modifying or gene therapies in SCD. This definition is in line and pertinent with the SOC group in the exa-cel model. The study used data from 94,616 people with SCD, mean age 26.6 (SD 22.5).

Survival probability was 0.980 (95%CI: 0.977, 0.984) at 18 years, 0.804 (95% CI: 0.795, 0.815) at 30 years, 0.628 (95%CI: 0.616, 0.641) at 45 years 0.267 (95%CI: 0.255, 0.279) at 65 years and 0.070 (95%CI: 0.064, 0.075) at 85 years old, respectively.
The study also provides curves of the survival probability for the general population and by gender (see Figure 1). The EAG digitised the curves by gender and applied the relevant rates in the model.

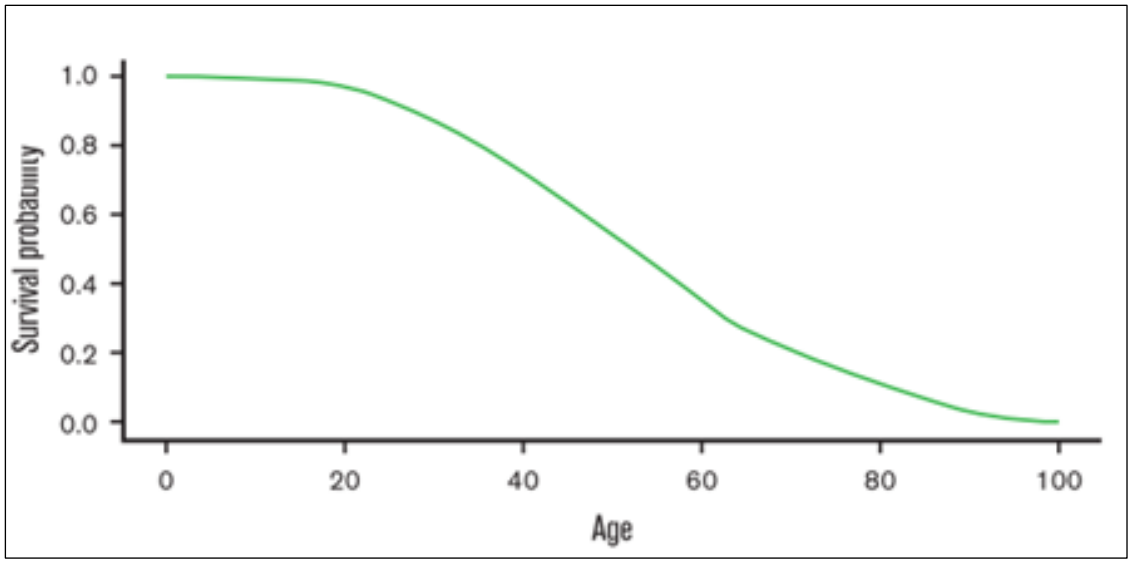


Figure 1: Probability of survival for the general population

2.1.2.2 Paulukonis et al.

Paulukonis et al (4) obtained all-cause mortality data for the African American population and the general population in Georgia and California using data from 2004 to 2008 from CDC's Wide-ranging Online Data for Epidemiologic Research (WONDER) MCOD queries; cases were selected using ICD-10 codes for a diagnosis of SCD, D57.0, D57.1, D57.2, D57.8 codes and were linked to mortality datasets. Combined mortality rates were 10.5 per 1000 patients per year for males and 9.8 per 1000 patient per year for females.

2.1.2.3 Pendergrast et al.

Pendergrast et al(5) conducted a study in Ontario (Study period 2007-2017) using three administrative databases, the Discharge Abstract Database, the National Ambulatory Care Reporting System and the Newborn Screening Ontario database. The authors identified 44,770 records with a diagnosis of SCD [ICD D570 (Sickle cell anaemia with crisis), D571 (Sickle cell anaemia without crisis), D572 (Double heterozygous sickling disorders) and

D578 (Other sickle cell disorders)] pertaining to 3,418 unique patients. The median age was 24 years 56% females and 492 newborns. Average number of hospital admissions per year was 4.92. A small fraction of the sample (10.8%, newborn proportions only) had a diagnosis of beta-thalassemia.

The mortality rate was 6.7% during the study period. The study does not state a rate but states the average age of death was 55 years old.

2.1.2.4 Brousse et al.

Brousse at al (2) was a study based on SNDS, administrative data from the French Health Systems Database. The study includes two cohorts, one with people with a diagnosis of SCD and a sub-cohort of people with severe SCD, for a total of 20,412 people. The study focuses on complication rates but also reports the mean age of death, 55 years old in the overall cohort; 43.5 in the most affected cohort. The number of deaths was 1,062 and 248 in the two cohorts, corresponding to a probability of 5.2% in the overall cohort and 5.8% in the severe cohort.

2.1.2.5 Gardner et al.

Gardner et al (6) was a study set up to ascertain the death rate in a cohort of 712 patients in a single centre in the UK. The authors noted how the mean age of death for SCD reported in the literature had steadily increased, from 42 to 48 years in 1994 (Platt et al) to 53 to 58 years in the Jamaican SCD cohort (Serjeant et al., (7, 8)) to 58 years in the US in 2014.

The study by Gardner reported an estimated median survival of 67 years (95%CI: 55, 78 years) for the HbSS/HbSb0 group. Estimated survival rates were 90% to 45 years (39-51 years), 80% to 51 years (95%CI: 44, 57 years), and 70% to 60 years (95%CI: 51, 69 years). Median survival in people with high hospital admission rates (>0.5 admissions per year) was 60 years.

2.1.2.6 Gluckman et al.

Gluckman et al (9) was a registry study of 1000 patients who underwent HSCT between 1996 and 2013 in 23 countries. Median age at entry for the adult group was 18 years old (range 16-46). The 5-year OS was 81% (95%CI: 74%, 88%) for patients older than 16 years.

2.1.2.7 EAG rationale for not using the ICER/Desai SMR values

1. Jiao et al (3) is a very large cohort obtained from Medicaid Analytical eXtract (MAX) data complemented by data from Medicare Part A and B – the study by Desai et al (10) is limited to Medicaid, so the more deprived bands of the population (Medicaid enrols by socio-economic status) whilst Medicare enrols by age – 65+, and other types of disability. The cohort is larger than that in Desai (double the size), importantly it includes a more complete cohort in terms of older people (mean age in Desai, approximately 15 years, mean age in Jiao, approximately 26 years, which is more in line with the model population).

   The enrolment of older people is necessary because SCD deaths occurring in older age characterise the end tail of the death distribution in the model – whilst the selection of the younger population means that all deaths that occur at young age will be captured but not those that occur at older ages – therefore the selection of the younger population has the automatic effect of lowering the mean age of death compared with the overall population with SCD – i.e., overestimating the death rate.

2. Desai et al (1) concludes that there is no difference in stratification of mortality by VOC after 35 years old therefore the Jiao data offer a better characterisation of death dynamics in the older age bands for the SCD population.

3. The Jiao cohort is more recent (2000 to 2013 Desai (1), 2008-2016 Jiao (3))

2.1.2.8 EAG's mortality analysis

The EAG chose to use the data from Jiao et al(3) as the base-case, because of the robustness of study methodology and the size of the cohort. This study will also support an important policy model that will become available in the near future and may become the reference for estimates of cost-effectiveness of therapies in SCD in the future.

Table 3 reports the mean and median survival predicted with the model under the three-mortality structure relevant for this appraisal: the company's preferred model structure (negative death probabilities); the structure that incorporates DSU advice (unconditional mortality) and the EAG preferred structure (unconditional mortality and Jiao data (3)).

Table 3: Estimated life expectancy (at birth) for exa-cel and SoC cohorts in the model, by model structure assumptions (mortality)

Mean survival estimated in model	**Company preferred structure**		**Unconditional mortality applied in the model (DSU recommendations)**		**Unconditional mortality + Jiao rates**	
	Exa-cel	70.26	Exa-cel	77.65	Exa-cel	77.92
	SoC	43.56	SoC	50.42	SoC	53.40

	Incremental	26.70	Incremental	27.23	Incremental	24.52
Median survival	Exa-cel	74.6 years	Exa-cel	81.4	Exa-cel	81.5
	SoC	44	SoC	52	SoC	52.6
	Difference	29.6	Difference	29.6	Difference	29.6
ICER (reference case 3.5% discount)	[redacted]		[redacted]		[redacted]	
ICER (non-reference case 1.5% discount rate)	[redacted]		[redacted]		[redacted]	
Breakdowns (3.5% discount)						
QALY, exa-cel	[redacted]		[redacted]		[redacted]	
Costs, exa-cel	[redacted]		[redacted]		[redacted]	
QALY, SOC	[redacted]		[redacted]		[redacted]	
Costs, SOC	[redacted]		[redacted]		[redacted]	

To assess the impact of using a non-reference discount rate, Table 3 also reports the ICERs discounted at 1.5%.

3 Complication rates

Issue 8 regarding the use of (all types) VOC rates being predictors in the model, Issue 9 (event rates in the model being partial to exa-cel) and issue 12, risk reduction based on assumptions, ultimately jointly affect credibility of event rates estimated in the model.
The model estimated lifetime rates for the following complications, by type:

Table 4: Acute and chronic complications

Acute complications	Chronic complications
Stroke	Avascular necrosis
Acute chest syndrome	Chronic kidney disease
Acute infections	Heart failure
Acute kidney injury/infarction	Liver complications
Gallstones	Neurocognitive impairment
Pulmonary embolism	Post-stroke
LEAG ulcers	Pulmonary hypertension
	Sickle retinopathy

Here below is Table 7 in the original EAG report, detailing the company's methodology used to populate the model with acute and chronic event rates.

Table 7: List of clinical parameters included in the model, with sources

Endpoint	Source of evidence		
	Monthly rate when VOC = 0	HR by VOC occurrence	Monthly rate among patients cured from SCD
Acute kidney injury/infarction	Yeruva 2016[59]	Yeruva 2016[59]	Assumption
Chronic kidney disease	Bradt 2020[60]	Bradt 2020[60]	
Stroke	Shah 2019[58]	Shah 2019[58]	
Acute chest syndrome	Shah 2019[58]		
Pulmonary embolism	Shah 2019[58]		
Pulmonary hypertension	Shah 2019[58]		
Acute infections	Shah 2019[58]	Assumption (same as stroke)	
Gallstones	Shah 2019[58]		
Leg ulcers	Singh 2016[61]		
Avascular necrosis	Shah 2019[58]	Assumption (same as pulmonary hypertension)	
Heart failure	Bradt 2020[60]		
Neurocognitive impairment	Cahill 2019[62]		
Sickle retinopathy	American Academy of ophthalmology: Incidence of proliferative retinopathy among HbSS patients		
Liver complications	Assumption		
Post-stroke	NICE SCD guideline 143 (appendix F)	Assumption	

The EAG identified event rates over the course of the model using the company's base-case (original mortality estimation approach) assumption, corresponding to the company's base-case ICER ([redacted]).

Table 5: Complication rates predicted in the model, company's base-case

	Rate applied to SOC (yearly)	Cumulative number, over the model	Cases per 100-patients year (lifetime)
Acute Complications			
Stroke	3.08%	N/a	44
Acute chest syndrome	5.63%	N/a	80
Acute infections	17.80%	N/a	144
Acute kidney injury/infarction	3.75%	N/a	49
Gallstones	53.47%	N/a	762
Pulmonary embolism	7.35%	N/a	105
Leg ulcers	22.53%	N/a	321
Chronic complications			
Avascular necrosis	11.23%	99%	99
Chronic kidney disease	4.32%	85%	85
Heart failure	3.10%	71%	71
Liver complications	2.02%	55%	55
Neurocognitive impairment	8.45%	97%	97

Post-stroke	As stroke	24%	24
Pulmonary hypertension	3.33%	74%	74
Sickle retinopathy	2.06%	62%	62

Table 5 shows a substantial disease burden calculated. Over lifetime, each patient develops an average of 15 acute complications and 5 chronic conditions.

Such estimates should be assessed against cases reported in relevant literature. A comparison of these rates was done using a non-systematic approach, which should nonetheless be sufficient to allow for a qualitative assessment of the nature of model estimated for the company's base case. The EAG manually identified a paper that presents robust data from a cohort of French SCD patients. The study by Brousse et al (2) was conducted with retrospective data from SNDS, with people with a diagnosis of SCD between 2012 and 2018. Complication data for 22,629 patients of which 4,270 with severe SCD were analysed. Modelled rates were also compared with rates reported in the paper by Shah et al (11) used in the company's model, and by the Vertex BOI study for the UK.

Brousse et al (2) was a study conducted in France using data from the French National Health Data System database (SNDS, Système national des données de Sante). The authors identified a population using "two VOCs in the year preceding the index date or four VOCs in the 2 years preceding the index date; the authors defined a VOC as a hospitalisation (excluding daycare hospitalizations) for VOC, hepatic sequestration, splenic sequestration, severe priapism or ACS. Therefore, this cohort is more severe than the reference cohort for the CLIMB-121 study (four VOCs, either outpatient or inpatient care). The authors also identify a "treatment intensification cohort" including people treated with hydroxyurea or HSCT. The HSCT alone could be a suitable proxy for exa-cel; however, the confusion with hydroxyurea implies that the "severe cohort" may still have high rates of follow-on complications despite treatment (the direction is unclear, HSCT should resolve all complications; hydroxyurea is in fact SOC in this appraisal so the direction of effect could be either way). 148 patients had received HSCT. The authors found 20,412 people with SCD, of which 4,270 most severely affected most severely affected at the index date. Female were the majority (57%, as in Jiao(3)) mean age was 24 years old. Most severely affected were younger (21.8 years). Rates of VOCs were 86.29 per 100 persons year. ACS rates were 12.9 per 100-persons year for the most severe cohort and 7.62 for the overall study population.

The CLIMB SCD-121 population was aged between 12 to 35 years - therefore the relevant rates from the Brousse et al were recalculated using the age distribution provided in the paper. The ERG adjusted the study rates to account for:

1. The exa-cel population was assumed to be equivalent to the most severe population in Brousse and to the severe population in the Vertex UK BOI study, although the group in the Brousse study does include HSCTs in that subgroup; To account for this, all events were attributed to the non-HSCT population, equal to 4,122; which is equivalent to assuming that people with HSCT reported zero events;
2. The population denominator in Brousse et al (2) was recalculated to also exclude children younger than 12 years old (Table 2 in Brousse), therefore reducing the denominator for the most severe population further, to 2,799, which is equivalent to assuming that of all events observed in the Brousse study, none occurred in children. This population was reapportioned to the distribution of cases by age, giving the following distributions for chronic complications during follow-up.

3.1 *Comparisons of model complication rates with rates reported in the literature*

The modelled event rates are compared in Table 6 to those from Brousse et al (2), from the Shah study (11) (used to inform hazard rates for the model complications in the company's base-case), as well as from the Vertex BOI study (UK). For the sake of comparability, the EAG recalculated the number of cases per 100-patients' years (acute complications) and incidence over the modelled lifetime for SOC (22 years) for chronic complications. In addition, the EAG applied all rates from Table 6 in the scenario, except for VOC rates, for which the company's base-case rates were retained. The rates of VOCs are changed from 4.2/year to 2.6/year in a later scenario illustrated in Table 8.

Table 6: Complication rates reported in model, compared with data from the literature

		Brousse (2023)		Shah (2019)	Udeze, UK BOI (2023)
		All population	Severe population		
Acute Complications (Cases per 100 patients' years)					
VOCs	93.90	33.6	57.1		6
Stroke	2.0	0.53	0.68	3.46	1
Acute chest syndrome	3.6	7.62	12.90	5.71	52
Acute infections	6.4	1.19*	1.78*	32.87	20
Acute kidney injury/infarction	2.2	n/a	n/a	n/a	n/a
Gallstones	34.1	1.89	3.04	4.52	29

Pulmonary embolism	4.7	0.7	1.4	2.08	6
Leg ulcers	14.4	n/a	n/a	n/a	26
Chronic complications (% over the course of the model or equivalent)					
Avascular necrosis	99%	20%	42%	69.8%	40%
Chronic kidney disease	85%	20%	23%	n/a	48%
Heart failure	71%	24%	41%	n/a	17%
Liver complications	55%	n/a	n/a	n/a	16%
Neurocognitive impairment	97%	n/a	n/a	n/a	14%
Post-stroke	24%	11%	20%	n/a	n/a
Pulmonary hypertension	74%	8%	15%	29.9%	20%
Sickle retinopathy	62%	n/a	n/a	n/a	12%

*Septicaemia, sepsis or meningitis

$For chronic complications, cumulative lifetime incidence was calculated for Brousse over the life-years estimated for SOC in the model (22.36) using probability from Brousse et al (median follow up of 7 years) converted to rate, scaled up to 22.36 years and reconverted to probability.

Modelled rates of complications appear high, and substantially higher than those reported in the literature, despite variability. One of the reasons why perhaps the rates were so high was that there was a computation error; when adding to the cumulative number, people at the previous cycle were not multiplied by the rate of death, in other words, people with complications at the previous cycle were not applied a death rate. Yet this error did not explain the much higher rates, which were due to the method of computation (non-conditional rates + HRs for hospitalisations applied to all VOCs, regardless of the severity of VOCs and including VOCs that did not lead to hospitalisation (see Discussion in the Section below).

The EAG applied the rates from Brousse et al (2) and Shah et al (12) (using the default company's rates when each paper did not provide) to assess the impact of those rates on the ICERs, also taking into account differences in preferred structure. Here below the resulting ICER under the three mortality scenarios (Company no adjustment, company independent mortality and Jiao data, independent mortality). Table 7 presents results for both the reference case and the non-reference case discount (1.5%).

Table 7: ICERs by source of complication rates, by source of mortality data

			Company base-case	**DSU, using company's SMR**	**EAG, using Jiao death rates**
Reference case	Company base case		[redacted]		
	Brousse	*All population*	[redacted]	[redacted]	[redacted]

3.5% discount		*Severe population*	[redacted]	[redacted]	[redacted]
	Shah	*Adding available data; rest of probabilities is from Brousse (severe)*	[redacted]	[redacted]	[redacted]
Non-reference case discount rate (1.5%)	Company base case		[redacted]		
	Brousse	*All population*	[redacted]	[redacted]	[redacted]
		Severe population	[redacted]	[redacted]	[redacted]
	Shah	*Adding available data; rest of probabilities is from Brousse (severe)*	[redacted]	[redacted]	[redacted]

The EAG hypothesised potential explanations why the modelled rate of complications in the model is so high. There may be consistency biases between complications rates and VOC rates on which the complication estimated rates depend.

Assumption 1: The overarching working hypothesis underpinning the cost-effectiveness is that Absence of VOCs is the marker of functional cure, and therefore, absence of VOC = no SCD-related events.

The model therefore calculates the burden of SCD directly from VOC rates in SOC, applying event rates directly from an equation which includes VOCs as a term (Shah et al (11)); whilst for exa-cel, no events are assumed throughout, postulated on the absence of VOCs over lifetime. The Shah risk equation is not applied to calculate VOC rates *after* exa-cel despite VOCs are observed.

Assumption 2: All VOC rates used in the model are consistent with each other. The EAG fact, this is not the case.

1. The definition of VOCs in CLIMB SCD-121 is different between “before the trial” and after exa-cel:
    a. the “baseline rate” of VOCs, i.e., the VOC rate in the 2 years before the trial, is obtained from patients’ medical history, i.e., including both hospitalisations and non-hospitalisation VOCs;
    b. the follow-on rate of VOCs, i.e. the rate of VOC following exa-cel, is calculated using *adjudicated* events
    c. The paper by Shah et al (11) does not mention adjudication, although the definition of Shah is less prone to subjective interpretation.

Therefore, VOC rates in CLIMB-121 are adjudicated. When adjudication is not used, there may be discrepancies *in interpretation regarding what is VOC.* This is worrying in the light of

the language used to describe these events: all events before exa-cel are adjudicated *VOCs*, contrasted with the view that all events after exa-cel are *pain episodes,* not VOCs.

Furthermore, the “baseline VOC” rate applied to SOC includes both hospitalisations and non-hospitalisations VOCs, whilst the hazard ratios assigned to each complication from Shah used a clear definition of VOC as hospitalisation-related.

> The distinctions above are not just semantics, because jointly they may result in a hard-to-quantify bias in the model in favour of exa-cel derived from the compound effect of four factors:
>
> 1. The application of high VOC rates to the SOC cohort, including non-hospitalised VOCs who are more subject to interpretation;
> 2. The application of HRs for complications derived from hospitalisation VOCs, which means baseline VOCs in the model are handled as if all VOCs in the SOC cohort were severe enough to lead to complications (as per the data and results in Shah et al(11));
> 3. The application of VOCs as a predictor and not as an independently modelled complication, contradicted by the regressions in Shah which clearly state that VOCs rates were dropped from the equations when the study sought to identify predictive equations coefficient
> 4. The assumption that absence of VOCs is equivalent to functional cure, which is applied inconsistently for people who report VOCs before and after exa-cel.

These inconsistencies jointly considered may explain why VOC rates and event rates in the model are so much higher than those found in other well conducted, robust studies, including the Vertex BOD studies. In addition, the company’s model does not take into account that the very analysis from Shah, showing that VOCs are not necessarily a predictor of complications; opinion also supported by clinical opinion obtained from the EAG before the completion of the EAG report in December 2023.

The interpretation of whether or not it is possible to use VOCs as a risk predictor in an equation may not have an easy solution.
After exa-cel, the model assigns zero events to the cohort which is “functionally cured”, whilst in fact three patients in the trial report adjudicated VOCs – therefore these patients, according to the model definition and the use of the VOC equation, lose their status of ”functionally cured”. The attribution of no complication risk to these post-exa-cel events

therefore is in contradiction with the assumption that VOCs is a predictor of complications in the very same model.
According to clinical opinion cited by the company (ID4016, Document B, page 17)," 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". Yet, in CLIMB-121, whilst most patients reached 12 months complete follow-up, only a minority of **four** patients reach the 2 years follow-up mark. The patients that report adjudicated VOCs after having received exa-cel do after the time window over which the primary endpoint of the trial is defined (12 months after the last blood transfusion given after exa-cel implant)

Therefore, the EAG believe that consistency in the model implies one of two scenarios:

1. Either the baseline rate from CLIMB SCD-121-all events – is used and therefore the CLIMB 121 shows that three patients had recurrent VOCs with exa-cel; in this case, the of risks of complication based on VOCs, using hazard rates directly taken from Shah, should be lowered because non-hospitalised VOCs may not be as severe as the VOCs used by Shah to calculate the HR in their study;

OR

2. The "hospitalisation" rate before exa-cel is used as VOC rate applied to SOC, and no recurrence is modelled – even if one CLIMB SCD-121 participant did report an adjudicated VOC hospitalisation, not a pain episode, and three other VOCs (not pain episodes) not associated with hospitalisations. This scenario is an optimistic scenario because it assumes no waning (i.e. no VOCs are reported in the longer term despite a few are observed in CLIMB 121)

The EAG prefers the use of hospitalisation VOCs:

1. All hazard rates are based on VOCs with hospitalisations, and the baseline rate using hospitalisations is available from CLIMB 121 (2.6 annualised rate, Table 10-3 CLIMB SCD-121 CSR, page 60),
2. The likelihood that the model estimates are affected by interpretation bias is reduced
3. The inclusion of longer-term probability of resurfacing of VOCs can be forgone, favouring exa-cel, given the unknown of long-term VOC-free status with exa-cel.

The ICER for the EAG's preferred approach has been obtained with the company's conditional mortality approach with negative death rates, and with the EAG / DSU unconditional mortality rate, both as per company ad as per Jiao's rates.

Table 8: ICERs with hospitalisation VOCs rates – by source of complication rates, by source of mortality data

		Using VOCs for hospitalisations	Company base case	DSU (with company's rates)	EAG, using Jiao death rates
Reference case	Company's base case		[redacted]		
	VOC rates based on hospitalisations		[redacted]	[redacted]	[redacted]
	Brousse	All population	[redacted]	[redacted]	[redacted]
		Severe population	[redacted]	[redacted]	[redacted]
	Shah	Adding available data; rest of probabilities is from Brousse (severe)	[redacted]	[redacted]	[redacted]
Non-reference case discount rate (1.5%)	Company's base case		[redacted]		
	VOC rates based on hospitalisations		[redacted]	[redacted]	[redacted]
	Brousse	All population	[redacted]	[redacted]	[redacted]
		Severe population	[redacted]	[redacted]	[redacted]
	Shah	Adding available data; rest of probabilities is from Brousse (severe)	[redacted]	[redacted]	[redacted]

4 Utility value following treatment with exa-cel

In the original EAG report, we mentioned that the value for longer-term utility with 'functional cure' with exa-cel was too high (0.92). The EAG undertook a scenario analysis with a lower utility value of 0.88 which resulted in an ICER of approximately [redacted] per QALY (reference case 3.5% discount).

Description	ICER	QALYs		Costs		Incremental	
Utility value following treatment with exa-cel	[redacted]	Exa-cel	SoC	Exa-cel	SoC	QALYs	Cost
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5 Discount rate and severity modifiers

The NICE Manual states that adjustments can be made to the Reference Case in particular cases. Specifically, of relevance for this Appraisal, the Company applied a priori two adjustments:

1. Non reference discount rate of 1.5%
2. Adjustment to utility weights in the model, a severity modifier, to take into account disease severity.

To assess the case for both, the EAG calculated the severity modifier factor and QALY shortfall for this decision problem and then assessed the case for the application of a non-reference discount rate.

5.1 *Severity modifier*

Briefly, the QALY shortfall is calculated as the absolute difference between

1. The quality adjusted life expectancy (QALE) for the SoC population, based on model results
2. The SOC-standardised general population QALE, calculated using the age and gender distribution of the alive SoC population in the model, multiplied by utility weights by age for the general population reported in McNamara et al. for each age band. This is the most recent source for granular, one-year age-specific distribution of utility weights in the UK.

The absolute shortfall was the difference between general-population-standardised QALE – the QALE for the SoC population, under current SoC.
The relative shortfall was the absolute shortfall divided by (2) the SoC-standardised general-population QALE.
The company reported a shortfall of 24.3 (absolute) or 71% (relative) calculated the non-reference discount rate of 1.5%, departing from the recommendations reported in the NICE Reference case manual. For the 3.5% discount rate, the values are 14.1 or 63%.

The severity modifier was calculated using the online calculator by McNamara et al (https://shiny.york.ac.uk/shortfall/).

The EAG recalculated the shortfall under the major scenarios considered varying by type of model structure (Table 9). Table 9 shows that the shortfall is highly sensitive to assumptions around model structure, complication rates used in the model and death rates.

Table 9:Severity modifier shortfall by type of model structure

Shortfall Discounted 3.5%	Company base-case	Unconditional mortality (DSU)	EAG, using Jiao death rates	EAG, Complication rates from Brousse	EAG, VOCs as hospitalisations	EAG's base-case
Expected QALE for general population	22.36	22.36	22.36	22.36	22.36	22.36
QALY with SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Absolute shortfall	13.42	12.5	12.48	10.43	9.94	9.94
Relative shortfall	60%	56%	56%	47%	44%	44%
Corresponding ICER (no severity modifier)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICERs – with severity modifier of 1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DSU, Decision Support Unit; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; SoC, Standard of care; VOC, vaso-occlusive crisis						

Some discounted absolute shortfalls are above 12, some are below, depending on the model methods. There is a clear driver for the severity modifier in the rates of complications applied in the model; all scenarios with lower complication rates than those included in the company's base case make the severity modifier fall below 12, the threshold at which NICE considers applying the modifier (Methods manual, Paragraph 6.2.17 page 167). With respect to mortality rates, the company's structure involves the highest modifier; the model structure recommended by the DSU and used by the EAG corresponds to a borderline severity modifier just above 12. All scenarios with the exception of the EAG's do not consider the probability that about 20% recipients do not receive exa-cel after having undertaken apheresis.

Please note the difference between scenario EAG / VOCs as hospitalisations and EAG base case differs by the addition of failure rates with exa-cel therefore no material difference exists in the SoC arms between these two scenarios.

Therefore, the EAG considers that no severity modifier should be applied.

5.2 *Non-reference discount rate*

With regards to the application of the 1.5% discount rate, the NICE Reference case manual states that three conditions need to apply:

- 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.

From the discussion regarding the modelling of the benefits of exa-cel, it is quite clear that criteria 2 and 3 are not satisfied. This is because all assumptions in the model are predicated on the promise of the technology, logically deducted by the general properties of the

underpinning biological mechanism. The submission does not detail the specific biological reasons on which this logic rests, whilst it is clear that there are no “evidence” grounds for such demonstration. In addition, biological plausibility is a necessary, but not sufficient, condition for demonstration of benefit. HTA has long rested on the need to observe, at least in part, whether and how biological mechanisms translate into patient benefit. Subjective evaluations regarding points 2 and 3 can inform some aspect of the model when evidence is lacking, however, they can do this at the cost of a very high degree of uncertainty. This means that it is not possible to qualify such complementation as “likely”, but simply as promised. The EAG believe that non-reference discounting cannot be applied to this technology.

6 The EAG base-case

To summarise, during TE, some issues were resolved, others remain outstanding. The list of issues and their impact on model results are reported in the Table 12.

After TE interactions and considering the scenarios undertaken in the model, the EAG’s base-case is defined as follows:

1. Modelling of unconditional death
2. Including outcomes for people who received apheresis but could not complete the process, due to exa-cel manufacture and implantation requirements.
3. Mortality rate applied in SOC as per Jiao et al (3)
4. Baseline rates of VOCs consistent with the definition of Shah, VOCs with hospitalisations
5. Complications as per Brousse et al (2) – in the severe population subgroup reported in the study.
6. Reference discount rate of 3.5% per annum.
7. No grounds for application of severity modifiers.

The resulting ICER is [redacted]. The stepped increments from the base-case are reported in Table 10 and corresponding breakdowns for the ICER in Table 11 .

Table 10: Incremental ICERs - EAG’s base-case

Issue number	Description	ICER	EAG’s change
	ICER before technical engagement	[redacted]	
Issue 11	The cost of supportive blood transfusions alongside	[redacted]	n/a

Issue number	Description	ICER	EAG's change
	implantations of exa-cel is not included in model costs.		
Issue 10	Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using distribution of patients' weight.	[redacted]	n/a
	Cost of plerixafor reduced	[redacted]	n/a
Issue 14	Application of reference case discount rate of 3.5%; no severity modifier	[redacted]	
Issue 6	The model does not have the requisites for a Markov structure	[redacted]	Use of DSU functionality built in company's model
Issue 7	Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	[redacted]	[redacted]
Issue 8	Vaso-occlusive crisis (VOC) rates as a predictor in a risk equation for acute and chronic complications	[redacted]	[redacted]
Issue 9	Modelling of adverse events is partial to exa-cel short list and selected events.	[redacted]	
Issue 12	Range of acute and chronic complications included in the model is large, but risk reduction is based on assumptions	[redacted]	[redacted]
Issue 13	**Underestimation of uncertainty in modelling of overall survival in exa-cel and standard of care.** Distributions not appropriately parameterised and some key inputs excluded from the probabilistic sensitivity analysis.	n/a	
Issue 14	Severity modifier	n/a	
Issue 15	Non-reference case distributional cost-effectiveness analysis	n/a	

Table 11: Break-down for Table 10, QALYs and costs

Issue number	Description	ICER	QALYs		Cost		Incremental	
	ICER before technical engagement	[redacted]	Exa-cel	SoC	Exa-cel	SoC	QALYs	Cost
Issue 11	The cost of supportive blood transfusions	[redacted]						-
Issue 10	Drug costs during apheresis, iron chelation regimens etc.	[redacted]						-
	Cost of plerixafor reduced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Issue 14	Application of reference case discount rate of 3.5%; no severity modifier	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Issue 6	The model does not have the requisites for a Markov structure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Issue 7	Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Issue 8	Vaso-occlusive crisis (VOC) rates as a predictor in a risk equation for acute and chronic complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Issue 9	Modelling of adverse events is partial to exa-cel short list and selected events.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Issue 12	Range of acute and chronic complications included in the model is large, but risk reduction is based on assumptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 12: List of issues and their current status, along with their impact on the company's base-case

Issue number	Description	Company base-case	DSU, using company's SMR	EAG, using Jiao death rates	Current status
ICER before technical engagement: [redacted]					
Issue 11	The cost of supportive blood transfusions alongside implantations of exa-cel is not included in model costs.	[redacted]	n/a	n/a	Resolved; Company implemented modification
Issue 10	Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using distribution of patients' weight.	[redacted]	n/a	n/a	Resolved, no impact
	Cost of plerixafor reduced	[redacted]	n/a	n/a	Resolved
Issue 14	Non-reference discount rate of 1.5% and application of severity modifier	[redacted]			Resolved. Non-reference case discount should not be applied a priori, case to be assessed when all other issues are resolved
Issue 6	The model does not have the requisites for a Markov structure	[redacted]	[redacted]	[redacted]	Partially resolved. Company maintains base-case with expanding cohort and negative death probabilities; but functionality has been built into the model to

Issue number	Description	Company base-case	DSU, using company's SMR	EAG, using Jiao death rates	Current status
ICER before technical engagement: [redacted]					
					rectify the misconception
Issue 7	Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	[redacted]	[redacted]	[redacted]	Partially resolved. **Company believes these do not apply.** Functionality is built into the model
Issue 8	Vaso-occlusive crisis (VOC) rates as a predictor in a risk equation for acute and chronic complications	[redacted]	[redacted]	[redacted]	**Not resolved: implementation in model resolved.** EAG also applied lower rate of VOCs consistent with CIMB SCD-121 CSR – 2.6 annualised rate for VOCs with hospitalisations (CSR, page 60, Table 10-3 **Outstanding:** • **Clinical discussion needed: does the absence of VOC translate directly in a cure (and specifically, in no hard-endpoints, acute and chronic complications**

Issue number	Description	Company base-case	DSU, using company's SMR	EAG, using Jiao death rates	Current status
ICER before technical engagement: [redacted]					
					(beyond quality of life) • The baseline VOC rate applied in the model is too high, propagating to excessive complication rates
Issue 9	Modelling of adverse events is partial to exa-cel short list and selected events.				**Not resolved** The EAG applied complication rates directly as reported in literature, based on real data - rather than estimating complication rates applying HRs not pertinently across different endpoints
Issue 12	Range of acute and chronic complications included in the model is large, but risk reduction is based on assumptions	[redacted]	[redacted]	[redacted]	Not resolved. Inconsistency between data generates overestimation of complications. To avoid inconsistencies, direct estimation of complication risks implemented from those reported in the literature.

Issue number	Description	Company base-case	DSU, using company's SMR	EAG, using Jiao death rates	Current status
ICER before technical engagement: [redacted]					
Issue 13	**Underestimation of uncertainty in modelling of overall survival in exa-cel and standard of care.** Distributions not appropriately parameterised and some key inputs excluded from the probabilistic sensitivity analysis.	n/a			n/a
Issue 14	Severity modifier				Severity modifier assessed; no case for application
Issue 15	Non-reference case distributional cost-effectiveness analysis				**n/a**

Table 13: Company deterministic base-case results, using 1.5% discount rate

Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity	ICER (£/QALY)	ICER with severity modifier
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted results									
ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, Life-year gained; QALY, quality adjusted life year; SoC, standard of care									

Table 14: Company deterministic results, using 3.5% discount rate

Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity	ICER (£/QALY)	ICER with severity modifier
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted results									
ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, Life-year gained; QALY, quality adjusted life year; SoC, standard of care									

In Table 13 and Table 14 we present results based on the company assumptions using the 1.5% and 3.5% discount rate, with and without severity modifier. In Table 13, using a 1.5% discount rate and without the severity modifier results in an ICER of approximately [redacted] per QALY. With the severity modifier results in an ICER of approximately [redacted] per QALY. In Table 14 using a 3.5% discount rate, results in ICERs of approximately [redacted] and [redacted], without and with severity modifier, respectively.

Table 15: EAG deterministic results, using 1.5% discount rate

Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity	ICER (£/QALY)	ICER with severity modifier
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted results									
ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, Life-year gained; QALY, quality adjusted life year; SoC, standard of care									

Table 16: EAG deterministic base-case results, using 3.5% discount rate

Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity	ICER (£/QALY)	ICER with severity modifier
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCEA-weighted results									
ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, Life-year gained; QALY, quality adjusted life year; SoC, standard of care									

In Table 15 and Table 16 we present results based on the EAG assumptions using the 1.5% and 3.5% discount rate, with and without severity modifier. In Table 15, using a 1.5% discount rate and without the severity modifier results in an ICER of approximately [redacted] per QALY. With the severity modifier results in an ICER of approximately [redacted] per QALY. In Table 16 using a 3.5% discount rate, results in ICERs of approximately [redacted] and [redacted], without and with severity modifier, respectively.

7 Probabilistic sensitivity analysis results

7.1 *Re-run of company's PSA*

On further inspection of the company's PSA, the EAG identified further concerns. Incidentally, the model made extensive use of non-transparent error catching formulae – both in traces and in the PSA. In the PSA, they had the effect of overriding the random values with the deterministic value when the random value was sampled as "error". This was the case of several parameters, for example, those that in the PSA were parametrised with beta distribution with negative parameters. The EAG addressed these concerns in the model and re-run the company's PSA based on a 1.5% and 3.5% discount rate, respectively, with the results presented in Table 17 and Table 18.

Table 17: Re-run of company PSA, using a 1.5% discount rate

Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity modifier	ICER (£/QALY)	ICER with severity modifier
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, Life-year gained; QALY, quality adjusted life year; SoC, standard of care

Table 18: Re-run of company PSA, using a 3.5% discount rate

Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity modifier	ICER (£/QALY)	ICER with severity modifier
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, Life-year gained; QALY, quality adjusted life year; SoC, standard of care

Figure 2 to Figure 3 report the cost-effectiveness plane based on the EAG re-run of the company's PSA both the non-reference case discount rate of 1.5% and reference case discount rate of 3.5%.

Figure 2: Cost-effectiveness plane, exa-cel vs SoC, company's base-case, using 1.5% discount rate

Figure 3: Cost-effectiveness plane, exa-cel vs SoC, company's base-case, using 3.5% discount rate

7.2 *EAG probabilistic sensitivity analysis results*

In Table 19 and Table 20, we present the PSA based on the EAG's preferred assumptions.

Table 19: EAG probabilistic results, using a 1.5% discount rate

Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity modifier	ICER (£/QALY)	ICER with severity modifier
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, Life-year gained; QALY, quality adjusted life year; SoC, standard of care									

Table 20: EAG probabilistic results on the base-case, using a 3.5% discount rate

Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity modifier	ICER (£/QALY)	ICER with severity modifier
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, Life-year gained; QALY, quality adjusted life year; SoC, standard of care									

Figure 5 to Figure 6 report the cost-effectiveness plane, and Figure 7, the cost-effectiveness acceptability curves (CEACs) for the EAG preferred model structure at both the non-reference discount rate (1.5%) and reference discount rate (3.5%).

The cost-effectiveness plane shows that the joint distribution of incremental costs and outcomes is entirely contained in the north-east quadrant, with exa-cel consistently more effective and more costly than SoC, for all scenarios considered.

Equally, there are no instances where the joint costs-QALY distributions fall under the £30,000 willingness-to-pay (WTP) threshold. When considering a £200,000 per QALY WTP, exa-cel is cost-effective under the non-reference case scenarios (1.5% discount rate) and under the company's scenario with reference case discount at 3.5%.

Figure 4: Cost-effectiveness plane, exa-cel vs SoC, company's base case – reference case with 3.5% discount and non-reference case with 1.5% discount and EAG – reference case 3.5% discount and 1.5% discount rates

Figure 5: Cost-effectiveness plane, exa-cel vs SoC, EAG's preferred model structure, using a 1.5% discount rate

Figure 6: Cost-effectiveness plane, exa-cel vs SoC, EAG's preferred model structure, using a 3.5% discount rate

Figure 7: Cost-effectiveness acceptability curves for exa-cel vs SoC, Company's preferred model structure and EAG's preferred model structure, reference case with 3.5% discount and non-reference case with 1.5% discount

8 Appendix – Cost and QALYs breakdowns

Appendix Table 1: ICERs by source of complication rates, by source of mortality data: Reference case 3.5% discount – ICER Breakdowns

Reference case, discount at 3.5%		Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity modifier	QALE - 3.5% discount	Shortfall	ICER	Severity modifier
Company base-case		SoC	[redacted]										
		Exa-cel	[redacted]										
Brousse	*All population*	SoC	[redacted]										
		Exa-cel	[redacted]										
Brousse	*Severe population*	SoC	[redacted]										
		Exa-cel	[redacted]										
Shah	*available data; rest of probabilities is from Brousse (severe)*	SoC	[redacted]										
		Exa-cel	[redacted]										
DSU, using company's SMR													
Brousse	*All population*	SoC	[redacted]										
		Exa-cel	[redacted]										
Brousse	*Severe population*	SoC	[redacted]										
		Exa-cel	[redacted]										
Shah		SoC	[redacted]										

Reference case, discount at 3.5%		Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity modifier	QALE - 3.5% discount	Shortfall	ICER	Severity modifier
	available data; rest of probabilities is from Brousse (severe)	**Exa-cel**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG, using Jiao death rates													
Brousse	*All population*	**SoC**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brousse	*Severe population*	**SoC**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shah	*available data; rest of probabilities is from Brousse (severe)*	**SoC**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DSU, Decision Support Unit; EAG, evidence assessment group; Inc., incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALE, quality adjusted life expectancy; QALY, quality adjusted life year; SMR, standardised mortality ratio; SoC, standard of care;

Appendix Table 2: ICERs by source of complication rates, by source of mortality data: Non-Reference case 1.5% discount – ICER Breakdowns

Non-reference case discount at 1.5%		Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity modifier	QALE - 3.5% discount	Shortfall	ICER
Company base case		SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brousse	*All population*	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brousse	*Severe population*	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shah	*available data; rest of probabilities is from Brousse (severe)*	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DSU, using company's SMR												
Brousse	*All population*	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brousse	*Severe population*	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shah	*available data; rest of probabilit*	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Non-reference case discount at 1.5%		Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity modifier	QALE - 3.5% discount	Shortfall	ICER
	ies is from Brousse (severe)											
EAG, using Jiao death rates												
Brousse	***All population***	**SoC**	[redacted]									
		Exa-cel	[redacted]									
Brousse	***Severe population***	**SoC**	[redacted]									
		Exa-cel	[redacted]									
Shah	***available data; rest of probabilities is from Brousse (severe)***	**SoC**	[redacted]									
		Exa-cel	[redacted]									

DSU, Decision Support Unit; EAG, evidence assessment group; Inc., incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALE, quality adjusted life expectancy; QALY, quality adjusted life year; SMR, standardised mortality ratio; SoC, standard of care;

Appendix Table 3: ICERs with hospitalisation VOCs rates – by source of complication rates, by source of mortality data – Reference case discount – ICER breakdown

Reference case, discount at 3.5%		Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity modifier	QALE - 3.5% discount	Shortfall	ICER	Severity modifier
Company base case		SoC	[redacted]										
		Exa-cel											
VOC rates based on hospitalisations		SoC											
		Exa-cel											
Brousse	*All population*	SoC											
		Exa-cel											
Brousse	*Severe population*	SoC											
		Exa-cel											
Shah	*available data; rest of probabilities is from Brousse (severe)*	SoC											
		Exa-cel											
DSU, using company's SMR													
VOC rates based on hospitalisations		SoC											
		Exa-cel											
Brousse	*All population*	SoC											
		Exa-cel											
Brousse	*Severe population*	SoC											
		Exa-cel											
Shah	*available data; rest of probabiliti*	SoC											
		Exa-cel											

Reference case, discount at 3.5%		Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity modifier	QALE - 3.5% discount	Shortfall	ICER	Severity modifier
	es is from Brousse (severe)												
EAG, using Jiao death rates													
VOC rates based on hospitalisations		**SoC**	[redacted]										
		Exa-cel											
Brousse	***All population***	**SoC**											
		Exa-cel											
Brousse	***Severe population***	**SoC**											
		Exa-cel											
Shah	***available data; rest of probabilities is from Brousse (severe)***	**SoC**											
		Exa-cel											

DSU, Decision Support Unit; EAG, evidence assessment group; Inc., incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALE, quality adjusted life expectancy; QALY, quality adjusted life year; SMR, standardised mortality ratio; SoC, standard of care;

Appendix Table 4: ICERs with hospitalisation VOCs rates – by source of complication rates, by source of mortality data – Reference case discount – ICER breakdown

Non-Reference case, discount at 1.5%		Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity modifier	QALE - 3.5% discount	Shortfall	ICER
Company base case		SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC rates based on hospitalisations		SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brousse	*All population*	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brousse	*Severe population*	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shah	*available data; rest of probabilities is from Brousse (severe)*	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DSU, using company's SMR												
Company base case	VOC rates based on hospitalisations	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brousse	*All population*	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brousse	*Severe population*	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]

Non-Reference case, discount at 1.5%		Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. QALY with severity modifier	QALE - 3.5% discount	Shortfall	ICER
Shah	***available data; rest of probabilities is from Brousse (severe)***	**SoC**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG, using Jiao death rates												
	VOC rates based on hospitalisations	**SoC**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brousse	***All population***	**SoC**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brousse	***Severe population***	**SoC**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shah	***available data; rest of probabilities is from Brousse (severe)***	**SoC**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DSU, Decision Support Unit; EAG, evidence assessment group; Inc., incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALE, quality adjusted life expectancy; QALY, quality adjusted life year; SMR, standardised mortality ratio; SoC, standard of care;

9 Table of the SMRs used in the EAG base-case

In we present the death probabilities applied in the EAG base-case. These probabilities were obtained from digitising figure 2 in Jiao et al. (2023).1 Further details are presented in section 2.1.2.1.

Appendix Table 5: Probability of death by gender applied in the EAG base-case

Mortality from Jiao												
	Males						Females					
Age	Prob (alive)	#Alive	#Dead (year)	Prob Dead (year)	Rate (year)	Prob (cycle)	Prob (alive)	#Alive	#Dead (year)	Prob Dead (year)	Rate (year)	Prob (cycle)
0	100.00%	94616	0	0.000%	0.000%	0.000%	100.00%	94616	0	0.000%	0.000%	0.000%
1	99.84%	94465	151	0.160%	0.013%	0.013%	99.97%	94589	27	0.029%	0.002%	0.002%
2	99.76%	94389	76	0.081%	0.007%	0.007%	99.94%	94561	28	0.030%	0.002%	0.002%
3	99.68%	94313	76	0.081%	0.007%	0.007%	99.91%	94534	27	0.029%	0.002%	0.002%
4	99.60%	94238	75	0.080%	0.007%	0.007%	99.88%	94507	27	0.029%	0.002%	0.002%
5	99.52%	94162	76	0.081%	0.007%	0.007%	99.86%	94479	28	0.030%	0.002%	0.002%
6	99.20%	93859	303	0.323%	0.027%	0.027%	99.84%	94466	13	0.014%	0.001%	0.001%
7	99.12%	93783	76	0.081%	0.007%	0.007%	99.78%	94405	61	0.065%	0.005%	0.005%
8	99.04%	93708	75	0.080%	0.007%	0.007%	99.71%	94345	60	0.064%	0.005%	0.005%
9	98.96%	93632	76	0.081%	0.007%	0.007%	99.65%	94285	60	0.064%	0.005%	0.005%
10	98.88%	93556	76	0.081%	0.007%	0.007%	99.59%	94225	60	0.064%	0.005%	0.005%
11	98.72%	93405	151	0.162%	0.013%	0.013%	99.52%	94165	60	0.064%	0.005%	0.005%
12	98.64%	93329	76	0.081%	0.007%	0.007%	99.36%	94014	151	0.161%	0.013%	0.013%
13	98.56%	93254	75	0.080%	0.007%	0.007%	99.28%	93939	75	0.080%	0.007%	0.007%
14	98.48%	93178	76	0.082%	0.007%	0.007%	99.21%	93864	75	0.080%	0.007%	0.007%
15	98.40%	93102	76	0.082%	0.007%	0.007%	99.05%	93713	151	0.161%	0.013%	0.013%
16	97.92%	92648	454	0.490%	0.041%	0.041%	98.73%	93413	300	0.321%	0.027%	0.027%

Mortality from Jiao												
	Males						Females					
Age	Prob (alive)	#Alive	#Dead (year)	Prob Dead (year)	Rate (year)	Prob (cycle)	Prob (alive)	#Alive	#Dead (year)	Prob Dead (year)	Rate (year)	Prob (cycle)
17	97.76%	92497	151	0.163%	0.014%	0.014%	98.41%	93112	301	0.323%	0.027%	0.027%
18	97.60%	92345	152	0.165%	0.014%	0.014%	98.25%	92961	151	0.162%	0.014%	0.014%
19	97.12%	91891	454	0.494%	0.041%	0.041%	97.93%	92661	300	0.324%	0.027%	0.027%
20	96.88%	91664	227	0.248%	0.021%	0.021%	97.77%	92510	151	0.163%	0.014%	0.014%
21	96.64%	91437	227	0.248%	0.021%	0.021%	97.14%	91908	602	0.655%	0.055%	0.055%
22	95.20%	90074	1363	1.513%	0.127%	0.127%	96.82%	91608	300	0.327%	0.027%	0.027%
23	94.48%	89393	681	0.762%	0.064%	0.064%	96.18%	91006	602	0.661%	0.055%	0.055%
24	93.76%	88712	681	0.768%	0.064%	0.064%	95.07%	89953	1053	1.171%	0.098%	0.098%
25	92.16%	87198	1514	1.736%	0.146%	0.146%	94.12%	89050	903	1.014%	0.085%	0.085%
26	90.08%	85230	1968	2.309%	0.195%	0.194%	93.64%	88599	451	0.509%	0.043%	0.043%
27	88.80%	84019	1211	1.441%	0.121%	0.121%	92.05%	87095	1504	1.727%	0.145%	0.145%
28	87.52%	82808	1211	1.462%	0.123%	0.123%	91.89%	86944	151	0.174%	0.014%	0.014%
29	86.24%	81597	1211	1.484%	0.125%	0.125%	90.62%	85741	1203	1.403%	0.118%	0.118%
30	85.52%	80916	681	0.842%	0.070%	0.070%	89.51%	84688	1053	1.243%	0.104%	0.104%
31	84.80%	80234	682	0.850%	0.071%	0.071%	88.55%	83786	902	1.077%	0.090%	0.090%
32	82.88%	78418	1816	2.316%	0.195%	0.195%	87.28%	82582	1204	1.458%	0.122%	0.122%
33	81.12%	76752	1666	2.171%	0.183%	0.183%	86.01%	81379	1203	1.478%	0.124%	0.124%
34	79.04%	74784	1968	2.632%	0.222%	0.222%	84.90%	80326	1053	1.311%	0.110%	0.110%
35	76.80%	72665	2119	2.916%	0.247%	0.246%	83.15%	78671	1655	2.104%	0.177%	0.177%
36	74.64%	70621	2044	2.894%	0.245%	0.244%	81.24%	76866	1805	2.348%	0.198%	0.198%
37	72.48%	68578	2043	2.979%	0.252%	0.252%	80.29%	75964	902	1.187%	0.100%	0.099%
38	71.28%	67442	1136	1.684%	0.142%	0.141%	78.22%	74008	1956	2.643%	0.223%	0.223%
39	70.08%	66307	1135	1.712%	0.144%	0.144%	76.63%	72504	1504	2.074%	0.175%	0.175%
40	67.68%	64036	2271	3.546%	0.301%	0.300%	75.20%	71150	1354	1.903%	0.160%	0.160%
41	65.28%	61765	2271	3.677%	0.312%	0.312%	73.29%	69345	1805	2.603%	0.220%	0.220%
42	63.36%	59949	1816	3.029%	0.256%	0.256%	72.18%	68292	1053	1.542%	0.129%	0.129%

Mortality from Jiao												
	Males						Females					
Age	Prob (alive)	#Alive	#Dead (year)	Prob Dead (year)	Rate (year)	Prob (cycle)	Prob (alive)	#Alive	#Dead (year)	Prob Dead (year)	Rate (year)	Prob (cycle)
43	61.76%	58435	1514	2.591%	0.219%	0.219%	69.79%	66036	2256	3.416%	0.290%	0.289%
44	59.52%	56315	2120	3.765%	0.320%	0.319%	68.52%	64832	1204	1.857%	0.156%	0.156%
45	56.80%	53742	2573	4.788%	0.409%	0.408%	66.77%	63178	1654	2.618%	0.221%	0.221%
46	55.76%	52758	984	1.865%	0.157%	0.157%	65.34%	61824	1354	2.190%	0.185%	0.184%
47	54.72%	51774	984	1.901%	0.160%	0.160%	63.43%	60019	1805	3.007%	0.254%	0.254%
48	52.64%	49806	1968	3.951%	0.336%	0.335%	62.00%	58665	1354	2.308%	0.195%	0.194%
49	50.24%	47535	2271	4.778%	0.408%	0.407%	60.25%	57010	1655	2.903%	0.245%	0.245%
50	48.48%	45870	1665	3.630%	0.308%	0.308%	58.82%	55656	1354	2.433%	0.205%	0.205%
51	46.56%	44053	1817	4.125%	0.351%	0.350%	56.44%	53400	2256	4.225%	0.360%	0.359%
52	44.32%	41934	2119	5.053%	0.432%	0.431%	55.17%	52197	1203	2.305%	0.194%	0.194%
53	41.92%	39663	2271	5.726%	0.491%	0.490%	53.42%	50542	1655	3.275%	0.277%	0.277%
54	39.84%	37695	1968	5.221%	0.447%	0.446%	51.67%	48887	1655	3.385%	0.287%	0.287%
55	37.92%	35878	1817	5.064%	0.433%	0.432%	49.92%	47233	1654	3.502%	0.297%	0.297%
56	35.84%	33910	1968	5.804%	0.498%	0.497%	48.33%	45729	1504	3.289%	0.279%	0.278%
57	33.28%	31488	2422	7.692%	0.667%	0.665%	46.58%	44074	1655	3.755%	0.319%	0.318%
58	31.36%	29672	1816	6.120%	0.526%	0.525%	44.67%	42269	1805	4.270%	0.364%	0.363%
59	29.44%	27855	1817	6.523%	0.562%	0.561%	43.24%	40915	1354	3.309%	0.280%	0.280%
60	27.36%	25887	1968	7.602%	0.659%	0.657%	40.06%	37907	3008	7.935%	0.689%	0.687%
61	26.24%	24827	1060	4.270%	0.364%	0.363%	38.79%	36703	1204	3.280%	0.278%	0.278%
62	25.12%	23768	1059	4.456%	0.380%	0.379%	37.04%	35049	1654	4.719%	0.403%	0.402%
63	23.20%	21951	1817	8.278%	0.720%	0.717%	35.14%	33243	1806	5.433%	0.465%	0.464%
64	21.44%	20286	1665	8.208%	0.714%	0.711%	32.59%	30837	2406	7.802%	0.677%	0.675%
65	20.32%	19226	1060	5.513%	0.473%	0.471%	31.48%	29784	1053	3.535%	0.300%	0.300%
66	18.72%	17712	1514	8.548%	0.745%	0.742%	29.89%	28280	1504	5.318%	0.455%	0.454%
67	18.08%	17107	605	3.537%	0.300%	0.300%	28.93%	27377	903	3.298%	0.280%	0.279%
68	17.44%	16501	606	3.673%	0.312%	0.311%	27.66%	26174	1203	4.596%	0.392%	0.391%

Mortality from Jiao												
	Males						Females					
Age	Prob (alive)	#Alive	#Dead (year)	Prob Dead (year)	Rate (year)	Prob (cycle)	Prob (alive)	#Alive	#Dead (year)	Prob Dead (year)	Rate (year)	Prob (cycle)
69	16.16%	15290	1211	7.920%	0.688%	0.685%	26.39%	24970	1204	4.822%	0.412%	0.411%
70	15.04%	14230	1060	7.449%	0.645%	0.643%	25.12%	23767	1203	5.062%	0.433%	0.432%
71	14.40%	13625	605	4.440%	0.378%	0.378%	23.85%	22563	1204	5.336%	0.457%	0.456%
72	13.76%	13019	606	4.655%	0.397%	0.396%	22.42%	21210	1353	6.379%	0.549%	0.548%
73	12.48%	11808	1211	10.256%	0.902%	0.898%	21.46%	20307	903	4.447%	0.379%	0.378%
74	11.36%	10748	1060	9.862%	0.865%	0.862%	20.51%	19405	902	4.648%	0.397%	0.396%
75	10.72%	10143	605	5.965%	0.512%	0.511%	19.55%	18502	903	4.881%	0.417%	0.416%
76	10.08%	9537	606	6.354%	0.547%	0.546%	18.76%	17750	752	4.237%	0.361%	0.360%
77	9.28%	8780	757	8.622%	0.751%	0.749%	17.81%	16847	903	5.360%	0.459%	0.458%
78	8.16%	7721	1059	13.716%	1.229%	1.222%	16.69%	15794	1053	6.667%	0.575%	0.573%
79	7.68%	7267	454	6.247%	0.538%	0.536%	15.58%	14741	1053	7.143%	0.618%	0.616%
80	7.20%	6812	455	6.679%	0.576%	0.574%	14.15%	13388	1353	10.106%	0.888%	0.884%
81	6.40%	6055	757	12.502%	1.113%	1.107%	13.20%	12485	903	7.233%	0.626%	0.624%
82	5.12%	4844	1211	25.000%	2.397%	2.369%	12.24%	11583	902	7.787%	0.676%	0.673%
83	4.64%	4390	454	10.342%	0.910%	0.906%	11.45%	10830	753	6.953%	0.601%	0.599%
84	4.16%	3936	454	11.535%	1.021%	1.016%	10.33%	9777	1053	10.770%	0.950%	0.945%
85	3.52%	3330	606	18.198%	1.674%	1.660%	9.06%	8574	1203	14.031%	1.260%	1.252%
86	2.72%	2574	756	29.371%	2.898%	2.856%	8.27%	7822	752	9.614%	0.842%	0.839%
87	2.40%	2271	303	13.342%	1.193%	1.186%	6.84%	6468	1354	20.934%	1.957%	1.938%
88	2.08%	1968	303	15.396%	1.393%	1.384%	5.88%	5566	902	16.206%	1.473%	1.463%
89	1.60%	1514	454	29.987%	2.971%	2.927%	5.56%	5265	301	5.717%	0.491%	0.489%
90	1.36%	1287	227	17.638%	1.617%	1.604%	4.45%	4212	1053	25.000%	2.397%	2.369%
91	1.12%	1060	227	21.415%	2.008%	1.988%	3.18%	3008	1204	40.027%	4.261%	4.171%
92	0.96%	908	152	16.740%	1.527%	1.515%	2.86%	2708	300	11.078%	0.978%	0.974%
93	0.49%	464	444	95.690%	26.201%	23.050%	2.07%	1955	753	38.517%	4.053%	3.972%
94	0.32%	303	161	53.135%	6.316%	6.121%	1.59%	1504	451	29.987%	2.971%	2.927%

Mortality from Jiao												
	Males						Females					
Age	Prob (alive)	#Alive	#Dead (year)	Prob Dead (year)	Rate (year)	Prob (cycle)	Prob (alive)	#Alive	#Dead (year)	Prob Dead (year)	Rate (year)	Prob (cycle)
95	0.17%	161	142	88.199%	17.808%	16.312%	1.43%	1354	150	11.078%	0.978%	0.974%
96	0.13%	125	36	28.800%	2.831%	2.791%	1.22%	1159	195	16.825%	1.535%	1.523%
97	0.10%	99	26	26.263%	2.539%	2.507%	1.02%	964	195	20.228%	1.883%	1.866%
98	0.08%	73	26	35.616%	3.669%	3.603%	0.81%	769	195	25.358%	2.437%	2.408%
99	0.04%	38	35	92.105%	21.158%	19.070%	0.61%	574	195	33.972%	3.459%	3.400%
100	0.00%	38	0	0.000%	0.000%	0.000%	0.40%	378	196	51.852%	6.091%	5.909%

Appendix Table 6: EAG's response to point's raised by the company

Company response	EAG response
The EAG is of the view that the economic model does not follow a Markov structure, and that as a result of the model structure the rates of chronic complications and mortality calculated in the model may be biased, and ultimately may invalidate the cost-effectiveness analyses and results.	The issue with the structure in that it violates the Markov structure assumptions – which are not limited to the application of Markov structures in heath economics; biased estimation is (one of) the consequence(s) of the model structure. The model was also reviewed by the DSU who found the same issue. The recommendations of both the DSU and the EAG have not been taken into consideration during technical engagement.
Mortality predicted by the company's model aligns with the available real-world evidence.	The appraisal of external literature should aim to come to a conclusion regarding the most likely survival for the cohort over the entire lifespan. Several studies found that the average mortality for people treated with SOC is well above 40 years; there is also consensus that the life span of people with SCD has much improved compared with 1994, the year when the first SCD cohort was studied. The company selected two sources of evidence regarding mortality, the Vertex burden of disease study, which has a very short follow-up for the mortality data, and a study by Piel et al (13) with 10 years follow up, based on hospital admission data. Other studies exist (a very crude search conducted by the EAG identified several, including large studies from the US (3, 4, 14, 15) Jamaica (7, 8), Canada (5) Europe (16) and UK (6, 17). The estimates for mean age in these various studies range between 41 and 58. Estimates of approximately 50 years life expectancy for patients with SCD are reported in the literature. This means that values in this range are possible, and that the company chose to consider a value close to the lower end of the estimates. The rationale that a study is in the UK is not sufficient, because this very rationale would exclude the majority of model parameters and of clinical efficacy data used in the model. The Vertex BOI study used an Index date of between 07-01-2008 and 06-30-2019; the mean follow-up for this cohort was 4.69, SD =2.86, meaning that 50% of the sample had less than 4.6 years of follow-up.

	For a mortality parameter, this is a very short follow-up to be able to estimate death rates for an entire cohort over the span of 78 years – the terms of the model. In addition, the cohort was 'young' in that the population included was in the majority of case younger than 35 years old. People that die earliest are generally the most severe, even in a severe cohort, so this approach may lead to overestimation of mortality rates. Piel et al (13) (mentioned by the company) use a severe cohort, their estimate is approximately 47 years old, in a range of 40-49; their cohort is for people with an average of 4.5-5.5 hospitalisation per year, therefore more severe than that considered in the model (2.6/annualised rate, CLIMB SCD-121 CSR). Mean age at mortality of 49-50 would be consistent with data from Piel et al (13)
The most significant critique within this issue, and the one to which the ICER will be the most sensitive, is mortality. Specifically, the model attempts to incorporate individual causes of mortality within a Markov cohort structure, which is challenging to achieve.	The model is most sensitive to complication rates; this was also the finding in the US ICER report cited by the company throughout. Most models are developed incorporating cause-specific deaths, but there are requisites, most importantly a structure of conditionality, and competing event analysis. The Vertex BOI offers such opportunity; a faster and less complicated application in line with conditional rates is also possible using data from Shah et al (11).
However, the most important question is whether the model predicts mortality aligned with that expected in the relevant UK SCD population. A large real-world retrospective study of UK SCD patients with similar characteristics to those considered eligible for exa-cel reported mean and median ages at death of 40.17 years and 41.00 years, respectively, for a matched severe SCD cohort of patients (18, 19). The company base case predicts mean and median age at death of 43.56 years and 44 years, respectively, which align closely with those of the retrospective UK burden of illness study, despite the complex route through which mortality has been modelled. An alternative approach proposed by the DSU,	The statement regarding whether or not the model estimates mortality in line with literature sources does carry little reassurance when the model structure is of concern; the estimate using the DSU method is compatible with external data and so is the EAG, but both carry no model structure flaw. The reason why the company's model is sensitive to mortality lies in the violation of the basic assumption of Markov models that there cannot be more people in the process than those that started. Predictions are therefore unreliable. The incorporation of the DSU approach (that the company chose not to use) shows that, when a correct methodology is used, the model is far less sensitive to death rates. Some considerations are important: 1. The DSU structure uses all cause standardised mortality ratios (SMRs) for the SCD population; therefore, the death rates include mortality related with any and all the complications that affect people

outlined below, generates less realistic predictions.	with SCD. The failure to apply complication-specific mortality does not explain the differences in mortality between the company's model and the DSU/EAG model. 2. In the company scenario, death is the result of both an SMR for SCD-all cause deaths (including cause specific deaths) + complication-specific death rates (the values of many being applied based on assumptions, see issue mentioned in the first EAG report but not addressed further); this leads to double counting of deaths 3. The issue above is data-driven and it is distinct from the overestimation that occurs when death rates apply to independent complication states, equivalent to assuming that people who report multiple complications also die multiple times.
Furthermore, implementation of this alternative approach reduces our base case ICER from [redacted] (severity and DCEA weighted) to [redacted]. In summary, despite its limitations, our original approach has better external validity for current SoC than alternative, simple methods proposed by the DSU. However, due to the error identified by the NICE DSU in the calculation of cumulative mortality (see below), the original model was also underpredicting survival in the exa-cel arm, which adversely impacted the ICER. The alternative approach used is described in Appendix, included within this response document.	The EAG also observed this effect in the SMR-unconditional model approach. This is an unintended consequence of the calculation of mortality rates in the original company model, with death rates at some point turning negative. Because the SoC cohort died off faster, it reached the point when deaths were higher than 100% faster; after which complication rates were becoming negative, i.e., SoC was gaining QALYs as (negative) death rates increased in time. At the same time, the error catching formula in the mortality calculation (i.e. replacing death % with 100% when these were going above 100%) was acting to 'hide' the issue.
Employing an alternative approach using different data generates less realistic survival estimates. One alternative would be to model survival based on VOC frequency alone, which avoids the issues with multiple sources of mortality. The US Institute for Clinical and Economic Review (ICER) recently published their	The rate indicated by Piel et al (13) is in substance a VOC-related mortality rate, so this would constitute a realistic approach for the model; Piel mentions 49 years old as the value found for one of the cohorts in the study.

final report on gene therapies for SCD (20), in which mortality rates for patients on SoC were estimated using standardised mortality ratios (SMRs) estimated from a large US SCD cohort. We have utilised these SMRs in order to estimate alternative mortality rates in the model (an approach also suggested by the NICE DSU). When this alternative approach is applied, the model predicts mean and median survival of 50.42 and 52.00, respectively, which is materially higher than observed in the real-world UK setting (18, 19).	
Issues with respect to cumulative mortality identified by the NICE DSU have been addressed. The NICE DSU report further identified what they considered was an error in the calculation of overall survival estimates: "*The DSU does not understand the company's rationale for estimating deaths in an additive fashion, rather than using conditional probabilities of dying. If all complication-related excess mortality risks are removed from the model, the cumulative probability of remaining alive in a given cycle should simply reflect the probability of being alive at the end of the previous cycle multiplied by one minus the conditional probability of all-cause death in the current cycle*."	The EAG agrees with the DSU. There are a few problems when estimating complication-related excess mortality conditionally in this model. 1. The company did not estimate complication rates from a dataset with patient-level data; therefore, a correlation matrix for those events was not available; 2. When using the hypothesis of non-mutually exclusive states for complications, conditional mortality rates does require a decision regarding which state is conditioned upon which other state. This step is normally unnecessary because in most models, complication rates are relatively low, but in this model, it does become an issue because the sum of people with complications goes well above the unity in the cohort. Based on these considerations, the EAG had advised that the model be rebuilt to establish a basic network of conditionality as that which can be deducted from the Shah paper, where for each complication, an equation was identified that included some (but not all) other complications – an approach tantamount to coming up with a logical structure for conditionality.
We were not able to reproduce Figure 1 of the DSU report in the model but have amended the Markov trace to estimate conditional probabilities of dying (activated in the model by selecting a new dropdown added to the bottom of the EAG Functionality sheet). This approach is also automatically	With this approach the company could have tested a scenario reproducing survival lower than 44 years, calibrating appropriate SMRs; to test whether the resulting SMR are realistic.

implemented when the ICER group SMRs are applied.	
Notably, when this conditional probability approach is applied, removing excess mortality generates overall survival identical to the general population survival (minor differences likely due to half-cycle corrections), further validating this amendment. The amendment increases life years (LYs) in both the SoC and exa-cel arms.	This is not correct. The application of the DSU and EAG approaches generate mortality estimates well below those for the general population for SOC – 50-53 years, but not for exa-cel, 78 years old, compared with the company's estimates of 44 years for SOC and 70 years for exa-cel. An important point, overlooked in this discussion, is that the marginal difference between comparators does not vary across the DSU correct model structure and the Company's non-conform model structure. The divergence in the ICERs is rather due to the implications of such structures on the modelling of complications. This is where the unintended consequences of the company's non-conform model structure appear in their full clarity. The formula that captures the conceptual error in the mortality rates is not applied to complication rates which are therefore unconstrained – i.e., non-conditional. The model assumes that exa-cel will avert the entire burden of disease, conditionally or unconditionally determined. The two factors jointly considered are such that rates of complications modelled are both overwhelming in SoC in the company's non-conform model, but also, turn negative (as explained above) in fact, causing the ICER to improve with the DSU/EAG preferred structure. Ultimately, the company's structure generates a base case ICER higher than it would be in a well-conceived complications conditional structure. The complications scenarios implemented by the EAG show such trend very clearly.

10 References

1. Desai RJ, Mahesri M, Globe D, Mutebi A, Bohn R, Achebe M, et al. Clinical outcomes and healthcare utilization in patients with sickle cell disease: a nationwide cohort study of Medicaid beneficiaries. Ann Hematol. 2020;99(11):2497-505.

2. Brousse V, Bernaudin F, Melaine A, Goguillot M, Gallagher M, Benard S, et al. Severity and burden of sickle cell disease in France: a nationwide real-world study. Haematologica. 2023;108(9):2476-86.

3. Jiao B, Johnson KM, Ramsey SD, Bender MA, Devine B, Basu A. Long-term survival with sickle cell disease: a nationwide cohort study of Medicare and Medicaid beneficiaries. Blood Adv. 2023;7(13):3276-83.

4. Paulukonis ST, Eckman JR, Snyder AB, Hagar W, Feuchtbaum LB, Zhou M, et al. Defining Sickle Cell Disease Mortality Using a Population-Based Surveillance System, 2004 through 2008. Public Health Rep. 2016;131(2):367-75.

5. Pendergrast J, Ajayi LT, Kim E, Campitelli MA, Graves E. Sickle cell disease in Ontario, Canada: an epidemiologic profile based on health administrative data. CMAJ Open. 2023;11(4):E725-e33.

6. Gardner K, Douiri A, Drasar E, Allman M, Mwirigi A, Awogbade M, et al. Survival in adults with sickle cell disease in a high-income setting. Blood. 2016;128(10):1436-8.

7. Serjeant GR. The natural history of sickle cell disease. Cold Spring Harb Perspect Med. 2013;3(10):a011783.

8. Serjeant GR, Chin N, Asnani MR, Serjeant BE, Mason KP, Hambleton IR, et al. Causes of death and early life determinants of survival in homozygous sickle cell disease: The Jamaican cohort study from birth. PLoS One. 2018;13(3):e0192710.

9. Gluckman E, Cappelli B, Bernaudin F, Labopin M, Volt F, Carreras J, et al. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. Blood. 2017;129(11):1548-56.

10. Desai AA, Machado RF, Cohen RT. The Cardiopulmonary Complications of Sickle Cell Disease. Hematol Oncol Clin North Am. 2022;36(6):1217-37.

11. Shah N, Bhor M, Xie L, Halloway R, Arcona S, Paulose J, et al. Evaluation of Vaso-occlusive Crises in United States Sickle Cell Disease Patients: A Retrospective Claims-based Study. J Health Econ Outcomes Res. 2019;6(3):106-17.

12. Ruiz MA, Shah BN, Ren G, Shuey D, Minshall RD, Gordeuk VR, et al. Thrombomodulin and multiorgan failure in sickle cell anemia. Am J Hematol. 2022;97(3):E102-e5.

13. Piel FB, Jobanputra M, Gallagher M, Weber J, Laird SG, McGahan M. Co-morbidities and mortality in patients with sickle cell disease in England: A 10-year cohort analysis using hospital episodes statistics (HES) data. Blood Cells Mol Dis. 2021;89:102567.

14. Allareddy V, Roy A, Lee MK, Nalliah RP, Rampa S, Allareddy V, et al. Outcomes of acute chest syndrome in adult patients with sickle cell disease: predictors of mortality. PLoS One. 2014;9(4):e94387.

15. Elmariah H, Garrett ME, De Castro LM, Jonassaint JC, Ataga KI, Eckman JR, et al. Factors associated with survival in a contemporary adult sickle cell disease cohort. Am J Hematol. 2014;89(5):530-5.

16. Cappelli B, Volt F, Tozatto-Maio K, Scigliuolo GM, Ferster A, Dupont S, et al. Risk factors and outcomes according to age at transplantation with an HLA-identical sibling for sickle cell disease. Haematologica. 2019;104(12):e543-e6.

17. Gladwin MT, Barst RJ, Gibbs JS, Hildesheim M, Sachdev V, Nouraie M, et al. Risk factors for death in 632 patients with sickle cell disease in the United States and United Kingdom. PLoS One. 2014;9(7):e99489.

18. Udeze C, Ly, N. F., Ingleby, C. et al. Mortality and clinical complications among patients with sickle cell disease with recurrent VOCs in England. British Journal of Haematology. 2023.

19. Vertex Pharmaceuticals Inc. Data on file. Sickle Cell Disease with recurrent VOCs and Transfusion-dependent β-thalassaemia: Economic and Clinical Burden of Disease in England. 2023.

20. Beaudoin F, Thokala P, Nikitin D, Campbell J, Spackman E, McKenna A, et al. Gene Therapies for Sickle Cell Disease: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review; 2023 13 July 2023.

Title: Exagamglogene autotemcel for treating sickle cell disease- EAG response to company factual inaccuracies queries

Produced by Warwick Evidence

Authors

Jo Parsons, Assistant Professor[1]
Emanuela Castelnuovo, Senior Health Economist[1]
Naila Dracup, Information Specialist[1]
Martin Connock, Honorary Senior Research Fellow[1]
Xavier Armoiry, Honorary Senior Research Fellow and Professor of Pharmacy[1,2,3]
Amy Grove, Professor of Health Technology Assessment and Implementation Science[1]
Peter Auguste, Assistant Professor in Health Economics & Decision Modelling[1]

[1]Warwick Evidence, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, CV4 7AL
[2]Claude Bernard University Lyon, Villeurbanne 69100, France
[3]Lyon University Hospitals- Hôpital Edouard Herriot Pharmacy department, 69003 Lyon, France

Correspondence to

Mr Peter Auguste
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry, CV4 7AL.

Date completed 20/02/2024

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/60/84.

Declared competing interests of the authors

Description of any pecuniary relationship with sponsors, both personal and of the TAR Centre. If there are none, please state 'none'.

Acknowledgements

We would like to thank Professor Baba PD Inusa, consultant paediatric haematologist, King's College, London and Dr Elizabeth Rhodes, consultant haematologist, St. George's University Hospitals NHS Foundation Trust who provided clinical support. Emeritus Professor Aileen Clarke, Professor of Public Health, and Health Services research, University of Warwick who quality assessed the EAG report.

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.

This report should be referenced as follows:

Parsons J, Castelnuovo E, Dracup N, Connock M, Armoiry X, Auguste P. Exagamglogene autotemcel for treating sickle cell disease, Warwick Evidence, 2023: A Single Technology Appraisal.

Contributions of authors

Jo Parsons (Assistant Professor), Martin Connock (Honorary Senior Research Fellow), Xavier Armoiry (Honorary Senior Research Fellow and Professor) and Amy Grove (Professor) reviewed and critiqued the clinical effectiveness evidence. Martin Connock reviewed and critiqued the statistics and undertook any additional statistical analyses. Xavier Armoiry reviewed and critiqued the mixed treatment comparisons. Naila Dracup (Information Specialist) critiqued the company's searches and undertook additional searches. Emanuela Castelnuovo reviewed and critiqued the cost-effectiveness evidence and undertook additional economic analyses. Baba Inusa (Paediatric Haematologist) and Elizabeth Rhodes provided expert clinical advice. Peter Auguste (Assistant Professor) reviewed the cost-effectiveness evidence and co-ordinated the project and the report.

Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

Table of Contents

Table of Tables

No table of figures entries found.

Table of Figures

No table of figures entries found.

Content of this document

In this document, we present the results of the probabilistic analyses undertaken by the EAG.

1 EAGs response to company's factual inaccuracy queries

Table 1: EAG's response to company's factual inaccuracy queries

Slide number	Company queries	EAG response
Part 1		
10	Data are generalisable to the UK population. Severity and VOC definitions vary – many people may meet criteria. CLIMB SCD-121 uses a clear definition. All patients will be reviewed for eligibility by the National Haemoglobinopathy Panel (NHP), a national multi-disciplinary meeting.	No factual inaccuracies. The EAG refers to the fact that the use of VOCs in the model takes data from studies that have different definitions of VOCs. The definition of VOCs in CLIMB-121 [[Protocol CTX001-121, Version 6.4 (EUR) Page 44] is different than that in Shah, where efficacy data are taken from. Adjudication processes in the various sources of evidence used in the submission are clearly explained elsewhere and referenced to by the EAG where appropriate. The statement of patients being reviewed by a clinical panel is of unclear relevance to this discussion point
12	EAG states: "EAG cannot find clinical evidence from CLIMB SCD-121 used in model". This is misleading: the primary outcome (96.6% VOC-free) and baseline outcomes were used in the model (as discussed on slide 13).	Rephrase: the data from CLIMB-121 are limited to the use of the per-protocol VOC-free rate used as primary outcome of the CLIMB-121 study, and some baseline data.

		EAG is unclear here if the company refer to values used in economic model or that originate from the submitted clinical evidence The EAG addressed elsewhere the issues associated with the use of historical VOC rates and definition used in the CLIMB-121 study. It is unclear what the company means by" baseline outcomes"- outcomes are never baseline. We interpret the company meant 'baseline characteristics" (CLIMB 121 CSR, Table 10-2 Subject Demographics (FAS and PES) from which mean age and gender %, % of transfusion received before entering the study, mean number of all VOCs were taken. By clinical evidence the EAG means – evidence (i.e., comparative differences between intervention and comparator), or data r.e. clinical outcomes subsequent to exa-cel. The EAG recognises we did not mention the 96.6%. Nonetheless, neither the protocol of CLIMB-121 or the CSR define the endpoint 'number of people who benefit". The company interprets that for the one patient who did have VOCs after exa-cel in the per-protocol primary endpoint analysis, a qualitative comparison between VOCs before and after transplant is a sufficient basis to state that the patient benefited. Similarly, for three people who had VOCs after exa-cel but not in the window period set for the primary analysis also benefited, using the same interpretation. [ID4016 Document B, page 83, quote: "Despite experiencing events adjudicated as VOCs, the remaining four patients have all demonstrated treatment benefit from exa-cel, and were VOC-free for a duration of 0.7 – 10.4 months at D120." Of these four people three can be identified from Figure 11-4 [CLIMB-121 CSR – Figure 11-4 page 77 reported at the bottom of

		this document] including the one patient who did not hit the primary endpoint. The remaining person is obtained from the CSR of CLIMB-131, limited to the per-protocol primary analysis.
14	EAG claims the level of evidence supporting exa-cel superiority relative to SoC is low. This is completely inaccurate and shows no understanding of the clinical issues. o There are issues with using SUSTAIN to show that more patients would have 0 VOCs: a) Less severe population – 2 VOC over 1 year only, i.e., not sustained (not 2 VOC over 2 years), less HbSS patients (70%), no ACS in follow-up. b) The figure shown in the table is the ITT analysis. If you review the paper, you can see that in the per protocol analysis, very few patients (5/41, 12%) were VOC-free. Main issue with protocol – not allowed to change dose or start HU – ITT is likely to be an over-estimate. o HOPE trial was a completely different population – patients only needed 1 VOC in the previous year, so not comparable as constitutes a much less severe (our medical adviser, Dr Jo Howard, was first author on the 2021 Lancet paper that reported these results) o Additional evidence showing that 10% of severe patients will have no VOC: EHA 2022, Medicaid recipients with 2 VOC/yr over 2 years – 10% had no VOC over 1 year. o Also, in the PES of CLIMB SCD-121, mean follow up is now 20.7 months – range out to 45 months post-washout – and only 1 additional patient has had a VOC. o There is extremely strong evidence supporting exa-cel superiority. The results from the trial are transformative – they would not be expected in any other context apart from allograft.	The statements are the result of the EAG'S appraisal; in addition, the EAG agreed that the ITC should not be used. Nonetheless, ITCs are a fundamental approach in evaluating the efficacy of a product over the competitors indirectly. The fact that there is no viable ITC is not a confirmation that exa-cel is superior to potential comparators. The fact remains that there is no direct or indirect demonstration of superiority from any study involving or comparing exa-cel, using any admissible method. There is no evidence-based approach that has shown the superiority of exa-cel. By the same token, there is no approach that has shown the inferiority of exa-cel. Te absence of such proofs do not constitute evidence of superiority of exa-cel. Specifically on some relevant points regarding the vaidity of the EAG's assessment, 1. the definition of patients in Sustain uses VOCs over a window of ***one year*** before baseline; by contrast, the Shah study, uses a window of ***six months*** patients history to identify patients eligible for inclusion, so any limitations in population selection that affect Sustain certainly also affect Shah, probably more so - yet Shah is vastly quoted in the submission and used as source for efficacy data throughout the submission, hence the approach to the two studies shows selective judgement in the use of external evidence. 2. ITT is a fundamental concept in HTA, because it shows the real efficacy of a product; there is overwhelming consensus that ITT analyses should form the basis of comparisons. The studies of exa-cel largely rely on non-ITT analyses.

17	"Deaths calculated by applying mortality rates independently to non-mutually exclusive complications → leads to model predicting death rates of 400% for SoC arm and over 500% for exa-cel arm". This is inaccurate and misleading; the model doesn't predict these rates 400% for SoC arm and over 500% for exa-cel arm.	The model uses error-capture formulae to 'delete' out implausible state occupancy; however, the source of error remains in the model and is manifest in the model estimating negative event probabilities. When removing those error-capture formulae, the model does indeed estimate 400% or more deaths. These findings have been confirmed by the DSU and violate the fundamental principles in good practice in modelling in health economics. A vignette illustrates in lay terms the effect of these error capture formulae: this vignette is important to understand what exactly happens in the model. • Let's assume that the model is made up by one patient. • Events calculated in the model are non-mutually exclusive, so - this patient can have (for the sake of the example) one stroke and also one pulmonary embolism. So – one person, two events • The model applies deaths to each acute event independently from one another. So (always for the sake of example) this person dies from the stroke; but the same person dies from the pulmonary embolism. So the model presents a situation where one person has two events (plausibly) but also can die twice. Generalising, for every person in the model, the model calculates two or more deaths. By the second model cycle in this vignette, the model has one person, two events, and two deaths.

		The role of the error capture formulae is that of overriding the number of deaths so calculated in such a way that the observer sees only one death in the model. Extending to the case where the model has a population of several individuals, the error capture formulae will kick in only when the total (doubly-counted) number of deaths will be higher that the size of the cohort (for the sake of example, 1000 people). However, these 1000 people will die off twice as faster as in a correctly specified model. This explains the very low life expectancy calculated for SOC in the vertex model. The issue does not affect exa-cel because there are very few events assigned there. The striking aspect of this structure is that no one could see that after the SOC cohort has died off (twice as fast), the model starts computing negative event rates (i.e. acute events) and as a result – negative death rates. So, people in the SOC cohort effectively are 'resuscitated'. The role of the error capture formula is again to hide this pattern which however makes the model not fit for purpose.
Part 2		
4	Inaccurate to say that only 4 patients have 24 months' follow-up; there are actually 17 patients with 24-months of follow-up (error repeated on slide 10).	No factual inaccuracy. **The EAG had taken this number from the CLIMB-121 CSR – Figure 11-4 page 77 – reported below in this document. The graph shows data locked at Interim analysis 2 (IA2), the data cut used by Vertex for the initial submission.** The follow-up (in months) for each participant can be read off from the graph on the right side. There are four people who hit 24.3, 24.1, 23.9- and 23.9-months follow-up. When the 24 months follow-up in CLIMB-121 is completed, patients are enrolled in 131. The 17 people referred to by the

		company are included not in CLIMB SCD-121 but in CLIMB-131. (Figure 16, at the bottom of this document, also included in D120 study report, submitted by the company during TE the 15 Jan 2024) Figure 16 shows that the people that have not yet completed CLIMB SCD-121 in fact are likely to drive a different picture with regards to the efficacy of exa-cel: [redacted] Whilst the primary endpoint results cannot be updated at this time because the 12 months follow-up have not been hit by all, there are already two additional people that have not hit the primary endpoint (VF12). The point raised for Slide 12 above where the EG did not acknowledge the 96.6% success rate at implantation will need to be updated in the next iteration of the model ([redacted] failure rate – these numbers are read off the graph in Figure 16, to avoid all misinterpretation)
5	Inaccurate to state company assumes that 100% of patients will achieve a VOC-free status; our assumption is 96.6% in line with CLIMB SCD-121.	Already addressed above, text will be changed.
9	**EAG: "Shah study failed to show "number of VOCs" as a significant predictor of risk in most complications" – This misinterpretation continues in slide 10.** **o Correction: This is misleading, the authors conclude: We found strong evidence that VOC is a key risk factor for severe clinical outcomes.** o EAG has a misinterpretation of the Cox proportional hazard model described in Shah et al. whereby for some acute complications baseline VOC was not a predictor as opposed to VOCs during follow up.	Not a factual inaccuracy. The company continues to confuse association with prediction. Shah includes strong evidence that VOCs are not a predictor but an association. The conclusions of Shah et al are not supported by the results presented in the paper. The table where Shah discloses that VOCs are excluded as predictor (stepwise regression etc..) have been presented by the EAG before. Shah et al overinterpret their results.

		The equations in Shah drop both VOCs at baseline and during follow-up. The likely reason why this happens is that the two variables are correlated hence they would be dropped in any regression model (stepwise or otherwise).
10	Please see comments under headings for slides 4 & 9.	
11	**There is no relapse as implied by the slide. VOCs are clearly linked to outcomes – overwhelming evidence going back to early 90s. This is whether these are inpatient, day unit, A&E visits. Whether a patient is an inpatient or attends day unit is related to local service provision not severity – so has more validity to use the wider definition of VOC including day unit and A&E attendances.** **o EAG state ' .. inconsistency in use (of VOCs) for people with VOCs in the exa-cel arm'. It is unclear what this means.** **o 'Need (to) accept trial shows 3 people had recurrent VOCs with exa-cel'. As above, acute pain is common after transplant and does not imply relapse or recurrence of disease.** o Definition of VOCs is crucial for committee to understand (our trial definition was inclusive)	1. The company confuses association with statistical prediction. Association is demonstrated, prediction is not. 2. Inconsistency in the definition of VOCs used in the model – see point above in slide 12. 3.All events in CLIMB 121/131 have been adjudicated; the examples given by the company are situations that constitute precisely the definition of VOCs. The reinterpretation of what is a VOC is misleading because it contradicts the assignation of events done by the adjudication committee in the trial, and it is in contradiction to the argument that access to services is a poor indicator, whilst at the same time arguing that a broader definition – presumably affected by service proximity – is better. CLIMB 121 / 131 clearly show that there are VOCs during follow up. Regardless of the interpretation of why some people access certain services or not, the statement of the company that VOCs based on the use of services is worrying in view of the use of VOCs as primary measure of efficacy. By the same token, it could be argued that absence of VOCs may be due to distance from services, that people with less severe VOCs would not report to services, that the trial is open-label so there are implicit incentives for those that have less severe VOCs not to report them or to seek care or to self-treat with pain treatment. The contrary can also be argued, that those that resolve to access services are in fact reporting extremely severe events, more severe than those reported at baseline in normal circumstances.

		The EAG however is reassured by the adjudication process; acute pain with use of pain medication is part of the definition of VOCs in CLIMB-121, these events have been adjudicated and therefore they are VOCs. It is crucial for the committee to understand that the use of different interpretations of what constitutes a VOC before the trial and after the trial has to effect of invalidating the clinical underpinning of the model. Data on adjudicated VOCS, events that fit the trial definition of VOCs, occur after exa-cel [data presented above] The emergence of VOCs after exa-cel is difficult to attribute to relapse or to lack of grafting or to recurrence. Semantics aside, CLIMB 121 does not provide the reassurance that these VOCs will disappear in the future, because of too short follow up. During part 1 of the CM, clinical opinion suggested that [redacted], the evidence for exa-cel is very far from covering this time-window therefore the EAG is of the opinion that high uncertainty remains.
13/ 14	EAG: “Modelled complication rates appear substantially higher than those reported in literature, particularly chronic events”. Correction: This is misleading, the EAG picked up the data from the wrong column. The correct rates can be found in “add clinical results” tab in the model. o The EAG have failed to note that the mortalities in Jiao apply to the entire sickle population and are not grouped by severity. The CLIMB SCD-121 trial only includes those with severe SCD (classified as 2 or more VOCs/year for 2 years) who have higher mortality than the general population and this is provided in the Desai paper.	No factual inaccuracies. The EAG recalculated those events using model traces. this is because the EAG found errors (stated in a previous document) in the calculation of event rates in the model provided by the company. The EAG also recalculated data for the comparison inflating rates provided in the literature. The methods have been explained elsewhere. The data provided by Desai are recalculated by the company using reasonable – but arbitrary – assumptions (specifically, conditional independence of SMR with respect to age and

		severity). Please note arbitrary does not mean inappropriate, it means – standard – no reason to refute but still assumptions. The EAG acknowledged in the original write up that Jiao does not provide a break-down by severity / VOCs etc. nonetheless, Jiao fills the gap in the Desai data, Jiao covers the older population and Desai does not; it is unknown which limitation is most important. Second, the difference between the company's mortality and that using Desai's data is much larger than that between Desai data and Jiao data. We believe that the issue is the result of the model miss-specification (the cycles of death and negative deaths in the company's model), much more impactful that that of the data source. The EAG already suggested that the 'DSU' model structure can be used to obtain the approx. 43 years life expectancy in the model that the company believes correct; this is by calibrating appropriate SMRs using the DSU structure, and then evaluating whether the resulting SMRs are plausible or not.
18/ 19	**(Should a severity modifier be applied? If so, which QALY weight should be used?)** o Inaccuracy: Resulting QALYs with SOC from the EAG are misleading due to incorrect model implementation.	No factual inaccuracy. The claim that the EAG model is incorrectly implemented should point to specific issues found in the model The company previously referred to the EAG's approach being" methodologically incorrect" but fails to specify which method specifically is violated.
NICE queries		
8	**The company also raised this last week: in the latest additional works document, table 3 has incorrect calculations of difference in median survival for exa-cel vs SoC (company preferred structure should be 30.6; DSU recommendations = 29.4; Jiao rates = 28.9).** o Are the median numbers presented on slide 8, correct?	Company is correct – slide 8 should be amended The medians are very similar nevertheless

18/ 19	Company base case SoC QALY value changes between slides – which is the correct value, 8.24 or 8.94?	8.94

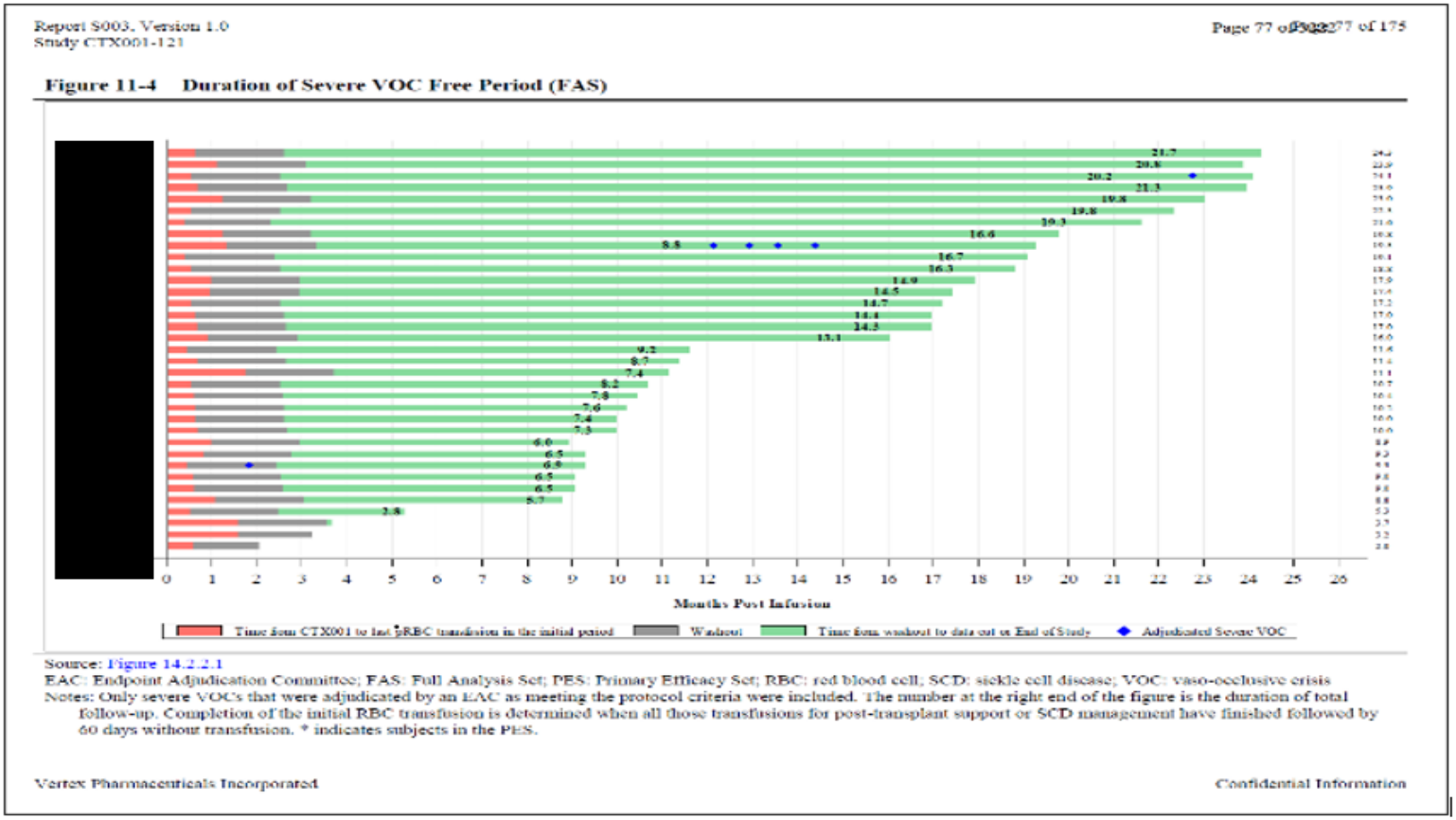
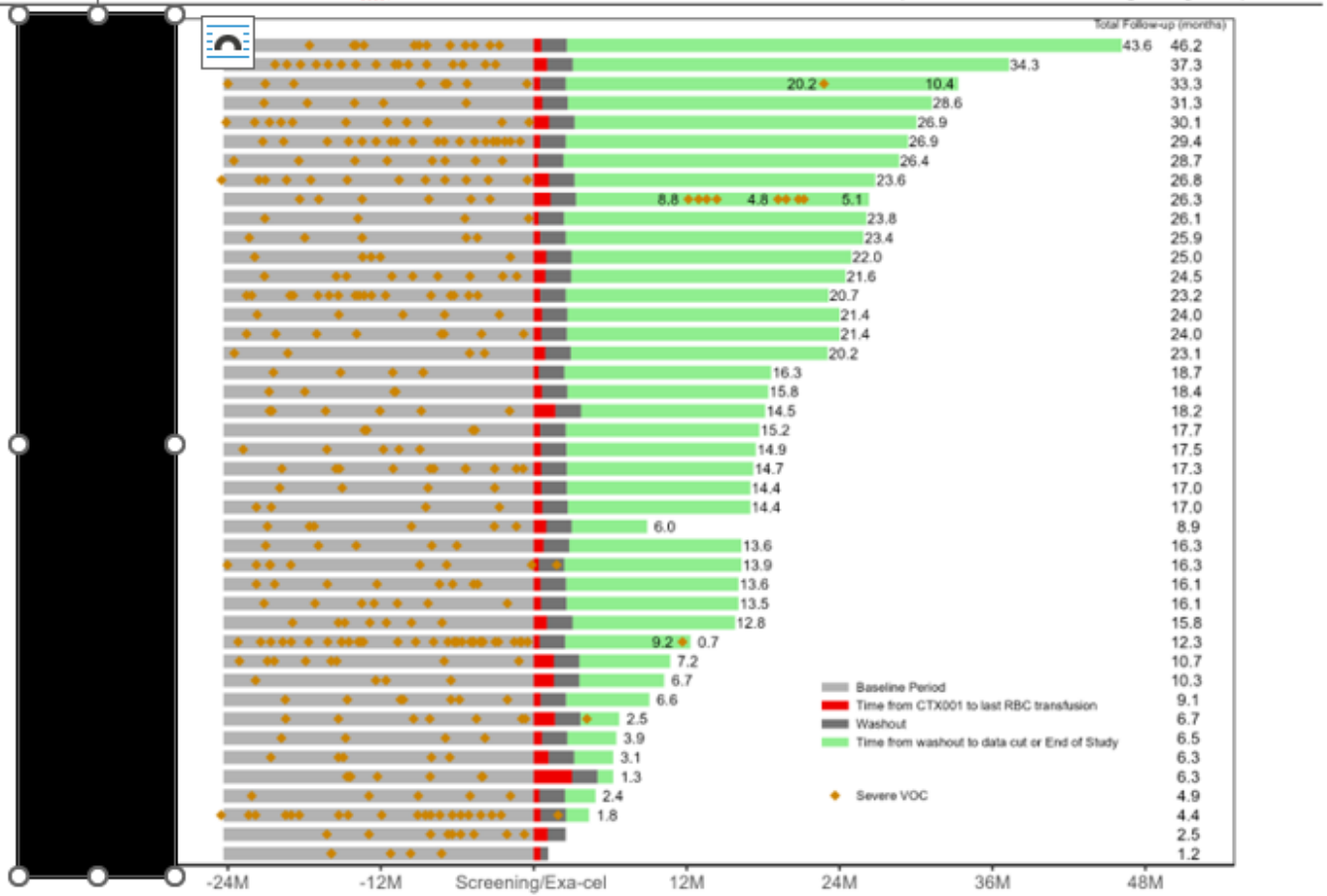


Figure 16 Historical and After Exa-cel Severe VOCs and Severe VOC Free Duration (Studies 121 and 131 [SCD]FAS)



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 sickle cell disease**
Topic ID: **4016**
Managed Access Lead: **Milena Wobbe**
Date of assessment(s): **08/01/2024**

Is Managed Access appropriate - Overall rating	Comments / Rationale
Committee judgement required	Data collection within Managed Access is feasible, with relevant data expected to be collected through the ongoing trial and an ongoing prospective observational cohort study. However, the majority of issues highlighted by the EAG cannot be resolved through further evidence collection and relate to the approach taken to model the benefit of exa-cel. The EAG have highlighted uncertainties that could somewhat be addressed through further data collection, such as changes in HRQoL, long-term safety profile and treatment durability. Longer-term data from the trial programme would be relevant to address these. However, with the exception of determining whether a 1.5% discount rate is appropriate (EAG14), these issues only have a relatively small impact on the ICERs presented. Additionally, the maximum length of data collection of 5 years (or the proposed 3 years by the company) would not fully resolve long-term uncertainties around safety or treatment durability and committee will need to make a judgement on whether the additional data would be sufficient to potentially enable a routine recommendation at the currently agreed price.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	Exa-cel for SCD meets the IMF eligibility criteria
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Unclear	Data collection within Managed Access is feasible, with relevant data expected to be collected through the ongoing trial and an ongoing prospective observational cohort study. However, the majority of issues highlighted by the EAG cannot be resolved through further evidence collection and relate to the approach taken to model the benefit of exa-cel. The EAG have highlighted uncertainties that could somewhat be addressed through further data collection, such as changes in HRQoL, long-term safety profile and treatment durability. Longer-term data from the trial programme would be relevant to address these. However, with the exception of determining whether a 1.5% discount rate is appropriate (EAG14), these issues only have a relatively small impact on the ICERs presented. Additionally, the maximum length of data collection of 5 years (or the proposed 3 years by the company) would not fully resolve long-term uncertainties around safety or treatment durability and committee will need to make a judgement on whether the additional data would be sufficient to potentially enable a routine recommendation at the currently agreed price.
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 - Major	The EAG questions the robustness of the company's model and its suitability for decision making. Potential equality issues with data collection during managed access. These would be minimised

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	Is the economic modelling and analyses provided suitable for making a managed access recommendation?
2	Would committee require further data collection to decide on whether a 1.5% discount rate is appropriate (see EAG14)?
3	Would 3 years (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?

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	01/12/2023

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	SCD is a severe life-long disease resulting in severe pain, chronic haemolytic anaemia, widespread organ damage and shortened life expectancy. The treatment options are limited. Unmet need is high. Exa-cel is a gene therapy using a person's own stem cells, "correcting" them and then putting back into person's body. This should reduce VOCs, and the company claims that exa-cel has curative potential.
Potential to provide significant clinical benefits to patients	SCD has a high treatment burden for patient and reduces life expectancy significantly. Exa-cel is potentially curative.
represents a step-change in medicine for patients and clinicians	Patients who are suitable for transplant but where no donor is available can benefit from this therapy This technology is also less risky than allogeneic stem-cell transplant and risk of rejection is also lower.
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	A significant number of uncertainties relate to modelling queries. The EAG does not believe that the company's model is suitable for decision making and has not provided any alternative ICERs. However, it is likely that the biggest impact on the cost-effectiveness calculations stem from the severity modifier, the application of the non-reference case DCEA and long term durability. Only the latter could be (partially) resolved through data collection - although data collection is limited to 5 years in the IMF, so the committee may not be satisfied that this would be sufficiently long to resolve the uncertainty.

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
EAG1	Single-arm trial with short-term follow-up	Clinical effectiveness evidence is based on a small study with short term follow-up and no comparator (CLIMB SCD-121)	There seems no feasible alternative approach that can resolve the issues associated with this study design.	Unquantified	More patients followed-up for longer in CLIMB SCD-121 would help but cannot resolve the fundamental issues.	CLIMB SCD-121 / N/A	Low	Longer term data would resolve some uncertainty in the intervention arm, but the lack of comparator remains an issue
EAG2	Generalisability of trial outcomes to NHS practice	The CLIMB SCD-121 study uses data collected across 16 study centres world-wide but only 1 UK site. The EAG has concerns over the difficulty to determine if the evidence reflects characteristics of patient population, and characteristics of standard of care and treatment received (before and during the trial period) in England and Wales, based on the small sample from the UK.	No feasible alternative seems available given that the data presented is based on so few UK SCD patients.	Unquantified	The EAG considers that additional evidence is required because the number of patients providing clinical evidence is small and their duration of follow-up is short; this is particularly the case from a UK perspective because of the extreme sparsity of UK participants.	EBMT registry	Medium	Number of patients, in particular UK-based patients is small - this will likely remain but further evidence could be collected on those UK-based patients via the EBMT registry during a period in the IMF.

EAG3	Trial sample size	The EAG has concerns around the small sample size in the CLIMB SCD-121 study. Analyses beyond about 12 months were based on severely diminishing numbers of patients. The FAS supplies data for more patients and longer maximum follow-up, but numbers followed up diminish rapidly beyond about a year, and the evidence is inadequate for robust decision making. This small sample size in the trial informing efficacy evidence results in uncertainty about the efficacy of exa-cel and limits the scope of robust inferences that can be drawn from the evidence.	Given the noted shortcomings in the available evidence the EAG cannot suggest an alternative approach that would not suffer from similar fundamental deficiencies.	Unquantified	While evidence suggests strong effectiveness of exa-cel for a limited number of patients in the short term the demonstration of prolonged effectiveness requires more patients to be followed up for a longer period. CLIMB SCD-121 cannot provide evidence for a comparator so this issue can only be satisfactorily resolved in a study with more patients, longer follow up, and an appropriate comparator arm to exa-cel.	CLIMB SCD-121 and CLIMB SCD-131 trials and EBMT registry	Low	Whilst the relative clinical effectiveness of exa-cel can only be studied in a study with an appropriate comparator arm, it should be noted that the CLIMB SCD-121 and CLIMB-131 trials (as well as the registry) could collect further efficacy data. However, patients numbers are likely to remain limited.
EAG4	Short-term follow-up of participants	As the study is still ongoing there is a lack of long-term follow up data available. Currently, the efficacy and safety findings are based on short follow-up for a couple patients. The company suggest that exa-cel is likely to restore patients with severe SCD to full or near-full health, but as no long-term follow-up data is yet available; it is impossible to assess the efficacy of exa-cel beyond the short term.	The only feasible alternative appears to be to await longer term evidence from CLIMB trials and to then assess effectiveness.	High	The EAG acknowledges that patients participating in CLIMB SCD-131 will be monitored for up to 15 years following exa-cel infusion, but these longer-term data are not available. Currently, CLIMB SCD-131 is hardly relevant for the decision problem.	CLIMB SCD-131	Medium	Whilst further follow-up is being collected, it is unlikely that sufficient data could be collected within the time frame of managed access (a maximum of 5 years). The impact of patients being modelled as "cured" has a significant impact on ICER.
EAG5	Lack of control/comparator arm	CLIMB SCD-121 is a Phase 1/2/3 single-arm, open-label, multi-site, single-dose study. The EAG notes that as a single-arm study, there are no randomised comparators or control groups in the CLIMB SCD-121 trial. Without a control group the EAG was unable to determine, with a reasonable degree of certainty the true impact of exa-cel.	None seem feasible given the nature of CLIMB SCD-121.	Unquantified	The EAG note that this issue cannot be resolved given the study design of CLIMB SCD-121.	N/A	No further data collection possible / proposed	

EAG6	The model does not have the requisites for a Markov structure	The model structure is not organised as a Markov structure. Deaths are calculated by applying each acute complication a death rate specific to the event, corrected by the proportion of alive population. This approach implies that deaths are counted for each event independently from other events. Although the (incremental) death rates are applied to the "alive" population, the "alive" population is determined in a circular manner, subtracting the number of total deaths in the model from 1. This circularity provides no guarantee that the sum of deaths is less or equal to the total number of people in the cohort. The overall effect is that some people may "die twice" at each cycle in the model, i.e., people in the model are "double counted". Because of the lack of face validity, rates of chronic complications and mortality calculated in the model may be biased.	Model rebuild using standard practices for Markov state-transition models.	Unquantified	Model rebuild using standard practices for Markov state-transition models.	Committee judgement required	No further data collection possible / proposed	
EAG7	Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	The exa-cel cohort showed that approximately 20% of people eligible for exa-cel in fact do not receive it. Some of the dropouts are due failure of apheresis (the process used to harvest cells from the patient) whilst others fail to obtain enough exa-cel for reimplantation (i.e., exa-cel yield falls below the lower bound for therapeutic efficacy). The latter group undergoes apheresis, accrues the cost of manufacturing exa-cel but drops out of the process just before myeloablation. After dropping out of the process, these patients continue to receive SoC.	Apheresis and myeloablation are not part of SoC, therefore they are only necessary if people are meant to receive exa-cel. As such, costs and outcomes for these people must be included in the model as part of the NHS perspective.	Unquantified	A small decision tree to calculate the probability of dropout after apheresis and of dropout after manufacturing of exa-cel but before myeloablation should be added. Once dropouts are accounted for, costs and longer-term outcomes for these people should be included in the exa-cel arm.	Further evidence submission ahead of ACM	No further data collection possible / proposed	

EAG8	VOC rates as a predictor in a risk equation for acute and chronic complications	The model extrapolates all longer-term events from hazard ratios of each event, multiplied by the rate of VOCs at each cycle. The rate of VOC is applied in the model as mean number of events per month; for each complication, this rate is multiplied by a hazard ratio, as if the number of VOCs were a term in a risk equation. Yet the original study with all likelihood did not use VOCs in this way; in any case, the original risk equations are not published. In addition, the original study did not show that the risk of complications is zero when patients report no VOCs, but only that the risk is reduced. Therefore, applying the "number of VOCs" as a significant independent variable, associated with a specific coefficient for the risk of acute and chronic complications in the manner of the model originates from a misinterpretation of the analysis in the original study (Shah et al 2019). Therefore, the number of VOCs per cycle (the intermediate outcome) cannot be used as an intermediate (surrogate) outcome in the model.	VOCs should be used to stratify risk, i.e., it should be used to identify two groups with different risks of certain events. VOCs, per se, should be used as one of the modelling relevant outcomes.	Medium	Methods used to incorporate VOCs should be modified.	Further evidence submission ahead of ACM	No further data collection possible / proposed	ICERs are expected to increase
EAG9	Modelling of adverse events is partial to exa-cel short list and selected events.	Adverse events with exa-cel are available from the CSR of CLIMB SCD-121. The company's model does not include these events on grounds that the HRG cost for myeloablation (obtained from standard NHS costs sources) already incorporates the adverse events of busulfan (the drug used during myeloablation) and other AEs. Whilst this is true, NHS costs cannot include adverse events for products not yet used in clinical practice.	AEs for exa-cel should be incorporated.	Medium	Rates of adverse events from CLIMB SCD-121 should be incorporated in the model.	Further evidence submission ahead of ACM	No further data collection possible / proposed	ICERs are expected to increase
EAG10	Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using distribution of patients' weight.	The costs of prescriptions that are patient-weight dependent should be calculated for all possible weights of the patient population (weight distribution). This is a well-established practice in cost-effectiveness modelling. The model does not allow for an easy incorporation of patient weight distribution because the formulae for calculating these costs are keyed into model traces, and across model cohorts and arms, all based on the average patient weight.	Costs for those drugs and relative procedures should be recalculated; the model should be modified to include an input for total costs of therapies by cycle.	Unquantified	Costs for those drugs and relative procedures should be recalculated; the model should be modified to include an input for total costs of therapies by cycle.	Further evidence submission ahead of ACM	No further data collection possible / proposed	

EAG11	The cost of supportive blood transfusions alongside implantations of exa-cel is not included in model costs.	The costs supportive blood transfusions alongside exa-cel have been included but limited to resource use well below the trial protocol. It is not known whether the use of supportive transfusions may become part of clinical protocols for the use of exa-cel. Whilst normally trial-driven costs should not be included in the model, the use of supportive transfusions may become a feature of the use of exa-cel in real practice.	Costs for supportive transfusions with exa-cel should be included in the model	Medium	Costs for supportive transfusions with exa-cel should be included in the model	Further evidence submission ahead of ACM	No further data collection possible / proposed	
EAG12	Range of acute and chronic complications included in the model is large, but risk reduction is based on assumptions	It is accepted practice that modelling of cost-effectiveness can rely on assumptions around certain parameters when evidence is missing. Nonetheless, the credibility of a model conceptualisation is a qualitative evaluation based both on the amount of evidence incorporated in the model as well as the plausibility of clinical relationships hypothesised in the model structure. For example, parameters and efficacy of exa-cel with regards to bone problems, neurocognitive problems, liver disease and sickle cell retinopathy are assumed based on parameters for pulmonary hypertension, in their turn based on assumptions. The extent of parameters and structural uncertainty in a cost-effectiveness model should not be overwhelming, to ensure that both the logic and the outputs of the model are plausible.	The gaps in the evidence should be recognised; the model should be grounded in evidence, most clinical events parameters should be derived from data, sparingly complemented by assumptions that can be logically defended. When certain clinical endpoints have no evidence base, they should be excluded from the model.	Unquantified	Either searching or developing more evidence for the major SCD endpoints could be helpful.	Further evidence submission ahead of ACM	No further data collection possible / proposed	
EAG13	Underestimation of uncertainty in modelling of overall survival in exa-cel and SoC. Distributions not appropriately parameterised and some key inputs excluded from the PSA.	The model PSA excludes stratified mortality rates and national statistics for background mortality. The use of these data in the model, including stratifications and data organised by age bands, is extensive; hence the exclusion from PSA drastically reduces the possibility of correctly accounting for uncertainty in the model.	Include all mortality data in the PSA.	Unquantified	Include all mortality data in the PSA.	Further evidence submission ahead of ACM	No further data collection possible / proposed	

EAG14	Inclusion of severity modifier and implementation of 1.5% discount rate	The calculation of the severity modifier is likely associated with extensive uncertainty that is difficult to quantify and may be underestimated in the base-case cost-effectiveness analysis, and the application of this modifier in addition to implementation of 1.5% discounting is likely to result in double counting and bias.	NICE stipulates that applying absolute and proportional shortfall calculations should include discounting at the reference-case rate of 3.5% per annum.	High	Model rebuild using standard practices for Markov state-transition models, which encompasses addressing the concerns raised and using a 3.5% discount rate.	CLIMB SCD-121, CLIMB SCD-131 / Committee judgement required	Low	According to the NICE manual, non-reference-case discounting can be applied when all of the following three criteria are met: - 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 If committee requests further HRQoL data, this could be addressed (partially) through a period within managed access by obtaining HRQoL data for people eligible for exa-cel but not receiving the intervention. It is not clear whether a period of up to 5 years would be sufficient to resolve this uncertainty. Committee judgement may depend on precedent set by ID4015 (exa-cel for treating transfusion-dependent beta-thalassaemia).
EAG15	Non-reference case distributional cost-effectiveness analysis	The inclusion of non-reference case distributional cost-effectiveness analysis. The underlying aversion to inequality appears to be based on opinion of a single expert and that a proxy for health deprivation has been employed.	Exclude DCEA from the base-case to be more in-line with NICE reference case.	High	Exclude DCEA from the base-case to be more in-line with NICE reference case.	Committee judgement required	No further data collection possible / proposed	

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	**Rationale/comments**
High	CLIMB SCD-131 is a long-term follow up study, collecting data on clinical outcomes. The efficacy of exca-cel is likely one of the main uncertainties the committee will want clarification on and the ongoing study protocol collects further data.

CLIMB SCD-121 Clinical trial data	
Anticipated completion date	Oct-24
Link to clinicaltrial.gov	https://clinicaltrials.gov/study/NCT03745287
Start date	Nov-18
Data cut presented to committee	Apr-23
Link(s) to published data	N/A
Description of trial	A Phase 1/2/3 single-arm, open-label study to Evaluate the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (CTX001) in Subjects With Severe Sickle Cell Disease, n=45 (estimated) - patients with severe SCD aged 12 - 35 years. Primary outcome measures are: - Proportion of subjects who have not experienced any severe vaso-occlusive crisis (VOC) for at least 12 consecutive months (VF12) - Proportion of subjects with engraftment (first day of three consecutive measurements of absolute neutrophil count [ANC] ≥500/μL on three different days) - Time to engraftment - Frequency and severity of collected adverse events (AEs) - Incidence of transplant-related mortality (TRM) within 100 days after CTX001 infusion - Incidence of TRM within 1 year after CTX001 infusion - All-cause mortality

CLIMB SCD-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	Whilst proposed data collection is feasible through the study protocol registered in the EU PASS Register following PRAC approval of the final protocol: "Long-term registry-based study of patients with β-thalassemia or sickle cell disease (SCD) treated with exagamglogene autotemcel (exa-cel)", concerns remain that it won't deliver necessary evidence in the timeframe allowed in the IMF. Furthermore, there is uncertainty over the number of patients who would be treated in the NHS during the IMF period.

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	Existing	Further data would be collected through the European Society for Blood and Marrow Transplantation (EBMT) Registry.
Prior experience with managed access	Medium	Registry has not previously been used within a NICE managed access agreement. However, a trial protocol, governance and deliverables have already been agreed as part of a research study.
Relevance of existing data items	High	The study protocol uses the registries to collect the data, and has data collection through the registries integrated into the study design - therefore the relevance of the data items should be extremely high.
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	Data from approx. 80% of European transplant centres are received ; The EBMT Registry holds data on patients receiving a haematological transplant procedure, as well as gene and cell therapies. Specific to this study, the EBMT includes patients with SCD and TDT receiving an allogeneic or autologous HSCT procedure and is expected to include patients with SCD and TDT receiving gene therapies once such therapies are approved and available commercially.
Data completeness	Medium	Data from approx. 80% of European transplant centres are received (75% autologous transplants, 80% for allogenic transplants). The risk of missing data or patients lost to follow-up are higher than in clinical trials. Does not measure HRQoL
Data accuracy	High	New forms to be included into register to have sufficient detail.
Data timeliness		
Quality assurance processes	Yes	The EBMT has robust quality assurance processes in place.
Data availability lag	High	The data collected would be made available approximately 12 months after data-cut off.
Data sharing / linkage		
New data sharing arrangements required?	No	

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	EBMT will collect data from Germany, France, Italy and the United Kingdom. There are 52 centres in the UK reporting outcomes in the EBMT currently.
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	Yes	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 - Major	The EAG's opinion is that it questions the company's model suitability for decision making. There are potential equality issues with data collection during managed access. These would be minimised through engagement with patient groups during any managed access.

		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?	Yes	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	Unclear	SmPC is ready but does not give much detail on patient safety and adverse events. Standardised checks will be in place. Company and providers are bound to report AEs to each others; any further reporting structures will likely be met with resistance.

		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	Not applicable	This is a one-off treatment. All patients who receive treatment during a managed access period would continue to receive benefits of treatment in the event of a negative NICE guidance update.
	If yes, have NHS England and the company agreed in principle to the exit strategy	Not applicable	

		Rating	Rationale / comments

Service implementation	Is the technology disruptive to the service	Yes	No current service provision available that could offer exa-cel, so new service provision would need to be set up. Patient demand is somewhat unknown but there is a time lag of about 7 months between patient identifaction and treatment start.
	Will implementation subject the NHS to irrecoverable costs?	Unclear	
	Is there an existing service specification which will cover the new treatment?	No	A new service specification will need to be set up.

		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	The company highlight patients in England with SCD 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.

References

Cookson R, Koh J (2023) Quantifying impact on health inequality in England: revised final report and web-based calculator. CHE Research Paper 193. Centre for Health Economics, University of York

Currie J, M Guzman Castillo, Adekanmbi V et al. (2019) Evaluating effects of recent changes in NHS resource allocation policy on inequalities in amenable mortality in England, 2007–2014: time-series analysis. Journal of Epidemiology and Community Health 73: 162

Hurley J, Mentzakis E, Wallip-Attaei M (2020) Inequality aversion in income, health, and income-related health. Journal of Health Economics 70: 102276

Love-Koh J, Cookson R, Claxton K et al (2020) Estimating social variation in the health effects of changes in health care expenditure. Medical Decision Making 40: 170–82

McNamara S, Holmes J, Stevely AK et al (2020). How averse are the UK general public to inequalities in health between socioeconomic groups? A systematic review. European Journal of Health Economics 21: 275–85

National Institute for Health and Care Excellence (2022) NICE Listens: health inequalities report.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

Patient expert statement

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

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

Information on completing this form

In part 1 we are asking you about living with sickle cell disease or caring for a patient with sickle cell disease. The text boxes will expand as you type.

In part 2 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.

NICE National Institute for Health and Care Excellence

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.

The deadline for your response is **5pm** on **18 January 2024.** 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, 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 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.

Patient expert statement

Part 1: Living with this condition or caring for a patient with sickle cell disease

Table 1 About you, sickle cell disease, current treatments and equality

1. Your name	Funmi Dasaolu
2. Are you (please tick all that apply)	☒ A patient with sickle cell disease? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with sickle cell disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Anthony Nolan & Sickle Cell 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: My role as patient and public representative on NHS England's Haemoglobinopathies Clinical Reference Group and the National

	Haemoglobinopathy Registry Steering and Data Groups. Plus, my involvement in local charity organisations. ☐ 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 sickle cell disease? **If you are a carer (for someone with sickle cell disease) please share your experience of caring for them**	Sickle Cell Disease affects all aspects of my life. Fatigue and pain (both acute and chronic) associated with the condition mean everyday activities ranging from personal care tasks to employment and socialising are very difficult. The unpredictability of pain episodes (crises) makes planning simple tasks extremely difficult. Trying to avoid crises often feels like walking a tightrope, it feels like there is very small margin for error. This constant juggling and balancing leads to mental exhaustion and impacts significantly on psychological well-being. Pain severity often results in frequent hospitalisation. Care received in hospital is often poor and inadequate. I often have to advocate for myself, whilst in excruciating pain, which is extremely difficult and increases the distress I experience. Awareness and understanding of the condition is extremely poor, I often have to educate and teach ward nurses about the condition, even when admitted onto Haematology wards. This exacerbates feeling of mistrust and leads to a lack of confidence in healthcare professionals and services. As such, I avoid seeking hospital care, even when experiencing a severe crisis due to fear of poor treatment and discrimination. My current treatment includes 4 weekly exchange blood transfusions, along with daily hydroxycarbamide. I find the need for recurrent transfusions particularly burdensome; I often have to plan my life around my transfusions. Despite this

	treatment regime, I continue to experience daily pain, episodes of crises and chronic fatigue.
7a. What do you think of the current treatments and care available for sickle cell disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Whilst current treatments offer some relief from symptoms, there are unable to offer a permanent cessation of problematic symptoms. As such, I feel there is a great need for curative therapies and treatments for individuals. I feel like I have reached the ceiling of what current treatments can offer, yet continue to experience severe symptoms. I cannot be transfused more frequently, and I am currently on the maximum tolerated dose of hydroxycarbamide. This creates feelings of despair and hopelessness. Current treatment options are extremely limited, new treatment options which previously held great promise like Voxelotor and Crizanlizumab are no longer viable options for patients. Exchange transfusions can offer great benefit, however, there is a shortage of ethnically matched blood for individuals, as well as, the burden of treatment experienced by individuals coupled with the psychological distress caused by poor venous access, making this treatment option difficult for patients to manage. Patients often find the need for daily medications, frequent clinic reviews, appointments and hospitalisations particularly taxing on all aspects of their health and well-being. It makes living a ‘normal’ life impossible. Moreover, hydroxycarbamide and exchange and top-up transfusions are not tolerated by all patients. This gap in treatment options, leave individuals without suitable treatment pathways, which adversely impact on quality of life.

	When compared to other conditions such as Cystic Fibrosis, Diabetes and Cancer, care available via the NHS for Sickle Cell Disease lags woefully behind. Sickle Cell Disease has been underfunded, under-resourced and not prioritised for decades. Basic standards of care are not being adhered to consistently across the nation. There remains a huge variety in quality of care across different regions, creating a postcode lottery for individuals.
8. If there are disadvantages for patients of current NHS treatments for sickle cell disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Hydroxycarbamide is not tolerated by everyone, it also requires frequent blood monitoring to ensure safety. This adds to the number and frequency of appointments for individuals. While offering significant benefits, exchange blood transfusions are problematic due to the duration and frequency of the procedure, and the lack of availability of appointments. Increased demand means patients are having to wait longer for appointments, increasing the likelihood of acute pain episodes. Venous access required for transfusions is also problematic for patients and can significantly affect the experience and duration of the procedure. Oral medications need to be taken daily, sometimes multiple times during the day. This care be difficult for patients to remember and adds to the mental burden of the condition. Patients also require time out of work/daily activities to attend transfusion and related hospital appointments. Moreover, recovery from transfusion can take several days post procedure before patients experience any benefit. Individuals can also experience transfusion side effects during and after the procedure, such as hives, itching, temperature, destruction of transfused cells etc.
9a. If there are advantages of exagamglogene autotemcel over current treatments on the NHS please describe these. For example, the effect on your	Exagamglogene Autotemcel offers a one-time (‘fix’) solution for patients. Whilst I acknowledge the actual treatment process and immediate period after will be long and arduous for individuals, the benefits seem to far outweigh the disadvantages.

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 exagamglogene autotemcel 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**	It would massively and drastically change my life, not only improving the quality of my life, but significantly affecting my ability to work, study, self-care and engage in normal everyday activities. It would mean freedom from pain crises, chronic fatigue, hospitalisations, regular transfusions, daily medicines, and regular hospital appointments. The difference would be night and day. It being a one-time fix for me is most appealing and important as it eradicates the daily need for symptom management, the recurrent need for transfusions, daily medications, and frequent hospital appointments. It is the cure I have been longing for. It eradicates the burden and demands of the condition, alleviating this would significantly increase quality of life for individuals. I find the constant pain, fatigue, transfusions, hospital appointments and hospitalisations the hardest/most burdensome aspect of the condition. It infringes on my all aspects of and my ability to live a 'normal' life, similar to that which my peers lead.
10. If there are disadvantages of exagamglogene autotemcel over current treatments on the NHS please describe these. For example, are there any risks with exagamglogene autotemcel? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Personally, the main disadvantages of Exagamglogene Autotemcel include the conditioning process, the requirement to be hospitalised for 2 months, and the potential effects this may have on fertility. Also, I worry about the long-term effects of the treatment. For example, what happens to individuals 10, 20, 30 years after treatment? Is there any risk of treated individuals developing malignancies in the immediate and long-term? What is the risk of death? I think the above needs to be thoroughly explored to ensure patients are able to make an informed decision. For individuals who want a family, fertility needs to be explored in depth, examining all eventualities.
11. Are there any groups of patients who might benefit more from exagamglogene autotemcel or any who may benefit less? If so, please describe them and explain why	My concern is Exagamglogene Autotemcel will only be available to patients with very severe disease. However, given the treatment process it is important patients are as well as possible to ensure they are able to tolerate the arduous process.

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 also worry about equal access and availability of this treatment nationally. Will this treatment be available to all individuals across the county, or just those who live in areas where there are specialist hospitals or a high population of the disease? This new treatment would particularly benefit those who have exhausted currently available treatment options, but may disadvantage those who do not have severe disease at present. However, given the severity and unpredictability of the condition over the course of an individual's lifespan, and the uncertainties regarding the impact of the condition in the future, it is necessary to consider whether it is ethically sound for patients to have to 'wait' until they deteriorate before being offered this treatment. It would also be useful for patients to have information on the treatment outcomes of individuals with Sickle Cell Disease and other conditions/co-morbidities such as Diabetes, stroke, renal disease etc. Such patients may not be as physically fit/well enough to undergo the treatment process.
12. Are there any potential equality issues that should be taken into account when considering sickle cell disease and exagamglogene autotemcel? Please explain if you think any groups of people with this condition are particularly disadvantage 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	In addition to my responses to question 11 above, I think careful consideration needs to be given to the ethnic, faith and cultural needs/aspects of individuals who are being offered this treatment. For example, does their particular faith have a stance on gene editing? How can the process be inclusive/adapted for these individuals? Just as blood transfusions are prohibited for Jehovah witness', equal consideration needs to be given to how this treatment will be received by individuals, the majority of which are of African and Caribbean descent and may be devout Christians/Muslims.

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Yes, there needs to be acknowledgement of the historic and systemic failings in care for this population of individuals.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Exagamglogene Autotemcel address the gap in treatment options, and offers a one-time curative solution for patients with Sickle Cell Disease, eradicating symptoms and drastically improving quality of life for individuals.
- Currently, treatment options for Sickle Cell Disease are extremely limited and burdensome for patients, none of which are curative.
- Care for individuals with Sickle Cell Disease has been underfunded, under-resourced and not prioritised for decades, resulting in not only historic, but current and systemic failings in care. Treatment for Sickle Cell Disease lags woefully behind when compared to similarly inherited and chronic conditions.
- Individuals need to be provided with all necessary information to ensure they are able to make a fully informed decision. Information needs to detail side effects including long-term effects/complications of the treatment (if any and if known).
- Due consideration needs to be given to the ethnic, faith and cultural needs of individuals being offered this treatment, most of which are of African and Caribbean descent.

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 for treating sickle cell disease [ID4016]

Patient expert statement

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

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

Information on completing this form

In part 1 we are asking you about living with sickle cell disease or caring for a patient with sickle cell disease. The text boxes will expand as you type.

In part 2 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.

NICE National Institute for Health and Care Excellence

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.

The deadline for your response is **5pm** on **18 January 2024.** 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, 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 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.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with sickle cell disease

Table 1 About you, sickle cell disease, current treatments and equality

1. Your name	Toby Bakare
2. Are you (please tick all that apply)	☒ A patient with sickle cell disease? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with sickle cell disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Anthony Nolan and the Sickle Cell 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 sickle cell disease? **If you are a carer (for someone with sickle cell disease) please share your experience of caring for them**	My experience of Sickle Cell divides mainly into life Pre and Post taking Hydroxyurea. Before taking Hydroxyurea, which I started on around 20 years ago, I missed a third to half of my schooling because of very frequent and moderately painful VOC's which had to be treated in hospital. I was hospitalised roughly 4-6 times a year and school in particular was difficult. Post taking Hydroxyurea my experience was different. I had fewer crises and was able to do more by way of school, education and eventually work. Along with experiencing puberty, taking Hydroxyurea did allow me to be more physically capable when well. Though VOCs and hospitalisations were down to once a year, or less, there were some significant problems still. The once a year or so crises were less frequent but far more painful as I got older. And the admissions became more dangerous. Increased analgesia, increased complications such as acute chest syndrome and a risk of sepsis happened much more often. Tiredness and fatigue, which could often lead to low-level Sickle Cell pain were issues throughout my life with Sickle Cell regardless of Hydroxyurea. They had negative consequences on my personal life. It was something I managed by not over-exerting myself wherever possible, not leaving the house if I didn't need to etc. This obviously had a detrimental impact on my quality of life and my career. As an adult I found myself in situations where not everyone knew what to do in the event of a crisis, for example if I was on holiday. This upped the likelihood of something tragic happening. The once a year crisis sounds tolerable compared to the situation when I was a child. But that once a year event was more traumatic and increasingly accessing acute care from ambulances and A&E was more and more difficult.

	The last half a dozen crises were particularly severe and made me consider having an allogeneic stem cell transplant more. The pain of a crisis as a child is horrific but in my experience it was something I could recover from relatively quickly. As an adult that wasn't the case. The physical and mental effects of a crisis last longer and so does the time it takes to recover. The consequences of a crisis are also greater - they include loss of employment and strained personal relationships. Because of this I took the alternative treatment options, i.e. a stem cell transplant much more seriously.
7a. What do you think of the current treatments and care available for sickle cell disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a) Firstly, I want to say the care I receive is, I believe, exceptional. My Clinical Nurse Specialist has known me since I was a baby, my consultants have known me since I transferred to adult services and that continuity of care is invaluable when it comes to discussing various treatment options. But there is a huge amount of variation in the care that can be offered from one hospital to another and one region to another. There are a lack of options for treating Sickle Cell Disease and not enough emphasis on improving quality of life. So that leads to analgesics being at the forefront of treatment options. In terms of treatments the options are limited and as I've got older I've found this more frustrating and harder to justify. Hydroxyurea was a significant drug treatment for me. It did also have significant drawbacks. Mainly around fertility and what my options were around having children which weren't known at the time of me starting on the drug. Other treatments I've had include transfusion and exchange programmes which provide amazing short term gains. Their availability and issues around overuse are well known. 7b) I am aware that sufferers of other similar hereditary and genetic conditions have hundreds of possible treatments available to them and at the moment Sickle Cell has two. It doesn't compare well.

	From what I've read (and having participated in trials myself) I know there are treatments in development for Sickle Cell Disease Disease and in theory young people who are unfortunate enough to have the disease are going to have access to a range of treatments that could work to improve their lives. I've spoken with people who are excited about the exciting treatments. My worry for them is that the reality will be different. In the here and now there is one drug (Hydroxyurea) and one radical treatment available (stem cell transplants). Both have drawbacks which need to be carefully considered and the radical treatment is only available if you are lucky enough to have a matching sibling donor. I do believe this should be expanded to include unrelated stem cell donors too, to give patients more options. What's on offer to care for people with Sickle Cell was once described to me as 'palliative' in the sense that treatments offer relief and comfort but essentially no cure for the underlying cause and little by way of improving quality of life. Because there were so few alternatives I took the prospect of a transplant seriously.
8. If there are disadvantages for patients of current NHS treatments for sickle cell disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	8a) The downsides of Hydroxyurea I've already touched on. There are fertility issues that arise from taking it, and it's necessary to monitor bloods while taking it, and when I did start on the drug, I would experience bouts of hair loss. The exchange and blood transfusions on offer aren't a long term solution with a shortage of donors and iron overload issues. As I became older the only way I could travel involved blood transfusions/exchange transfusions in the run up and an oxygen machine to prevent hypoxia while on a plane. That's a huge logistical challenge in ones personal life and a non-starter in my professional life. There are also issues of Iron overload which I dealt with from overly frequent blood transfusions.
9a. If there are advantages of exagamglogene autotemcel over current treatments on the NHS please describe these. For example, the effect on your	I can answer from the point of view of having had a sibling matched donor for a stem cell transplant.

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 exagamglogene autotemcel 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**	In my life at the moment, I am healthier, fitter and stronger than at any point in my life before and I'm already capable of a range of activities and exercise that I wasn't able to do before the transplant, so I believe I made the right decision already. I've begun cycling to work daily and been hiking and fishing in the last year. These are things that would have been out of the question before the transplant as I would not have been fit enough to engage. In cool or cold weather doing these activities could aggravate a crisis putting me out of action for a couple of weeks. I am now living a life where physical exertion isn't creating a catastrophic set of circumstances but is just an everyday part of life. I'm not experiencing pain which is a great boost to my mood and I have more energy and spend less of my time ill. I can feel the legacy of 33 years of Sickle Cell in my body and that means there are limits to what I can do but the sense of optimism energy is very clear. A really important benefit for me is that I no longer feel inhibited in my career or that my medical condition has the potential to put others in danger as any Sickle Cell Crises at work will obviously mean you can't do your job. More broadly the exagamglogene autotemcel treatment would offer all these benefits that I've mentioned but to many more people because it wouldn't need a sibling donor. 9b) The improvements in my quality of life are the biggest change for me. It's a different approach to daily life, work, travel, family life and career now that I'm not burdened with pain and having Sickle Cell. 9c. Exagamglogene autotemcel treatment would eliminate all the downsides I mentioned as you would no longer have to take Hydroxyurea, the only treatment available. Issues around fertility might be the only exception as it

	can also arise as a complication from the disease as far as I'm aware. There would also be no need to have a blood transfusion/Exchange anymore as you would be producing blood which doesn't Sickle/cause a crisis and so not have to deal with Iron overload issues (something I have experienced myself). Because there is no donor the chances of graft vs host disease are greatly reduced and so the likelihood of a any kind of rejection. The time needed on immunosuppression is also reduced I believe. This would be a big benefit as recovery time and the time when you are more vulnerable is greatly reduced.
10. If there are disadvantages of exagamglogene autotemcel over current treatments on the NHS please describe these. For example, are there any risks with exagamglogene autotemcel? If you are concerned about any potential side effects you have heard about, please describe them and explain why	As far as I'm aware the most prohibitive issue around this new treatment is the cost as the trials that have been done show that it's very effective. On a more personal level the main difficulty I have found has been in the post-transplant period involving immunosuppression. Infections which weren't easily diagnosed and were a tough mental challenge when they occurred in the first 6 months after transplant. A year on from my transplant I am having to wait before I can start to taper off the immunosuppression tablets which has been difficult as I'm keen to fully experience life post having Sickle Cell disease. But to be very clear I do not put these as bigger disadvantages than Hydroxyurea or blood exchanges/transfusions.
11. Are there any groups of patients who might benefit more from exagamglogene autotemcel or any who may benefit less? If so, please describe them and explain why	I do think if suitable any treatment that offers a cure for Sickle Cell can be of benefit to all sufferers.

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	The younger you have a treatment that is effectively a cure the longer you can live a life without Sickle Cell Disease. But there are improvements in quality of life which I think should be made available to older people also. I was 33 years old when I had my transplant and I think it may have been available to me sooner but it wasn't made available on the NHS to adults. Now that I have experienced life without having Sickle it's something I wish had happened to me sooner, and I'm sure many adults with Sickle Cell would feel the same. There may be people who would benefit more, particularly those who are more ill, more often. Deciding who is more worthy is an ethically tricky think I believe.
12. Are there any potential equality issues that should be taken into account when considering sickle cell disease and exagamglogene autotemcel? Please explain if you think any groups of people with this condition are particularly disadvantage 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.	Yes, I believe so. The number of treatments for Sickle Cell is a lot less than when compared to other similar genetic conditions. I think there has historically been a lack of research and awareness around Sickle Cell and that has fed through into a lack of treatment options. To now have treatments that are approved and not have them be available for cost reasons would be two steps forward and one step back in my view. There is also the issue of sufferers in other countries such as USA having the access to this treatment while those in the UK might not which I think should be considered.
13. Are there any other issues that you would like the committee to consider?	Briefly, I want to address the point around finances and cost effectiveness of stem cell treatments vs conventional treatments. I'm not able to provide a figure but I'm sure that tablets and a lifetime of admissions as well as regular blood transfusions/exchanges will over the course of a lifetime amount to a large 6 or 7 figure sum. I believe that curing a disease like Sickle Cell could also be have an

	upside in freeing capacity and not being a cheaper treatment option over the course of a lifetime of a patient.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- My own life before the transplant was manageable thanks to Hydroxyurea, but I still had multiple severe crises.
- As well severe crises my quality of life was poor with Sickle impacting my everyday life adversely.
- Post transplant my health and quality of life has improved dramatically, and I believe that would be the case for anyone having a Stem –Cell transplant.
- Compared to painful crisis the side effects of the stem cell transplant I've had have been so far been fairly minimal.
- It is a historically underfunded and under researched disease so it's positive news that treatments are being developed, provided they make their way to patients

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 for treating sickle cell disease [ID4016]

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 (see section 1.1). 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 **18 January 2024.** 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

Part 1: Treating sickle cell disease 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 and UCLH
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with sickle cell disease? ☒ A specialist in the clinical evidence base for sickle cell disease or technology? ☒ Other (please specify): Peer review lead
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 sickle cell disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To reduce mortality, reduce end organ damage and 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)	Reduction in painful episodes, improvement in morbidity via stabilisation of prior organ damage and lack of development of new end organ damage
10. In your view, is there an unmet need for patients and healthcare professionals in sickle cell disease?	There is a significant unmet need in sickle cell disorder. Currently with the withdrawal of crizanlizumab we are in a position where we can only offer transfusion, transplant and hydroxycarbamide to patients living with the disorder. Patients have been stigmatised by the health care system and funding has not been sufficient for many decades for clinical services and for research. Currently with sibling transplants in adults over 80% of eligible patients cannot receive this intervention due to no appropriate donor and therefore alternatives are required. Currently haplo-identical transplant is via trial only despite excellent results being published at ASH in 2023
11. How is sickle cell disease 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?	The current options for treatment in the UK are currently: a) Supportive care (includes folic acid, penicillin and analgesia) b) Hydroxyurea c) Clinical trials including haploidentical transplant d) Transfusion – simple top up and red cell exchange e) Sibling allogenic transplant There are national clinical guidelines used in the treatment of this condition from NICE and the British Society of Haematology as well as the standards of care for sickle cell disorder. There are also the Peer review standards for the care of people with haemoglobinopathies. The pathway has previously been variable but the introduction of the haemoglobinopathy networks has improved this and all high cost or novel therapies are referred to the National Haemoglobinopathy panel. This would be the route taken for choosing patients selected for this therapy via local networks and specific JACIE accredited centres only would be able to deliver it.

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 therapy will be in addition to current treatment offer for those patients who do not have a sibling donor (as per the trial) with the same eligibility criteria. The healthcare resource would be the same for provision outwith of the cost of the cellular product and support costs post delivery. The cellular product would be delivered in specialist services with transplant and red cell services present on the same site. The therapy is like the delivery of any cellular therapy and therefore no new facilities would be required but there may be the need to expand existing services.
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 think that for patients who are eligible for this therapy it will expand their curative options which are currently minimal outwith of those outlined above. From the trial data I would expect a similar impact on quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The patients would need to meet specific criteria to be eligible for this treatment as per the clinical trial.
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)	I think that this will be similar in delivery purposes for the patients and healthcare professions to deliver given the specialist requirements to deliver cellular therapy. Follow-up will be similar to a related sibling transplant.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting treatment will require sign off by the national haemoglobinopathy panel and patients will have to meet criteria for them to have the required conditioning therapy which is standard for any cellular therapy ie cardiac and renal functional levels.
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 challenge is with patients who have life-long conditions that their baseline is all they know and therefore improvements in quality of life (or at least their baseline level) can be overestimated.
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 this is a step-change in the management of sickle cell disorder and potentially transformative for patients who are currently unable to access curative therapy and therefore long term morbidity and quality of life benefits.
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 side effects are mainly related to the conditioning chemotherapy and are universal to all such interventions. This technology has no risk of graft vs host disease which is a risk of allogeneic transplants.
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?	Yes the trials reflect the UK population and current UK clinical practice and current data about outcome related variable ie VOC. Hb F (also an outcome measure) is also the best described modifier of severity in SCD. VOC is well recognised as a marker of mortality and has been well described in the literature. Not aware of any current adverse effects in this clinical trial.

• 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?	
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 real world evidence present as yet
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	There are significant equalities issues with regard to all haemoglobinopathy patients including sickle cell disorder. Sickle cell has faced significant challenges with regard to funding and systemic racism particularly within the NHS. All patients with sickle cell disorder are fundamentally disadvantaged due to their condition, missing educational and work opportunities and decreased life expectancy and increased morbidity.

• 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.	

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

Single-arm trial with short-term follow-up	Single arm studies are an accepted approach for gene therapy trials in blood disorders including haemophilia and also in other non-genetherapy haematopoetic indications. This is a novel therapy approach but the long term data in gene therapy in the immunodeficiency setting leads to confidence in this as an approach with curative intent and its long lasting effect. The outcomes for sickle cell in the current setting are limited with significant documented morbidity, loss of economic and social productivity and will extend the curative option to the more than 80% of eligible patients who do not have a matched sibling donor.
Generalisability of trial outcomes to NHS practice	The trial population is entirely generalisable to the NHS population and practice. The impact of improved Hb F has been well documented in numerous populations around the world. The trial population was derived from 16 high to middle income countries without endemic sickle cell population who would represent the UK population. The delivery of the therapy within the NHS setting would involve both specialist sickle cell teams (as commissioned by NHSE) and JACIE accredited cellular therapy services.

Trial sample size	Currently there are 30 patients in the primary efficacy set of whom 29 have met the primary endpoint for a mean duration of 22.4 months. This sample size is one of the largest in the literature and reflects that this is a novel therapy and the appropriately stringent criteria for recruitment.
Short-term follow-up of participants	This is a novel therapy approach but the long term data in gene therapy in the immunodeficiency setting leads to confidence in this as an approach with curative intent and its long lasting effect. The outcomes for sickle cell in the current setting are limited with significant documented morbidity, loss of economic and social productivity and will extend the curative option to the more than 80% of eligible patients who do not have a matched sibling donor. The improvements in outcomes with patients who have related transplants show significant improvements in outcomes despite the increased risks of GVHD in this setting.
Lack of control/comparator arm	This question is a repetition of the single-arm question above
The model does not have the requisites for a Markov structure	The statement in the EAR regarding “Exclusion of relapse rate” and its effect on the Markhov structure may be what this is related to. Gene therapy unlike allogeneic stem cell transplant involves recipient receiving their own modified stem cell after conditioning therapy. Unlike allogeneic transplantation where a state of tolerance needs to be achieved and hence there may be a risk of late graft rejection, as the recipient is immunologically identical this risk will not be present leading to late relapses. The language here is very “white cell” and this is a chronic long term red cell disorder rather than an acquired cancer which I find problematical and am concerned that this hasn’t been considered.
Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	Agree with EAR findings that it is reasonable to include the cost for patients who undergo apheresis but do not proceed with gene therapy.

Vaso-occlusive crisis (VOC) rates as a predictor in a risk equation for acute and chronic complications	As per my other response please see the below: There is strong evidence that the frequency of VOC and admissions are related directly to poor outcomes and early death. Platt et al in 1994 reported that mortality was the highest in patients who were symptomatic ie those who have VOCs. This was further illustrated in the King's College Hospital cohort in Blood in 2016 (Gardner et al 2016) which showed that those with 2 or more admissions per year had a significantly higher risk of death. This was illustrated by a reduced mean life expectancy to 41 years in the severe phenotype disease. This has been further confirmed by HES data and the American Cooperative Study of Sickle Cell Disease. However it should be noted that this may be an underestimate as much of the damage in SCD is silent including renal impairment, chronic liver disease etc and this is an increasing issue as our patients age. Unfortunately due to historic underfunding and prejudicial attitudes little data on the aging and natural history of sickle cell disorder are unavailable. The EAR report also repeatedly notes splenic infarction as a complication that is not considered in the structure. In sickle cell patients with SS (homozygous) sickle many authors have shown hypospenia and asplenia to occur early in life (by age 6) and even in patients with a spleen visible on imagining there are usually features on the blood morphology to indicate hyposplenia. Hyposplenisim is presumed in all patients with sickle cell disease and appropriate measures including penicillin prophylaxis is commenced at 3 months of age and vaccinations against encapsulated organisms through life. This is the purpose of the inclusion of sickle cell disease in the perinatal screening programme.
Modelling of adverse events is partial to exa-cel short list and selected events.	It is reasonable to exclude the side effects directly attributable to Busulphan as standard NHS costs already incorporates the adverse events associated.
Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using	Not able to comment here due to significant variability in this patient population and the timing of interventions

distribution of patients' weight.	
The cost of supportive blood transfusions alongside implantations of exa-cel is not included in model costs.	Transfusion is part of standard care for patients with SCD, it is used to rescue patients in clinical difficultyin the acute clinical situation, manage disease complications and prophylactically to prevent severe complications. A significant number of the patients who would be considered for this intervention will already be on chronic transfusion programmes and therefore this would not be an additional cost.
Range of acute and chronic complications included in the model is large, but risk reduction is based on assumptions	This reflects the variable phenotype and severity in people with sickle cell disorder but the underlying polymerisation of HbS and subsequent vaso-occlusion and haemolysis are contributory to all. Hb F directly inhibits polymerisation as well as reducing the overall amount of Hb S so would have an additive improvement with this cellular therapy.
Underestimation of uncertainty in modelling of overall survival in exa-cel and standard of care. **Distributions not appropriately parameterised and some key inputs excluded from the probabilistic sensitivity analysis.**	Not able to comment
Inclusion of severity modifier and	In section 1.3.8 in discussing the EAR report seems to equate the significant inequity experienced by patients with SCD when utilizing healthcare similar to other rare conditions they note "same could be said

implementation of 1.5% discount rate	of most orphan conditions". I would strongly refute this. SCD is a condition affecting people from predominantly BAME groups, the most common presentation is acute and severe pain episodes which are unpredictable, haveno pathognomic features and often may not even have abnormal clinical findings on review. Multiple patient surveys across many different health settings including the APPG report published in November 2021 in the UK, have all demonstrated the gaps in care, and the effect that both overt and institutionalised racism has on the care patients receive. This is unique to SCD and is not replicated in any other rare condition. Without recognition of this then the premise on which the EAR adjudicates on the weighting of inequality is biased.
Non-reference case distributional cost-effectiveness analysis	Unable to comment
Are there any important issues that have been missed in EAR?	

NICE National Institute for Health and Care Excellence

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.

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.

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

Clinical expert questions:

- How generalisable is the CLIMB 121 clinical trial to the population that would receive exa-cel in NHS clinical practice?

This data is highly generalisable to the UK sickle cell population. I assume this query is because there were no UK sites used in the trial. There is no evidence that prior patient interventions e.g. transcranial dopplers and hydroxyurea have had differing impacts in the UK population. The causative genetic mutation is universal. From a transplant perspective the UK governance from a clinically laboratory perspective is the same if not more robust than the sites used in the trial.

- How would people with sickle cell disease (SCD) be selected for exa-cel in the NHS if approved? If this is different to the inclusion criteria of CLIMB SCD-121, please outline how and why it would be.

Currently there are robust processes in place for the screening and selection of all patients who are being considered for high cost or novel therapies. This includes discussion at a variety of levels including local (specialist haemoglobiniopathy team) regional (haemoglobinopathy coordinating centre) and national (national haemoglobinopathy panel). This leads to robust and clear selection of patients which would be in line with the CLIMB 121

- Does the absence of VOC (Vaso-occlusive crisis) translate directly in a cure? Specifically, does it mean that someone would have no acute and chronic complications?

There is strong evidence that the frequency of VOC and admissions are related directly to poor outcomes and early death. Platt et al in 1994 reported that mortality was the highest in patients who were symptomatic ie those who have VOCs. This was further illustrated in the King's College Hospital cohort in Blood in 2016 (Gardner et al 2016) which showed that those with 2 or more

admissions per year had a significantly higher risk of death. This was illustrated by a reduced mean life expectancy to 41 years in the severe phenotype disease. This has been further confirmed by HES data and the American Cooperative Study of Sickle Cell Disease.

However it should be noted that this may be an underestimate as much of the damage in SCD is silent including renal impairment, chronic liver disease etc and this is an increasing issue as our patients age. Unfortunately due to historic underfunding and prejudicial attitudes little data on the aging and natural history of sickle cell disorder are unavailable.

- Are VOCs a predictor of complications? Does the number of VOCs influence SCD complications, or just the presence of VOCs i.e., with or without any VOCs? How strong is this association? Are other disease symptoms beyond VOCs important in determining extend of SCD severity?

As per above VOCs are an important predictor of complications and mortality however this excludes patients with haemolytic phenotype who are less likely to get acute pain but due to chronic severe anaemia and endothelial dysfunction are more likely to get specific end organ damage for example pulmonary hypertension and renal dysfunction. Sickle cell disorder is a highly diverse group from a phenotype perspective – numerous studies have attempted to elucidate genetic and other biological markers however the reliable associations are Hb F level and presence of alpha thalassaemia trait but there is extensive literature on some genetic polymorphisms and specific complications.

- What would constitute a cure in terms of outcomes? How much follow-up time post intervention would be needed to be sure in the durability of effect?

This is a rather unrealistic question – in the malignant setting 5 years is used and perhaps could be applied here for equity purposes? I think that a cure could be stability of chronic complications and lack of development of new complications resulting from sickle cell disorder.

- How plausible, in your clinical opinion, is treatment effect waning with exa-cel?

Currently there is no evidence of waning of the Hb F level at over 3 years follow up. Given that this is an autologous transplant there is unlikely to be waning after this date by any known mechanisms.

- How would you describe the quality of life of a person with SCD following treatment with exa-cel who are VOC-free? Would other aspects of SCD impact quality of life even if VOC-free status following exa-cel treatment is achieved?

Quality of life is challenging to assess in patients who have life long chronic disorders as their baseline is all they have ever experienced. Previous studies have however shown a poor baseline quality of life. The unpredictable nature of sickle cell disorder adds a further challenge for patients and their planning and working as per non-affected individuals. However quality of life data from the trial suggest restoration of a normal quality of life post treatment with some patients experiencing above standard measures (potentially reflecting the above challenges).

With regard to non-VOC related impacts I think we have to acknowledge that societal and NHS specific racism with regard to this group are chronic and that these issues may be ongoing and the impact is underestimated historically although hopefully this is now changing. Providing this as a treatment option can only improve their economic and social productivity.

- Please see the list of acute and chronic complications below and the estimated incidence of these estimated in the economic model:

Complications included in the company model:

The overall lifetime incidence of acute complications for the standard of care group in the company model

Stroke	ACS	Infection	AKI	Gallstones	PE	Leg ulcers

0.83	1.49	7.90	0.46	1.09	0.51	3.33

The lifetime risk of ever having experienced each chronic complication in the standard of care group in the company model

CKD	PH	Avasculer	HF	Neuro	Post stroke	Ret	Liver
35.99%	24.76%	53.95%	23.37%	48.25%	19.43%	28.51%	16.29%

- Are all of these complications relevant to SCD?

Yes – all are relevant to SCD but the list is not complete. I would add priapism and resultant loss of function, fat embolism, osteomyelitis (although could be covered by infection), acute multiorgan failure, the broad term of sickle hepatopathy (in its multiple forms) and potential impacts on fertility.

- How valid are the estimated incidence of these events in the economic model? Are you able to provide alternative estimates/sources?

Numbers are reasonable but does not include some significant complications

- Life expectancy:
  - What is the current life expectancy of people with SCD in the UK?

The NHR suggests that the majority of patients die during their 5th or 6th decade although significant mortality in earlier decades. However many patients accrue significant morbidity prior to death all of which feeds into costs of care. Would currently estimate that life expectancy is 10-20 years less than ethnically matched controlled populations.

- How does this vary with severity of disease and other disease characteristics?

As per above - life expectancy reduced for all patients but evidence points to the impact being increased for patients with regular VOCs (including those at home).

- What is the current life expectancy for people with SCD with recurrent vaso-occlusive crises who have the βS/βS, βS/β+ or βS/β0 genotype, for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available (i.e within the exa-cel marketing authorisation).

These are significantly different conditions ie SS and SB0 are biologically identical conditions are treated as such within most clinical studies. SB+ is highly variable depending on the severity of the B mutation and how much Hb A is produced and the presence or absence of alpha-thalassaemia trait. Again as per above markers of severity are not robust outside of Hb F and alpha thalassaemia trait and number of VOCs.

- What would you expect the population included in the CLIMB 121 trial's life expectancy to be if they had not had exa-cel?

As per above these patients would die 10-20 years younger than ethnically matched controls. There is no "good" version of sickle cell disorder and patients inevitably die of complications of the condition.

- What have you based these estimates on and are there sources you can reference for these estimates?

Published data from UK and USA:

Lubeck D, Agodoa I, Bhakta N, et al. Estimated Life Expectancy and Income of Patients With Sickle Cell Disease Compared With Those Without Sickle Cell Disease. *JAMA Netw Open.* 2019;2(11):e1915374. doi:10.1001/jamanetworkopen.2019.15374

Lanzkron S, Carroll CP, Haywood C. Mortality Rates and Age at Death from Sickle Cell Disease: U.S., 1979–2005. *Public Health Reports*. 2013;128(2):110-116. doi:10.1177/003335491312800206

Kate Gardner, Abdel Douiri, Emma Drasar, Marlene Allman, Anne Mwirigi, Moji Awogbade, Swee Lay Thein; Survival in adults with sickle cell disease in a high-income setting. *Blood* 2016; 128 (10): 1436–1438. doi: https://doi.org/10.1182/blood-2016-05-716910

Michael R. DeBaun, Djamila L. Ghafuri, Mark Rodeghier, Poulami Maitra, Shruti Chaturvedi, Adetola Kassim, Kenneth I. Ataga; Decreased median survival of adults with sickle cell disease after adjusting for left truncation bias: a pooled analysis. *Blood* 2019; 133 (6): 615–617. doi: https://doi.org/10.1182/blood-2018-10-880575

- Would you expect differences in adverse events between treatment with exa-cel and an allogenic SCT? Can you comment on the impact of these events?

The differences are based on the type of cellular therapy used and the conditioning chemotherapy which varies in the paediatric and adult patient populations.

The standard of care is a reduced intensity conditioning protocol for those with sibling donors in the adult population although a standard protocol would be used in younger patients (under 19 years of age) unless specific contraindications. The majority of patients eligible for transplant do not have appropriate donors (80%). The standard adult regime is TBI and immunosuppression based regime causing similar issues to the busulphan regime used in autologous transplant with exa-cel. Cytopenias, mucositis, risk of infections and infertility. With all chemotherapy regimes there is a risk of secondary malignancy. With regard to allogeneic transplant (sibling and haplo transplants) there is also the potential risk of graft-vs-host disease requiring longer term immunosuppression and risk of viral reactivation which are not present in the autologous setting. With allogeneic transplant there is

also potential early and late graft failure although we have limited data in this setting.

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

Clinical expert questions:

- How generalisable is the CLIMB 121 clinical trial to the population that would receive exa-cel in NHS clinical practice?

The evidence from CLIMB 1221 can safely be generalised to the UK sickle population. There is no evidence that sickle disease within the trial is phenotypically different to that of a UK SCD population. It is the same genetic disease and clinical practice is similar. The UK teams who would deliver the therapeutic pathway and aftercare will include JACIE accredited transplant teams working in conjunction with sickle expert haematologists. Although the results of stem cell transplantation for other haematological diseases are not directly generalisable it is worth pointing out the UK results are as good if not better than anywhere else in the world.

- How would people with sickle cell disease (SCD) be selected for exa-cel in the NHS if approved? If this is different to the inclusion criteria of CLIMB SCD-121, please outline how and why it would be.

In terms of appropriate case selection, national joint transplant and sickle MDTs are already in place. If gene editing were approved potential cases would be discussed in such fora to ensure consistency and collect outcomes nationally. Selection criteria would be kept in line with CLIMB 121.

- Does the absence of VOC (Vaso-occlusive crisis) translate directly in a cure? Specifically, does it mean that someone would have no acute and chronic complications?

The absence of VOC does not translate directly to cure however there is evidence that frequent VOC is a marker of severe disease and early death. Published data on survival in adults with sickle cell disease in a high-income setting (King's College Hospital, UK) in the journal Blood in 2016 illustrated that those with more frequent admission (>2 pa), related to VOC events, had a demonstrably higher risk of death, and that individuals with an apparent severe phenotype disease have a significantly reduced life expectancy with the mean age at death of 41 years. Similar poor outcomes were seen on a larger dataset composed of a decade of HES data for patients coded as having sickle cell disease in the UK and in the American Cooperative Study of Sickle Cell Disease.

A better comparator might be annualised VOC events and measures of end organ damage/function. This data takes longer to accumulate. Clear definitions of chronic organ dysfunction and ideal methods for evaluating organ function in sickle cell disease have not been established. All centres caring for patients with SCD see increasing numbers of patients with organ dysfunction, and premature death as a consequence. There are minimal data on the natural history of the later life complications of this awful disease.

- Are VOCs a predictor of complications? Does the number of VOCs influence SCD complications, or just the presence of VOCs i.e., with or without any VOCs? How strong is this association? Are other disease symptoms beyond VOCs important in determining extend of SCD severity?

The absence of reliable blood markers or other objective tests to measure the disease related damage in SCD is a problem for clinical research, investigators are forced to use severity measures related to documentable clinical events like pain. Real world evidence suggests that frequent pain and hospital admission are linked to survival but this is not the whole story. The attritional and continuous nature of the small vessel damage in SCD means that visible clinical events do not always reveal the complete picture. For example, those with very high haemolysis rates may also get chronic organ

complications with relatively little pain. With respect to the utility of gene editing in SCD and its ability to transform lives; the presence of pancellular HbF at high levels is protective for all patients as evidenced by excellent outcome in S/ hereditary persistence of foetal haemoglobin (HPFH) and the complete absence of sickle events in the first few months of life when high levels of pancellular HbF are the norm.

- What would constitute a cure in terms of outcomes? How much follow-up time post intervention would be needed to be sure in the durability of effect?

The presence of persisting pancellular HbF levels of the values seen in the trial are highly likely to constitute a cure. Post successful treatment patients with prior sickle cell disease become phenotypically similar to those with sickle/ HPFH. Individuals with SHPFH are symptom free, do not suffer chronic organ damage and are expected to have a normal life expectancy. To answer the question of "how long does follow up need to be to be assured of cure?" Current available data do not suggest any decline in effect and indeed there is no mechanism by which editing levels should wane. As this is a new treatment, patients will need to have HbF levels measured at least annually for reassurance.

- How plausible, in your clinical opinion, is treatment effect waning with exa-cel?

Encouragingly, at this stage there is no evidence of waning of the HbF level or decline of the gene editing effect at more than 3 years of follow up. There is no mechanism by which BCL11A editing should wane beyond this time.

- How would you describe the quality of life of a person with SCD following treatment with exa-cel who are VOC-free? Would other aspects of SCD impact quality of life even if VOC-free status following exa-cel treatment is achieved?

The quality of life data from the trial suggest restoration of a normal quality of life for patients post treatment, with some measures above population norms.

I do not find this surprising. Previous studies in sickle cell disease demonstrate a poor baseline quality of life with some domains showing worse results than other chronic diseases such as cystic fibrosis, asthma or end stage renal failure. This matches my personal experience in providing care for these patients over a 30+ year period. I think it unlikely that other aspects of sickle cell disease would impact adversely on quality of life post treatment.

From a lived experience point of view the plight of individuals with this disease has long been underestimated by healthcare workers and policy makers. Unlike other disease groups they do not have a strong voice nationally. The Sickle World Assessment Survey and PISCES studies (https://doi.org/10.1186%2F1477-7525-3-50) drive home the burden of this disease from a social and economic perspective.

Please see the list of acute and chronic complications below and the estimated incidence of these estimated in the economic model:

Complications included in the company model:

The overall lifetime incidence of acute complications for the standard of care group in the company model

Stroke	ACS	Infection	AKI	Gallstones	PE	Leg ulcers
0.83	1.49	7.90	0.46	1.09	0.51	3.33

The lifetime risk of ever having experienced each chronic complication in the standard of care group in the company model.

CKD	PH	Avasculer	HF	Neuro	Post stroke	Ret	Liver
35.99%	24.76%	53.95%	23.37%	48.25%	19.43%	28.51%	16.29%

- Are all of these complications relevant to SCD?

  These conditions are all relevant to SCD, indeed there are other acute and chronic complications which have not been included.

These would include priapism, erectile impotence, girdle syndrome, acute intrahepatic cholestasis, hepatic infarction and sequestration, osteomyelitis, fat embolism, acute multiorgan failure, renal papillary necrosis. This is not a complete list. I also note that chronic pain has not been mentioned though this is increasingly recognised as a significant issue by patient groups and clinical teams. Unlike many other diseases the natural history of sickle cell disease is poorly studied with scant reliable data. Our current ageing population is, after all, the first UK generation to be cared for with such a range of multiple organ specific co-morbidities.

How valid are the estimated incidence of these events in the economic model? Are you able to provide alternative estimates/sources? Evidence presented at the British Society for Haematology meeting 2023 linking primary care and hospital statistics offer comparable estimated incidences.

For the reasons outlined above the figures within the company's model are reasonable. However, I would suggest that the chronic organ risks provided are incomplete and likely to be significant underestimates.

- Life expectancy:
    - What is the current life expectancy of people with SCD in the UK?

      Data from the UK National Haemoglobinopathy Registry suggest the largest proportion of patients die during the 5th and 6th decade (though there are still significant numbers of deaths in younger patients) despite the availability of standard the interventions transfusion and hydroxycarbamide. There is likely to be significant underreporting of deaths on this database

because of the lack of administrative support for submission of details. Single centre studies are in keeping with this figure, documenting a significant reduction in life expectancy in the region of 1-2 decades compared to the general population.

- How does this vary with severity of disease and other disease characteristics?

  Those patients who present more frequently with vaso-occlusive events are at greatest risk of early death but the reality is of reduced life expectancy for every patient.

- What is the current life expectancy for people with SCD with recurrent vaso-occlusive crises who have the βS/βS, βS/β+ or βS/β0 genotype, for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available (i.e within the exa-cel marketing authorisation).

  Much of the available evidence is based on studies with SS and Sβ0 thalassaemia. These diseases should be regarded as biologically identical. Sβ+ is not a single disease, its severity depends on the β thalassaemia mutation and how much residual function that permits. Some patients have no or minimal symptoms yet others maybe clinically indistinguishable from Sβ0 thalassaemia. Life expectancy for those with recurrent vaso-occlusive events is in the 5th decade of life. I reiterate the point that reliable measures of severity are difficult to come by and all patients with the more severe genotypes will have reduced life expectancy compared to the non-sickle population. Although there may be more severe phenotype SS disease there are no good or mild types.

- What would you expect the population included in the CLIMB 121 trial's life expectancy to be if they had not had exa-cel?

Please see above.

- What have you based these estimates on and are there sources you can reference for these estimates?

  Please see the following references on life expectancy in UK and US.

  10.1182/blood-2018-10-880575

  https://doi.org/10.1182/blood-2016-05-716910

  https://doi.org/10.1177%2F0033354913128002O6

  Estimated Life Expectancy and Income of Patients With Sickle Cell Disease Compared With Those Without Sickle Cell Disease | Hematology | JAMA Network Open | JAMA Network

- Would you expect differences in adverse events between treatment with exa-cel and an allogenic SCT? Can you comment on the impact of these events?

The principle of gene editing therapy means the conditioning procedure is a form of autologous stem cell transplant (where the stem cells have undergone manipulation. The adverse events therefore are in line with autologous transplant for other diseases such as lymphoma. These are primarily the effects of conditioning chemotherapy, such as short term cytopenia, mucositis and infection risk which resolves on recovery of counts. Longer term effects of busulfan includes second malignancies. A recent analysis of large number of post-transplant recipients treated with busulfan containing regimes suggests the risk is low in paediatric populations (<0.5%) and under 5% in adults **https://doi.org/10.1002/pbc.30738**). *Busulfan usage may also lead to infertility and eligible patients will need to consider fertility preservation pre-conditioning (as they also do pre allogeneic transplant).*

Allogeneic stem cell transplantation (SCT) is a more complex pathway involving the engraftment of a new bone marrow and immune system. NHSE

approved SCT in 2020 using a form of low intensity conditioning for patients with severe sickle cell disease. Experience of this treatment is now growing in the UK though the numbers of transplanted patients are in the low teens. It is important to note that only around 20% of eligible patients will have a fully HLA matched sibling donor limiting its utility. The conditioning regime uses low dose total body irradiation (TBI) and immunosuppression to prepare the patient for the donor marrow. The effects of this conditioning are similar autologous transplant ie cytopenia, mucositis and infection risk however there are longer term risks. Like busulfan, TBI may lead to infertility or longer-term risk of bone marrow damage. After blood count recovery the patient will need to remain on immunosuppressive drugs increasing drug toxicity and infection risk, this requires monitoring of drug levels and may need to be continued long term. There is a significant risk of transplant failure in 15-20% patients in the short term and relatively short follow up means there are few data on the incidence of late graft failure.

Title: Exagamglogene autotemcel for treating sickle cell disease- additional work post-ACM1

Produced by Warwick Evidence

Authors

Jo Parsons, Assistant Professor[1]
Emanuela Castelnuovo, Senior Health Economist[1]
Naila Dracup, Information Specialist[1]
Martin Connock, Honorary Senior Research Fellow[1]
Xavier Armoiry, Honorary Senior Research Fellow and Professor of Pharmacy[1,2,3]
Amy Grove, Professor of Health Technology Assessment and Implementation Science[1]
Peter Auguste, Assistant Professor in Health Economics & Decision Modelling[1]

[1]Warwick Evidence, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, CV4 7AL
[2]Claude Bernard University Lyon, Villeurbanne 69100, France
[3]Lyon University Hospitals- Hôpital Edouard Herriot Pharmacy department, 69003 Lyon, France

Correspondence to

Mr Peter Auguste
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry, CV4 7AL.

Date completed 26/02/2024

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/60/84.

Declared competing interests of the authors

Description of any pecuniary relationship with sponsors, both personal and of the TAR Centre. If there are none, please state 'none'.

Acknowledgements

We would like to thank Professor Baba PD Inusa, consultant paediatric haematologist, King's College, London and Dr Elizabeth Rhodes, consultant haematologist, St. George's University Hospitals NHS Foundation Trust who provided clinical support. Emeritus Professor Aileen Clarke, Professor of Public Health, and Health Services research, University of Warwick who quality assessed the EAG report.

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.

This report should be referenced as follows:

Parsons J, Castelnuovo E, Dracup N, Connock M, Armoiry X, Auguste P. Exagamglogene autotemcel for treating sickle cell disease, Warwick Evidence, 2023: A Single Technology Appraisal.

Contributions of authors

Jo Parsons (Assistant Professor), Martin Connock (Honorary Senior Research Fellow), Xavier Armoiry (Honorary Senior Research Fellow and Professor) and Amy Grove (Professor) reviewed and critiqued the clinical effectiveness evidence. Martin Connock reviewed and critiqued the statistics and undertook any additional statistical analyses. Xavier Armoiry reviewed and critiqued the mixed treatment comparisons. Naila Dracup (Information Specialist) critiqued the company's searches and undertook additional searches. Emanuela Castelnuovo reviewed and critiqued the cost-effectiveness evidence and undertook additional economic analyses. Baba Inusa (Paediatric Haematologist) and Elizabeth Rhodes provided expert clinical advice. Peter Auguste (Assistant Professor) reviewed the cost-effectiveness evidence and co-ordinated the project and the report.

Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink.

Table of Contents

Table of Tables

Content of appendix

The analyses undertaken in this appendix are summarised as follows, and based on email correspondence:

1. Undertake scenarios using the committee's preferred assumptions as stated in Table 1.

2. Committee preferred assumptions + correction of utility calculation in exa-cel arm.

3. Committee preferred assumptions + correction of utility calculation in exa-cel arm + correcting ACS issue in the model to avoid double counting.

    a. With this, could you also provide an explanation in terms of what has changed in the model e.g., has the ACS complication costs and disutilities been set to 0 and are these fully captured within the VOC cost/disutilities?

Table 1: Committee's preferred assumptions

Model considerations	**Assumption**
Model structure	Alternative
SoC SMR	Company - Desai / ICER
Treatment failure	Include cost and outcomes
Baseline VOC rate	Hospitalisation VOC
Complications	Not predicted by VOCs, use Brousse severe population rates
Utilities	0.88
Adverse events	Exclude
Severity weight	1
Discount rate	3.5%

ICER, Institute for Clinical and Economic Review; SMR, standardised mortality ratio; SoC, Standard of care; VOC, vaso-occlusive crises

1.1 *Cost effectiveness results using committee's preferred assumptions*

Table 2: Deterministic base-case results, using the committee's preferred assumption

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years

Table 3: Deterministic base-case results, marginal increments using the committee's preferred assumption

Model considerations	Assumption	ICER
Base case		[redacted]
Model structure	Alternative	[redacted]
SoC SMR	Company - Desai / ICER	[redacted]
Treatment failure	Include cost and outcomes	[redacted]
Baseline VOC rate	Hospitalisation VOC	[redacted]
Complications	Not predicted by VOCs, use Brousse severe population rates	[redacted]
Utilities	0.88	[redacted]
Adverse events	Exclude	[redacted]
Severity weight	1	[redacted]
Discount rate	3.50%	[redacted]

ICER, Institute for Clinical and Economic Review; SMR, standardised mortality ratio; SoC, Standard of care; VOC, vaso-occlusive crises

1.2 *Committee preferred assumptions and correction of utility calculation in exa-cel arm*

Table 4: Deterministic base-case results, using the committee's preferred assumption and correction of utility calculations

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years							

1.3 *Committee preferred assumptions and correction of utility calculation in exa-cel arm and correcting ACS issue in the model to avoid double counting*

This scenario has been implemented setting the rates oof ACSs equal to zero. In terms of practical changes in the model, a formula sets the cell value to zero or to the company's ACS state occupancy formula when this change is activated via a drop-down menu. The original total costs and utilities calculations formulae remain as per company's implementation.

Because the death rate in the model is non-conditional, life years for both strategies remain the same. Total utilities and total costs are reduced by the proportion of ACSs in exa-cel and in SoC.

The cumulative number of ACSs in the model, before this change, was 7.4.

Table 5: Deterministic base-case results, using the committee's preferred assumption

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years							