Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende exagamglogene autotemcel (exa-cel, Casgevy) til behandling af patienter ≥ 12 år med svær seglcellesygdom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. exagamglogene autotemcel til SCD
2. Forhandlingsnotat fra Amgros vedr. exagamglogene autotemcel til SCD
3. Ansøgers endelige ansøgning vedr. exagamglogene autotemcel til SCD
4. Vedr. langtidseffekt af exa-cel, fagudvalgets forperson, Jesper Stentoft
5. Medicinrådets anvendelse af alvorlighedsprincippet

8. januar, 2025

Vertex Pharmaceuticals' kommentarer til Medicinrådets rapport om exagamglogene autotemcel (exa-cel) til behandling af svær seglcellesygdom (SCD)

Vertex Pharmaceuticals takker Medicinrådet for den grundige rapport og ønsker at gøre Rådet opmærksom på en række vigtige observationer og perspektiver.

Exa-cel er en potentiel helbredende behandling for unge patienter med en livsbegrænsende og livstruende genetisk blodsygdom

Exa-cel beskrives i EMA's evalueringsrapport som "a major therapeutic advantage" for SCD-patienter med indikationen.[1] Vi finder det derfor yderst relevant og velbegrundet at inddrage alvorlighedsprincippet i beslutningsgrundlaget for vurderingen af SCD. Som nærmere beskrevet i Vertex' kommentarer til TDT-rapporten, relaterer det sig også for SCD til alle de fem særlige tilfælde, hvor alvorlighedsprincippet kan inddrages.[2]

Livslang effekt med en ny type genterapi

Exa-cel er en ny type genterapi, hvor patienternes egne stamceller redigeres ved hjælp af CRISPR/Cas9-teknologi for at opnå en kurativ effekt. Redigeringen er irreversibel og overføres til celler, der deler sig. Vertex' kommentar til TDT-rapporten forklarer, hvorfor effekten forventes at være livslang.

Det er usandsynligt, at smerteepisoder hos nogle få exa-cel behandlede patienter i studiet er relateret til vaso-okklusion eller HbS

I undersøgelsen oplevede et lille antal exa-cel behandlede patienter episoder med akut smerte. Det er usandsynligt, at disse episoder skyldes vaso-okklusion, og de repræsenterer ikke behandlingssvigt eller manglende respons på exa-cel. I lyset af den brede definition af VOC, der bruges i studiet, betyder det, at dette uundgåeligt vil omfatte patienter, der oplever akutte smerter, der ikke er relateret til VOC.

Smertehændelser vides at forekomme efter allo-HSCT, især i det første år efter transplantation, og de er mere hyppige hos patienter med kroniske smerter/tidligere opioidforbrug og hyperalgesi. Disse hændelser ville blive karakteriseret som VOC, hvis de skete i studierne, selvom det ville være umuligt for patienter at have en VOC efter en allo-HSCT, da de ikke længere producerer røde blodlegemer, der indeholder HbS.

Varigheden af HbS post exa-cel er relateret til virkningsmekanismen af exa-cel via HbF-induktion og er ikke relateret til tilstedeværelsen af akutte smerteepisoder. Selvom HbS stadig produceres, er tilstedeværelsen af HbF ved niveauerne observeret i den kliniske undersøgelse over de HbF-niveauer, der vides at være beskyttende i SCD-HPFH. Dette er pancellulært HbF i niveauer, der er tilstrækkelige til at hæmme polymerisation af HbS og til at gøre patienten asymptomatisk.

De sundhedsøkonomiske analyser underestimerer betydeligt de besparelser, der kan opnås ved kurativ behandling af SCD

Omkostningerne til udskiftningstransfusioner i Medicinrådets hovedscenarie er baseret på en alt for lav DRG-takst. Derfor har Medicinrådet lavet en mere nøjagtig beregning ved hjælp af mikroomkostninger, der omfatter omkostninger til blod, laboratorietest,

[1] https://www.ema.europa.eu/en/documents/assessment-report/casgevy-epar-public-assessment-report_en.pdf
[2] medicinraadet.dk

sygeplejersketid, lægetid og patienttid. Omkostningerne er stadigvæk lave, da de ikke omfatter udgifter til senge eller stole på klinikken og aferese-maskinen. Beregningen af mikroomkostninger er dog betydeligt mere præcis end DRG-taksten, og vi opfordrer Medicinrådet til at inddrage de beregninger for at sikre et reelt sammenligningsgrundlag.

Rapporten præsenterer en *break-even analyse*, hvor kun omkostningerne til exa-cel og transfusioner er inkluderet. Besparelser forbundet med ikke at skulle behandle de komplikationer, som exa-cel forventes at forebygge, er ikke medtaget. Det giver ikke et retvisende billede, da disse besparelser udgør 1,7 millioner kroner (diskonteret) i Medicinrådets cost-utility analyse. Dertil kommer, som også beskrevet i forhold til TDT-rapporten de betydelige gevinster i resten af samfundet ved kurativ behandling af SCD.

Diskonteringsrenten på 3,5 % reducerer den akkumulerede livstidsværdi af exa-cel betydeligt

Det er i andre sammenhænge sat spørgsmålstegn ved brugen af en diskonteringsrate på 3,5% i evalueringer af genterapier.[3]. Umiddelbare behandlingsudgifter diskonteres ikke, mens sundhedsgevinster (QALYs) og besparelser, akkumuleret over en livstid kraftigt udvandes. Medicinrådet bør beregne med forskellige diskonteringsrenter, jf. tabel 1.

Tabel 1: Effekt af tidsdiskonteringsrente på cost-utility resultater[4]

Diskonteringsrente	ICER (Rapportens grundscenario med AIP)	[redacted]
3,5%	733 tkr	[redacted]
3% (ref. TLV Sverige)	522 tkr	[redacted]
3% for omkostninger, 1,5 % for QALYs (ref. Holland)	332 tkr	[redacted]
0%	Dominant (flere QALYs, lavere omkostninger)	[redacted]

Opsummering

Samlet set viser de kliniske data og de økonomiske analyser, at exa-cel forventes at give transformative gevinster for patienter, de danske regioner og for det danske samfund. Exa-cel adresserer meget målrettet det markant udækkede medicinske behov hos patienter med SCD og frigør samtidig mange specialistressourcer på hospitalerne.

Investeringen ved exa-cel er omkostningseffektiv og værdifuld i forhold til listeprisen, især når alvorlighedsprincippet tages i betragtning, og de mere retvisende beregninger anvendes. [redacted]

Vertex opfordrer Medicinrådet til at anbefale exa-cel som standardbehandling til berettigede SCD-patienter, som ellers ikke har adgang til kurativ behandling af deres alvorlige og livsforkortende tilstand.

[3] https://dagenspharma.dk/er-den-nuvaerende-praksis-med-diskontering-i-sundhedsoekonomisk-evaluering-misvisende/
[4] Resultat från Vertex' replikering av DMC:s cost-utility modell (micro-cost. för transfusioner)
[5] Scenarie med de mere retvisende transfusionsomkostning og 3,5% disckonteringsrente

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17.02.2025
CAF/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	26. februar 2025
Leverandør	Vertex Pharmaceuticals
Lægemiddel	Casgevy (exagamglogene autotemcel, exa-cel)
Ansøgt indikation	Exa-cel er indiceret til behandling af svær seglcellesygdom (SCD) hos patienter i alderen 12 år og ældre med tilbagevendende vaso-okklusive kriser (vaso-occlusive crises, VOC), for hvem hæmatopoietisk stamcelle (HSC)-transplantation er velegnet, og hvor et human leukocytantigen (HLA)-matchet beslægtet HSC-donor ikke er tilgængelig
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel, ATMP

Prisinformation

Casgevy vurderes til to indikationer på samme Medicinrådsmøde; beta-talassæmi og seglcelleanæmi. Amgros har forhandlet følgende pris på Casgevy (exagamglogene autotemcel, exa-cel):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	AIP (DKK)	Tidligere forhandlet SAIP (DKK)	Tidligere forhandlet rabat ift. AIP	Ny forhandlet SAIP (DKK)	Ny forhandlet rabat ift. AIP
Casgevy	3 x 106 CD34+ celler/kg (minimum sdosis)	14.130.300	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling til begge indikationer.

Aftaleforhold

Amgros vil indgå en aftale med leverandøren, hvis Medicinrådet anbefaler Casgevy til begge ansøgte indikationer, som behandles på samme møde i Medicinrådet. Aftalen er baseret på Amgros' standardaftale for ATMP'er, der rummer forhold for bl.a. logistik flow, persondata og kvalitet. Aftalen vil gælde hurtigst muligt efter Medicinrådets anbefaling, når disse forhold er forhandlet på plads. Amgros forventer, at aftalen kan starte senest den 01.05.2025 og gælde 4 år frem. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence på området.

Casgevy er en engangsbehandling, og lægemiddeludgiften ses i tabel 1.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Endnu ikke ansøgt	
England	Anbefalet	Link til anbefaling
Sverige	Endnu ikke ansøgt	

Opsummering

[redacted]

Application for the assessment of Casgevy™ in the treatment of severe sickle cell disease

Contact information

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Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
	Unpublished information

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AAAPT	ACTTION-APS-AAPM Acute Pain Taxonomy
AAV	Adeno-associated virus
ACS	acute chest syndrome
AE	Adverse event
AIC	Akaike information criterion
AIP	Pharmacy purchase price [Apotekets inköpspris]
ASCQ-Me	Adult Sickle Cell Quality of Life Measurement Information System
ASCT	Adult Sickle Cell Quality
ASH	American Society of Haematology
ATC	Anatomical Therapeutic Chemical
BEGR	Medicines only to be dispensed to hospitals
BIC	Bayesian Information Criterion
BIM	Budget impact model
BMD	Bone Mineral Density
BMJ	British medical journal
BMT	Bone marrow transplantation
BOI	Burden of illness
BP	Body pain
BPI	Brief Pain Inventory - Short Form
BSH	British Society for Haematology
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CI	Confidence interval
CIC	Cardiac iron content
CKD	chronic kidney disease
CPRD	Clinical Practice Research Datalink
CNS	Central nervous system
COI	Cost-of illness
CRIPSR	Clustered regularly interspaced short palindromic repeats
CSF	Colony stimulating factor
CTCAE	Common Terminology Criteria for Adverse Events
CUA	Cost utility analysis
DALY	Disability-adjusted life years
DCEA	Distributional cost-effectiveness analysis
DDD	Domain-Driven Design
DEXA	Dual-energy X-ray absorptiometry
DFO	Desferrioxamine
DFP	Deferiprone
DFX	Deferasirox
DHTR	Delayed hemolytic transfusion reaction
DICE	Discretely integrated condition event
DK	Denmark
DKK	Danish Kronor
DMC	Danish Medicines Council
DNA	Deoxyribonucleic acid
DRG	Diagnosis related groups
DSA	Deterministic sensitivity analysis
EBMT	European Society for Blood and Marrow Transplantation
ED	Emergency department
EHA	European Haematology Association
EMA	European Medicines Agency
EMBASE	Excerpta medica Database
ENERCA	European Network for Rare and Congenital Anaemias
ERG	Evidence Review Group
EPAR	European public assessment report
EQ-5D-5L	EuroQoL Quality of Life Scale – 5 dimensions – 5 levels of severity
EQ-5D-Y	EuroQoL Quality of Life Scale – 5 dimensions - youth
ER	Emergency room
EU	European Union
EXA	Exagamglogene
FACT	Flexible Assertive Community Treatment
FAS	Full analysis set
FDA	Food and Drug Administration
FLACC	Face, Legs, Activity, Cry, Consolability
GBP	Pound sterling
G CSF	Granulocyte-colony stimulating factor
GPs	General practitioners

GVHD	Graft versus host disease,
HAS	[Haute Autorité de santé] French National Authority for Health
Hb	Haemoglobin
HbA	Adult haemoglobin
HbF	Foetal haemoglobin
HCC	Hepatocellular carcinoma
HCRU	Health care resource utilization
HEOR	Health economics and outcomes research
HLA	Human leukocyte antigen
HLH	Hemophagocytic lymphohistiocytosis
HPFH	Hereditary persistence of fetal hemoglobin
HRQOL	Health-related quality of life
HRU	Health care ressource utilisation
HSC	Hematopoietic stem cell
HSCT	Haematopoietic stem cell transplant
HSUV	Health state utility values
HSV	Health state values
HTA	Health technology assessment
HUI3	Health utilities index mark 3
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
ICT	Iron chelation therapy
IMD	Index of Material Deprivation
INAHTA	International Network Association of Health Technology Assessment
IPD	Individual participant data
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intre venous
KSA	Kingdom of Saudi Arabia
LDH	lactate dehydrogenase
LFI	Late fatal infection
LIC	Liver iron concentration
LOSC	Low burden (O- and SC-ICT)
LSC	Low burden (SC-ICT)
LY	Life years
LYG	Life years gained
MAA	Marketing Authorisation Application
MAIC	Matching-adjusted indirect comparison
MCID	Minimal clinically important difference
MESH	Medical Subject Headings
MRI	Magnetic resonance images
MUD	Matched unrelated donor
NBS	Medicines only to be dispensed to hospitals or prescribed by specialist
NHS	National Health Service
NIC	National Informatics Centre
NICE	National Institute for Health and Care Excellence
NR	Not reported
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drugs
NTDT	Non-transfusion-dependent thalassemias
OR	Odds ratio
PES	Primary efficacy set
PICO	Patient, intervention, comparator, outcomes
PRIME	PRIority Medicines
PRO	Patient reported outcomes
PSA	Probability sensitivity analysis
PSSRU	Personal Social Services Research Unit
PT	Patient
QALE	Quality adjusted life expectancy
QALY	Quality adjusted life years
QC	Quality control
RBC	Red blood cell
RBCT	Red blood cell transfusion
RBCX	Red blood cell exchange
RCGP	Royal College of General Practitioners
RCT	Randomized controlled trial
RNA	Ribonucleic acid
RR	Rate ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SCD	Sickle cell disease

SCPC	sickle cell-related pain crises
SD	Standard deviation
SE	Standard error
SF	Serum ferritin
SF-36/12	Standard form 36/12
SII	Slope index of inequality
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SOC	Standard of care
STA	Single technology assessment
TAFE	Technical and further education
TBA	To be added
TCD	transcranial Doppler
TDT	Transfusion-dependent β-thalassemia
TI	Transfusion independent
TIF	Thalassemia International Federation
TRM	Transplant-related mortality
TTO	Time trade off
UK	United Kingdom
VAS	Visual analogue scale
VOC	Vaso-occlusive crisis
VOD	Veno-occlusive liver disease
VT	Vitality
WBC	White blood cell
WTP	Willingness to pay
XO	Xanthine oxidase

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Casgevy™
Generic name	Exagamglogene autotemcel (exa-cel)
Therapeutic indication as defined by EMA	The treatment of severe SCD in patients 12 years of age and older with recurrent vaso-occlusive crisis (VOC) who have the βS/βS, βS/β+ or βS/β0 genotype, for whom hematopoietic stem cell transplant (HSCT) is appropriate and for whom a human leukocyte antigen (HLA) -matched related hematopoietic stem cell donor is not available (1)
Marketing authorization holder in Denmark	Vertex Pharmaceuticals (Ireland) Limited Unit 49, Block F2, Northwood Court, Santry, Dublin 9, D09 T665, Ireland
ATC code	B06AX05
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	Approved on February 13th, 2024
Has the pharmaceutical received a conditional marketing authorization?	Yes, see Summary of Product Characteristics, section E
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, exa-cel was designated as an orphan medicinal product on 9 January 2020 for the treatment of SCD.
Other therapeutic indications approved by EMA	Exa-cel is also approved for the treatment of transfusion dependent β thalassemia (TDT) in patients 12 years of age and older for whom a hematopoietic stem cell transplant (HSCT) is appropriate and for whom a human leukocyte antigen (HLA) matched related hematopoietic stem cell (HSC) donor is not available
Other indications that have been evaluated by the DMC (yes/no)	No

Overview of the pharmaceutical	
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Exa-cel is a semi-transparent dispersion for infusion. Casgevy is supplied in vials containing 1.5 mL to 20 mL. One or more vials are packed in a carton. One carton may contain up to 9 vials. The number of vials is specific to each patient's dose. Each vial contains 4 to 13 × 106 cells/mL suspended in cryopreservative medium. Each vial contains 1.5 to 20 mL of exa-cel.

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Exa-cel is indicated for the treatment of severe SCD in patients 12 years of age and older with recurrent VOCs for whom HSC transplantation is appropriate and a HLA-matched related HSC donor is not available
Dosage regiment and administration	Casgevy is intended for autologous use. Treatment consists of a single dose containing a dispersion for infusion of viable CD34+ cells in one or more vials. The minimum recommended dose of Casgevy is 3 × 106 CD34+ cells/kg of body weight. The lot information sheet (LIS) provides additional information pertaining to dose.
Choice of comparator	The SCD patients in scope for this assessment are currently treated with standard of care (SOC) including hydroxyurea (HU), red blood cell (RBC) exchange transfusions, and pain management to prevent and manage acute and chronic complications.
Prognosis with current treatment (comparator)	Life expectancy for patients with SCD is reduced by over 30 years compared to that of the general population underscoring the morbidity and mortality associated with SCD. The mean age of death (standard deviation [SD]) for patients with SCD with recurrent VOCs in England was 40.17 years (14.09), which is >40 years lower than the modal age of death for the general population in the UK (females: 89.3 years; males: 87.1 years) (2, 3).
Type of evidence for the clinical evaluation	CLIMB SCD-121 (NCT03745287) in severe SCD. This is a single-arm, open-label, multi-site, single-dose Phase 1/2/3 study in subjects with severe SCD. The study evaluates the safety and efficacy of autologous CRISPR-Cas9 Modified CD34+ human hematopoietic stem and progenitor cells (hHSPCs) using CTX001. Patients enrolled in CLIMB SCD-121 are eligible to roll over into long-term follow-up Study CTX001-131, evaluating the long-term safety following exa-cel infusion for up to 15 years.
Most important efficacy endpoints (Difference/gain	In an interim analysis, 28 of 29 patients (96.6%) achieved the primary endpoint defined as being free of severe VOCs for at least 12 consecutive months. 29 of 29 patients (100%) achieved the key secondary endpoint of being free from inpatient hospitalisations due to severe VOCs.

Summary	
compared to comparator)	Before treatment with exa-cel, the 29 patients had on average 3.9 severe VOCs per year, and 2.7 inpatient hospitalisations for severe VOCs per year.
Most important serious adverse events for the intervention and comparator	No patients in the clinical trial experienced SAEs related to exa-cel. However, some experienced SAEs are related or possibly related to busulfan. The type and incidence of SAEs were consistent with that anticipated due to myeloablative conditioning, autologous HSCT, and the underlying disease.
Impact on health-related quality of life	The primary outcomes in the studies relate strongly to patients' HRQOL as VOCs cause pain that is often severe and deliberating. In terms of patient reported outcomes., [redacted]
Type of economic analysis that is submitted	Markov model
Data sources used to model the clinical effects	CLIMB-121 trial
Data sources used to model the health-related quality of life	CLIMB-121 trial
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs (DKK)	[redacted]
ICER (DKK/QALY)	123 628 (discount rate 3.5%), dominant (discount rate 1.5%), dominant (undiscounted)
Uncertainty associated with the ICER estimate	[redacted]
Number of eligible patients in Denmark	[redacted]
Budget impact (in year 5) (DKK)	[redacted]

Abbreviations: VOC = vaso-occlusive crisis; HSCT = hematopoietic stem cell transplant; HLA = human leukocyte antigen; HSC = hematopoietic stem cell; ICT = iron chelation therapy; SAE= serious adverse events; RDC = red blood cell; ICER = incremental cost-effectiveness ratio; SoC = standard of care; QALY = quality adjusted life years

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

In 2016, the DMC was mandated by the Board of Directors of the Danish Regions to include severity of disease in the decision making of recommendations for pharmaceuticals. In this way, the DMC can accept a greater willingness to pay for patient groups that have worse health based on a consideration that this has higher moral value. The DMC has suggested five different situations where it may be appropriate to include severity in the decision making process (4). These are listed in below, along with a description of how they relate to exa-cel for the treatment of SCD in Denmark.

Situation	Relevance for exa-cel for the treatment of TDT in Denmark
The intervention is aimed at children and young adults (0-25 years)	The pool of eligible patients is currently mixed in age but it is expected that the majority is below 25 years of age. After five years it is expected that the incident patients are all treated in early adolescence.
The intervention provides a functional cure for a disease associated with premature death	SCD with recurrent vaso-occlusive crises is associated with premature mortality. The life-expectancy is approximately 40 years, which is 40 years shorter than in the general population (see section 3.1.2.6)
The intervention prevents or modifies chronic disability or other symptoms that are life limiting and can provide a functional cure	Exa-cel was developed as a one-time treatment leading to a functional cure. As shown in the clinical trial program, exa-cel is effective in making SCD patients free of vaso-occlusive crises (see section 6), which in turn prevents severe SCD-related chronic complications (see 3.1.2.2)
The intervention targets a severe, chronic disease	SCD is a severe, chronic disease characterised by disability due to episodes of intense pain, severe chronic complications and premature mortality (see section 3.1.2)
The intervention is the only disease modifying treatment providing a functional cure	Exa-cel is the only potentially curative treatment available for SCD patients for whom HSCT is appropriate and for whom an HLA-matched related hematopoietic stem cell donor is not available.

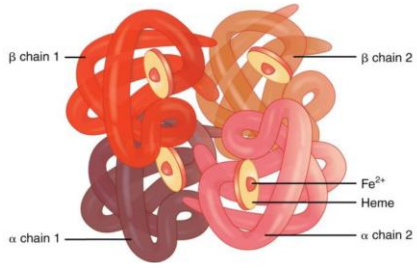
Abbreviations: TDT = Transfusion-dependent thalassemia, A form of β--thalassemia in which patients require lifelong regular blood transfusions to survive; HSCT = hematopoietic stem cell transplant; HLA = human leukocyte antigen; HSC = hematopoietic stem cell
Source: (4)

3.1 The medical condition

3.1.1 Aetiology and pathophysiology

Haemoglobin (Hb) is a tetrameric protein, composed of four globin subunits, each associated with a haem group which contains one iron atom that can bind to an oxygen molecule (Figure 1). Different combinations of globin subunits give rise to multiple types of Hb, which predominate at different stages of life (embryonic, foetal, and adult). The predominant Hb type in adults is haemoglobin A (HbA) (5).

Figure 1. Molecular structure of haemoglobin A



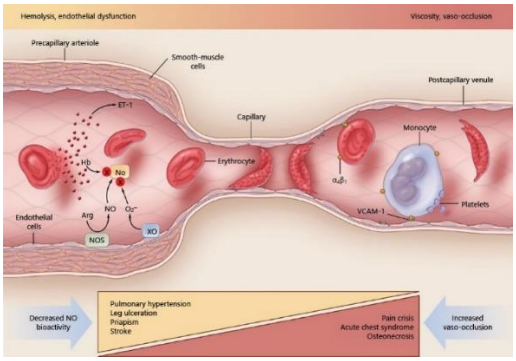
Abbreviations: Fe^{2+} = iron
Source: (6)

Sickle cell disease (SCD) is an umbrella term describing a group of inherited diseases characterised by mutations in the HBB gene encoding β-globin. SCD is characterised by the expression of abnormal, sickle haemoglobin (HbS), which arises from a point mutation in the HBB gene resulting in a single amino acid substitution of glutamic acid with valine at position 6 (Glu6Val) of the β-globin subunit of HbA. Deoxygenated HbS polymerises within the red blood cells (RBCs) gives them a characteristic sickle shape from which the disease takes its name and make them rigid and fragile (5, 7). This leads to a range of acute and chronic complications.

In SCD, HbS polymerises abnormally into rod-shaped structures and, as HbS polymers extend, they deform RBCs and interfere with their flexibility, shape, and rheological and physical properties (5, 8). Vascular occlusion (vaso-occlusion) of small and large blood vessels arises due to a complex process involving increased adhesion of sickle RBCs to each other and to endothelial cells (5, 8, 9). Activated endothelial cells produce inflammatory mediators, leading to a chronic inflammatory state (5). As a result, sickle RBCs, neutrophils, and platelets become more adhesive, causing obstruction of small blood vessels, blocking blood flow to tissues, and resulting in severe pain and organ infarction (5) (Figure 2).

Haemolysis is another mechanism contributing to the pathology of SCD and occurs as a result of the damage and dysfunction of the RBC membrane (5, 8). Sickle erythrocytes are highly unstable with a median survival that is shortened by 50 – 85% compared to normal erythrocytes, which have a lifespan of approximately 120 days (10). Intravascular haemolysis releases the contents of a RBC, including nitric oxide, into plasma. Free Hb released from damaged RBCs scavenges nitric oxide, resulting in further vascular injury and endothelial dysfunction (5) (Figure 2). The normal shape of the RBC can be restored through reoxygenation, breaking down the HbS polymer. This prompts a perpetuating cycle of sickling and unsickling that adversely affects the RBC membrane and ultimately leads to haemolysis (7).

Figure 2: Vaso-occlusion and haemolysis in the pathology of SCD



Abbreviations: Arg = arginine; ET-1 = endothelin-1; Hb = haemoglobin; NO = nitric oxide; NOS = nitric oxide synthase; O2–= superoxide; XO = xanthine oxidase; VCAM-1 = vascular-cell adhesion molecule 1.
Source: (9)

3.1.2 Symptoms and clinical manifestations

3.1.2.1 Clinical burden of VOCs

Vaso-occlusion crises (VOCs) are a hallmark clinical feature of SCD, manifesting as the abrupt onset of severe, acute, and debilitating pain (7, 11, 12, 13). VOCs that cause intense pain often require medical interventions at the emergency room and long-term hospitalisations are not unusual (11). VOCs are indirectly linked to end-organ damage and early mortality.

VOCs are experienced by patients with SCD due to the cycle of blood vessel occlusion, impaired oxygen supply, and tissue injury from infarction and reperfusion (7, 8, 14, 15). These events are often accompanied by acute onset of severe pain that commonly manifests in the extremities, chest, and back, as dactylitis (severe pain of the hands and feet), or as priapism, i.e. painful erection that lasts for hours without sexual stimuli (see section 3.1.2.4) (7, 16).

The frequency of pain crises varies considerably among patients, with some patients having more frequent and severe pain and others having a relatively low frequency of pain (17). VOCs can start in childhood and are a common initial symptom leading to diagnosis in children not diagnosed through newborn screening (18). VOCs can be triggered by illness, dehydration, stress, wind speed, or pain itself; however, they may also occur unpredictably and without warning (11, 17, 19). VOCs may also occur on the background of progressively diminishing vital organ function (15).

VOCs may present as pain crises alone but may also be associated with additional complications. In a US analysis of Medicaid Analytic Extracts database capturing 8,521 adults with SCD, as many as 22,631 (29.7%) of 76,154 VOCs captured in the study were associated with concomitant comorbidities, such as infections, fever, pulmonary disorders, cerebrovascular conditions, and thrombosis (20). A recent systematic literature review (SLR) of global real-world evidence reported a mean or median frequency of VOCs that varied from 0 to 18.2 episodes per year (based on 33 studies) (21). However, it should be noted that the definitions of a VOC varied between individual studies (21).

3.1.2.2 VOC impact on complications

An analysis of the UK Hospital Episodes Statistics (HES) database reported an association between the frequency of VOCs and the risk of several other SCD complications (22). The risk of priapism, osteomyelitis, and acute chest syndrome (ACS) were increased ≥5-fold in SCD patients experiencing ≥3 VOCs in the past year compared with those experiencing no VOCs (22). 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 SCD patients with ≥3 VOCs in the past year compared with those experiencing no VOCs (22).

Acute and chronic complication rates were also higher in patients with SCD with recurrent VOCs than in matched controls. The most common acute complications that patients with SCD with recurrent VOCs experienced (mean rate per patient per year [PPPY]) were gallstones (0.29), leg ulcers (0.26), infections (0.20), and acute renal failure (0.13), while the most prevalent chronic complications were cardiopulmonary complications (30.2%), bone and joint problems (25.8%), and retinal disorders/retinopathy (18.5%). Subgroup analyses revealed that older age, a higher number of VOCs in the follow-up period, and receiving a transfusion in the 2-year baseline period were associated with higher mortality and complication rates. Receipt of transfusions at baseline was, however, likely an indicator of recurrent VOCs or end-organ damage, given there are currently no other effective treatments for this patient group (23).

3.1.2.3 Acute chest syndrome

ACS is an acute pulmonary complication of VOCs that occurs in SCD patients and a major cause of morbidity and mortality that requires immediate intervention regardless of the patient's age. ACS is characterised by the presence of a new pulmonary infiltrate and is associated with pneumonia-like symptoms, pain, or fever (8). ACS is a frequent cause of acute lung disease in children with SCD, and may be an initial diagnosis at presentation to the hospital or may develop during a hospitalisation for a VOC (24). ACS may progress very rapidly, worsening within 24 hours from mild hypoxemia to acute respiratory failure (24). Notably, 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 (25). Further, 18 (3%) patients died, mostly from bronchopneumonia and pulmonary emboli (6 cases each) and infection was a contributing factor in 56% of the deaths (25). 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 (26).

Several risk factors for the development of ACS have been identified, including: young age, low HbF, high steady-state Hb, high steady-state white blood cell count, severe genotype (defined as HbSS and HbSβ0), >3 severe VOCs in the preceding year, asthma or airway hyperreactivity, tobacco smoke exposure, and recent surgery (24).

In terms of direct causes of ACS, three major precipitating events have been identified: pulmonary infection, embolisation of bone marrow fat, and intravascular pulmonary sequestration of sickled erythrocytes, resulting in lung injury and infarction (9). ACS is relatively common. In a SLR and meta-analysis of 8 cohort studies, pooled ACS incidence in children with SCD was 12.55 (95% CI: 7.70–17.41) per 100 patient-years (27). Among adults, an analysis of the UK HES database reported that 27% of 15,076 SCD patients

experienced an ACS event (28). In a German study of statutory health insurance claims data in patients with SCD, the incidence of ACS was reported at 82 per 1,000 patient-years in 2019 (29).

3.1.2.4 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 stimulus (30). The pathophysiology of priapism in SCD has been linked to the severity of intravascular haemolysis (31). Due to its character painful priapism is categorised as a VOC in the relevant clinical trials (see sections 5.1.1., 5.1.2 and 5.1.4.).

3.1.2.5 Splenic sequestration

Splenic sequestration is a complication of SCD that predominantly affects young children (32). In children with SCD, the abnormal sickle RBCs become trapped in the spleen (32). Typically, this self-resolves or results in the formation of isolated areas of congestion and fibrosis (32). With repeated episodes of auto infarction and scarring, the spleen in children with SCD gradually loses function and decreases in size (32). Resulting functional asplenia leaves patients at risk for life-threatening infections, including pneumonia, sepsis, and meningitis (7). However, in some cases, the obstruction of the spleen spreads, causing the spleen to rapidly fill with RBCs and a large percentage of the blood volume to become trapped in the spleen, leading to a sequestration crisis (32).

Acute splenic sequestration is characterised by a rapid swelling of the spleen and a sudden decrease in Hb levels and is a leading cause of mortality in infants with SCD (5). Immediate management of splenic sequestration crises usually involves restoring the circulating blood volume with RBC transfusions and potentially intravenous fluids (32). However, 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 (32). Due to its severe character, splenic sequestration is categorised as a VOC in the relevant clinical trials (see sections 5.1.1., 5.1.2 and 5.1.4.).

3.1.2.6 Mortality

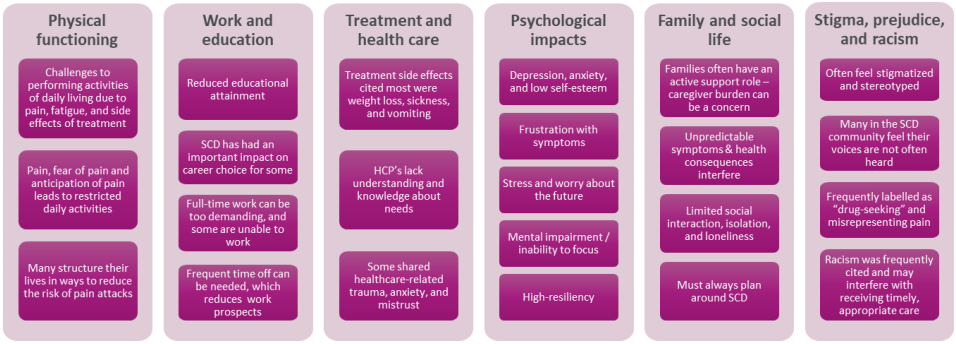
Although survival estimates have improved over the last few decades, life expectancy for patients with SCD is reduced by over 30 years compared to that of the general population (2, 3), underscoring the morbidity and mortality associated with SCD. The mean age of death (standard deviation [SD]) for patients with SCD with recurrent VOCs in England was 40.17 years (14.09), which is >40 years lower than the modal age of death for the general population in the Denmark (females: 83.4 years; males: 79.6 years) (23, 33). Importantly, severe VOCs are a marker of SCD severity and pose a risk of premature mortality (34). A recent analysis of the UK Clinical Practice Research Datalink (CPRD) linked to the HES databases further substantiated the association between VOC frequency and mortality, as well as the risk of acute and chronic complications. Compared with controls matched on age, sex, geographic region of general practice, and ethnicity, patients with SCD with recurrent VOCs (defined as ≥2 VOCs over two consecutive years; mean of 5.84 VOCs PPPY) had significantly higher mortality (0.16 per 100 person-years [PY] in controls vs. 0.78 per 100 PY in SCD patients with recurrent VOCs) (23). VOCs requiring an emergency room [ER] visit or hospitalisation are also a risk factor for premature mortality. In a prospective study of 264 US adults with SCD from the Bethesda Sickle Cell Cohort Study, the risk of death

was significantly higher in patients with ≥1 VOC requiring hospital admission or ER visit than in those with no such VOC events. Median age at death was 55.8 years in those with ≥1 VOC requiring hospital admission or ER visit, compared with 66.2 years in those with no VOCs requiring no hospitalizations or ER visits (34).

3.1.2.7 Health related quality of life

Patients with SCD have substantially impaired health-related quality of life (HRQoL). In a cross-sectional online survey of US patients with SCD, the estimated utility derived from the EQ-5D-5L was 0.733 (95% CI: 0.713 to 0.753) for US SCD patients with long-term organ damage and 0.775 (95% CI: 0.725 to 0.826) for those with ≥1 ER admission in the past year with no organ damage (35). In comparison, US general population utility has been estimated at 0.851 (95% CI: 0.839 to 0.863) (36). SCD severely impairs all aspects of HRQoL, including physical, mental, and social functioning. Patients with SCD report impaired HRQoL related to physical wellbeing, with the physical functioning domain being worse than or comparable to that of patients with other chronic diseases or cancer (37). Patient perspectives on SCD clearly reflect the generalised, profound adverse impact of SCD and the degree to which it affects their lives (38, 39, 40). The disease is highly unpredictable, and the symptoms occurring "without rhyme or reason" severely limit patients in their daily functioning (39, 40). In a series of interviews and focus group discussions conducted by QC Medica for Vertex, patients reported the disease to impact almost all aspects of daily life (40). Notable concepts mentioned in these discussions are illustrated in Figure 3.

Figure 3: Summary of the impact of SCD on patient lives



Source: (41)

3.1.2.8 Impact of SCD on caregivers

Qualitative interviews conducted in the US with 8 matched patient and caregiver pairs revealed that patients and caregivers alike worry about progressive physical limitations, organ damage, and death, especially as the patients were approaching the average life expectancy for people with SCD, i.e. >30 years reduced compared to the general population (see section 3.1.2.6) (42). While patients and caregivers differed in the perception of care that the caregivers provide, the caregivers described the issue of balancing patients' independence with their limitations related to SCD (42). Caregivers of children with SCD have been shown to have a lower quality of life compared with the general population (43). The impact of SCD on the wider family, particularly children of SCD patients, is also notable with caregivers of SCD patients balancing caring for their spouse and their children (42) and the children themselves struggling to understand the nature of SCD and potentially facing bullying from their peers related to their parent's condition (40).

3.1.3 Diagnosis of SCD

Denmark has implemented a national screening programme for haemoglobinopathies which is integrated in the Danish Health Authorities recommendations for pregnancy care (44). Genetic counselling programs play a great role in preventing the disease (45). The screening programme focuses on the antenatal detection of parental carrier status, including screening for α- and β-thalassaemia and haemoglobin (Hb) S, C, E, D, H and O-Arab. The programme targets women with ethnic origins in high-risk countries (defined as a prevalence of haemoglobinopathies ≥1%) during their first pregnancy. In Denmark, where antenatal care is managed primarily by general practitioners (GPs) and community midwives, the screening programme for haemoglobinopathies relies on GPs identifying women's ethnic origins already in family planning care preconception or at their first antenatal visit (44). This effort is driven by potential disease severity along with cost-effectiveness due to high treatment costs for society and families (46, 47). Regrettably, only a third of Denmark's target population receives screening, leaving a significant proportion without such choice (48).

3.2 Patient population

Globally, an estimated 5.7 million people were living with SCD in 2019, corresponding to 0.08% of the world population (49). Due to the protection against severe malaria associated with the sickle cell trait, SCD prevalence is high in regions where malaria is endemic, including sub-Saharan Africa, the Mediterranean, the Middle East, and India (3, 49, 50). However, historical and current migration patterns have broadened the global distribution of SCD (3). In 2019, SCD was estimated to affect less than 2 in 10,000 people across the European Union (EU) and thereby falls below the ceiling for orphan designation used by the European Medicines Agency (EMA) of 5 in 10,000 people (51).

Dr. Andreas Glenthøj, Head of the Danish Centre for Hemoglobinopathies at Rigshospitalet, has reported that in 2023 there were approximately 120 patients with a diagnosis of SCD in Denmark. Despite treatment with hydroxyurea (HU) and/or red blood cell exchange (RBCX) around [redacted] patients are suffering from ≥2 VOCs per year and around [redacted] of these patients are sufficiently fit for hematopoietic stem-cell transplantation (HSCT) but there is no available human leukocyte antigens (HLA) matched donor available (52).

Table 1. Incidence and prevalence of patients eligible for exa-cel in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prevalence in Denmark	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Global prevalence	Approx. 100 000				

Note: Global estimated prevalence of patients with the βS/βS, βS/β+ or βS/β0 genotype, and ≥2 VOCs per year is based on data from the United States, United Kingdom, France, Germany, Italy, KSA, Canada, Belgium, Netherlands, Spain, Greece, Switzerland, Austria, and Denmark. Local prevalence is estimated based on clinical expert.
Source: (52, 53)

The estimated number of patients expected to be treated with exa-cel in the coming 5 years are included in the table below. The total number of patients across the 5 years

sums to [redacted] and are based on assumptions of no access restrictions from a financial or capacity perspective.

Table 2. Estimated number of SCD patients expected to be treated with exa-cel in the coming 5 years

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Estimated number of patients with the βS/βS, βS/β+ or βS/β0 genotype, and ≥2 VOCs per year where a HLA-matched related hematopoietic stem cell donor is not available
Source: (52)

3.3 Current treatment options

In Denmark, the Dansk Pædriatisk Selskab has issued general treatment guidelines and recommendations for monitoring, and treatment of acute and chronic SCD-related complications (54). Hematopoietic stem cell transplantation (HSCT) is the only potentially curative treatment option but is not an option for the SCD patients in scope for this evaluation as they don't have an available matched related HLA-matched donor. The indication for HSCT depends on symptoms and complications, as well as the availability of a matched donor. When HSCT is indicated, a family investigation is started, including HLA typing of parents and siblings. If a matched family donor isn't identified, a request for a matched unrelated donor (MUD) can be considered (54). Haplo-identical bone-marrow transplants are sometimes considered, but are very rarely performed in Denmark due to the associated risks for graft complications and are not seen as a preferred pathway (55).

Standard of care (SOC) is the only treatment option for SCD patients with recurrent VOC for whom an HSCT is appropriate but can't be performed as there is no available HLA-matched related donor. SOC consists of hydroxyurea (HU), red blood cell (RBC) transfusions and iron chelation therapy (ICT). SOC can ameliorate some complications of the disease but are often unsuccessful in completely preventing them, and despite treatment with SOC, patients still experience frequent VOCs (5, 56, 57, 58). Although not relevant as a treatment option in Denmark, Voxelotor should be mentioned as it is approved by EMA. Voxelotor does not address the underlying cause of the disease (59) and is not used or recommended as standard treatment in Denmark (52).

Most SCD patients need only occasional transfusions, but patients with severe SCD and recurrent VOCs receive several planned exchange transfusions per year (52). Transfusions come with a risk of iron overload, alloimmunisation, and delayed haemolytic transfusion reactions (DHTR) (5, 7, 60). Because of this, the donor blood needs to be both genotype and phenotype matched. This requirement for perfectly matched blood combined with the large blood volumes needed for every exchange transfusion makes the identification and mobilisation of blood donors very challenging and resource demanding. In case of iron excess due to frequent transfusions, treatment with deferoxamine, deferiprone or deferasirox is used., ICT should start if P-ferritin is persistently above 1500 μg/L (54).

Treatment of VOCs includes paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). If the pain cannot be alleviated with these, hospitalisation and treatment with opioids should be considered. In cases of fever or other signs of infection, antibiotic treatment with pneumococcal coverage adapted to the clinical situation should be considered and treatment for atypical bacteria could be considered in situations of

pulmonary symptoms. Low molecular weight heparin in the prophylactic dose is recommended for most adult hospitalised patients with sickle cell crisis, but there is a lack of definite evidence for this, and hence is not recommended for children with SCD. Other acute complications include fever and infections, stroke, acute anaemia, liver sequestration, acute chest syndrome, and priapism where clear treatment guidelines also exist (54).

All patients in Denmark with severe SCD are monitored at the Danish Centre for Haemoglobinopathies at Rigshospitalet, Copenhagen, which is the largest diagnostic, clinical, and research facility for rare anaemias in the Nordic countries.

3.4 The intervention

The body is capable of producing different forms of haemoglobin, with the different variants being the primary form at specific times during life (Appendix L, Section L.1). In patients with SCD, the condition presents as the body converts the production of haemoglobin from foetal haemoglobin (HbF; two alpha-globin chains, with two gamma-globin chains) to adult haemoglobin (HbA, two alpha-globin chains, with two beta-globin chains). SCD is characterised by the expression of abnormal, sickle haemoglobin (HbS) instead of HbA.

Exa-cel is a novel gene therapy representing genetically modified autologous CD34+ cell enriched population that contains human HSPCs edited by CRISPR/Cas9 at the erythroid-specific enhancer region of the *BCL11A* gene. The ultimate goal of this modification is to reactivate the expression of the gamma globin chains in erythroid precursors and red blood cells. The expression of gamma-globin makes it possible for HbF to be formed, and thus overcome the deficiency of haemoglobin. The activation of the production of the gamma globin chain takes place at the deoxyribonucleic acid (DNA) level. The CRISPR/Cas9 system consists of the combination of the Cas9 enzyme coupled to single-stranded ribonucleic acid (RNA), which serves as a conductor for the enzyme. The entire complex is capable of recognising specific DNA and binding to it. The adjustment that is then made is carried out very accurately. In this process, no unwanted other modifications to the DNA take place. The CRISPR/Cas9 system targets a specific *Enhancer* in the BCL11A gene. This adaptation leads to sustainable reactivation of the production of the gamma globin chain, which normally decreases shortly after birth (61).

Due to word limitations in the core part of the document, a schematic representation of the functioning of the CRISPR/Cas9 system is shown in Appendix L, Section L.2. The exa-cel manufacturing process is described in Appendix L, Section L.3. We highly recommend reading these sections. An overview of exa-cel is included in Table 3 below.

Table 3. Overview of intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	For the treatment of severe SCD in patients 12 years of age and older with recurrent VOCs, for whom HSCT is appropriate and for whom an HLA-matched related hematopoietic stem cell donor is not available.
Method of administration	Intravenous

Overview of intervention	
Dosing	Exa-cel is intended for autologous, one-time, single-dose intravenous use. The minimum recommended dose is 3×10^6 CD34+ cells/kg. A single dose of exa-cel is composed of one or more vials, with each vial containing 4 to 13×10^6 cells/mL suspended in cryopreservative medium. Each vial contains 1.5 to 20 mL of exa-cel.
Dosing in the health economic model (including relative dose intensity)	TBA
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Exa-cel is intended for one-time, single-dose intravenous use.
Necessary monitoring, both during administration and during the treatment period	Short-term monitoring: Standard procedures for patient management after HSCT should also be followed after exa-cel infusion. Any blood products required within 3 months from exa-cel infusion should be irradiated. While restarting iron chelation after exa-cel infusion may be necessary, the use of non-myelosuppressive iron chelators should be avoided for at least 3 months and use of myelosuppressive iron chelators for at least 6 months after exa-cel infusion. Phlebotomy can be used in lieu of iron chelation, when appropriate. The EMA label additionally stipulates that the patient's vital signs should be monitored every 30 minutes from when the first vial of exa-cel is infused until 2 hours after the last vial of exa-cel is infused.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	A single dose of exa-cel is composed of one or more vials, with each vial containing 4 to 13×10^6 cells/mL suspended in cryopreservative medium. Each vial contains 1.5 to 20 mL of exa-cel.

3.4.1 The intervention in relation to Danish clinical practice

It is expected that every patient treated with exa-cel will lead to substantial resource savings at the transfusion clinics and the blood banks in Denmark. As described in 3.3, the current SOC for patients eligible for exa-cel includes frequent RBCXT requiring large volumes of perfectly matched blood. In addition, these transfusions require access to apheresis machinery which is at high demand at the transfusion centres as these are used to treat many severe indications. It is further expected that management of acute and chronic complications of SCD will not be needed following treatment with exa-cel. Patients treated with exa-cel are expected to be followed-up on a yearly basis at the Danish Centre

for Haemoglobinopaties at Rigshospitalet, and that outcomes will be registered in the national registry.

3.5 Choice of comparator

As described in section 3.3, current SOC of SCD patients with recurrent VOCs largely relies on optimisation of HU, RBC exchange transfusions, and pain management to prevent and manage acute and chronic complications of SCD (5, 62). SOC (hydroxyurea and iron chelation therapy) is selected as comparator for the cost-effectiveness analysis as that is the only available treatment option for patients with SCD in Denmark.

Table 4. Overview of the comparator hydroxyurea

Overview of comparator	
Therapeutic indication	Indicated to reduce the frequency of recurrent, moderate-to-severe, painful sickle cell crises and the need for blood transfusions.
Method of administration	Oral
Dosing	Starting dose of 15 mg/kg/day, and usual maintenance dose is between 15-30 mg/kg/day
Dosing in the health economic model (including relative dose intensity)	Starting dose of 15 mg/kg/day, and usual maintenance dose is between 15-30 mg/kg/day. Assume patients entering the model had already achieved the lowest stable dose per product information, i.e., 15mg/kg/day.
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Use of hydroxyurea should be discontinued at least 8 weeks prior to start of mobilization and conditioning.
Necessary monitoring, both during administration and during the treatment period	No
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	100

Table 5. Overview of the comparator deferiprone (iron chelation therapy)

Overview of comparator	
Therapeutic indication	Treatment of transfusional iron overload due to sickle cell disease.
Method of administration	Oral (tablet)
Dosing	Given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight.
Dosing in the health economic model (including relative dose intensity)	A total daily dose of 75 mg/kg body weight.
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Iron chelators should be discontinued at least 7 days prior to initiation of myeloablative conditioning, due to potential interaction with the conditioning agent.
Necessary monitoring, both during administration and during the treatment period	No
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	100

3.6 Cost-effectiveness of the comparator

SCD patients with recurrent VOCs require lifelong treatment with HU, RBC transfusions and ICT. These interventions are clearly effective, but they do not fully prevent VOCs and other SCD-related complications such as priapism, osteomyelitis, and ACS. Consequently, the patients' health-related quality of life (HRQoL) is severely impaired despite SOC and the treatment burden is significant. In addition, SCD causes negative impacts on almost every aspect of patients' lives, including daily activities and psychosocial well-being (63). Regular RBCXT come with a significant treatment burden to patients and their carers who must plan their lives around the regular frequent hospital visits. SOC does not prevent

patients with severe SCD from experiencing frequent VOC that have a detrimental impact on their quality of life, and also require substantial healthcare resources to treat.

Resource utilization associated with SCD is substantial and increases in patients with high VOC burden or end-organ damage (64, 65). Based on a retrospective analysis of the US Medicaid population from 2013 to 2017, the average annual time spent receiving healthcare services was 55 to 62 days per patient for those with any end-organ damage versus 21 to 25 days per patient for those without end-organ damage (64).

Despite the above, no relevant Danish health economic evaluations of SOC or any individual components thereof (e.g. HU or ICT) have been identified.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Efficacy outcomes included in the application are listed in Table 6.

Table 6. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
VF12 [Included in CLIMB SCD-121]	≥12 consecutive months	Proportion of patients who do not experience a severe VOC for at least 12 consecutive months (VF12) following exa-cel infusion. A minimum of 12 months duration of absence of severe VOCs was robust and considered to be highly unlikely due to chance, in patients who had ≥2 severe VOCs per year in the 2 years before screening. A severe VOC is defined as any 1 of the following events: Acute pain event that requires a visit to a medical facility and administration of pain medications (opioids or IV NSAIDs) 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	Evaluated from 60 days after last RBC transfusion for post-transplant support or SCD disease management. EAC adjudicated historical VOCs (during the 2 years before screening) and on-study VOCs to ensure that the events met the study definition of a severe VOC. Historical VOCs that occurred within the 2-year period before screening, including those which may have begun just before the 2-year window and ended during the 2-year window, contributed to the determination of eligibility. Planned subgroup analyses for the primary endpoint included analyses by age at screening (≥12 to <18 and ≥18 to ≤35 years of age), genotype (βS/βS and non-βS/βS), sex, and an analysis in the subgroup of patients with ≥3 VOCs per year for

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in haemoglobin concentration of ≥2 g/dL	the prior 2 years at baseline.
HF12 [Included in CLIMB SCD-121]	≥12 consecutive months	The proportion of patients free from inpatient hospitalisation for severe VOCs for at least 12 months (HF12) following exa-cel infusion	Evaluated from 60 days after last RBC transfusion for post-transplant support or SCD disease management
Time to engraftment	From CTX001 infusion up to 2 years after CTX001 infusion	Engraftment is defined as the first day of 3 consecutive measurements of absolute neutrophil count (ANC) ≥500/µL on 3 different days without use of unmodified CD34+ cells after reaching the nadir, defined as ANC<500/µL.	
Duration of severe VOC-free in patients who have achieved VF12	From 60 days after last RBC transfusion up to 2 years after CTX001 infusion	See definition of severe VOC above (VF12)	
Patients who have achieved at least 90%, 80%, 75%, 50% reduction from baseline in annualised rate of severe VOCs for patients who did not achieve VF12	Up to 24 months starting after Month 12 post exa-cel infusion.	See definition of severe VOC above (VF12)	Descriptive summaries
Relative reduction from baseline in annualised rate of severe VOCs for patients who did not achieve VF12	Up to 24 months starting after Month 12 post exa-cel infusion	See definition of severe VOC above (VF12)	Descriptive summaries
Relative reduction from baseline in annualized rate of inpatient	Up to 24 months starting after Month 12	See definition of severe VOC above (VF12)	Descriptive summaries

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
hospitalisations for severe VOCs for patients who did not achieve HF12	post exa-cel infusion		
Relative reduction from baseline in annualised duration of inpatient hospitalisations for severe VOC for patients who did not achieve HF12	Up to 24 months starting after Month 12 post exa-cel infusion	See definition of severe VOC above (VF12)	Descriptive summaries
Proportion of patients with sustained HbF ≥20% at the time of analysis for at least 3 months, 6 months, or 12 months	Starting 60 days after last RBC transfusion for post-transplant support or SCD management	Sustained HbF means elevated levels of HbF for 3 months, 6 months or 12 months.	Corresponding two-sided 95% exact Clopper-Pearson CI.
Relative reduction from baseline in number of units of RBC transfused for SCD-related indications	Up to 24 months starting after Month 12 post exa-cel infusion	Relative reduction in reticulocyte count, indirect bilirubin, haptoglobin, lactate dehydrogenase.	Descriptive summary
HbF (g/dL and %)	From 60 days after last RBC transfusion up to 2 years after exa-cel infusion	HbF (g/dL and %)	Measured in central laboratory Summarised as continuous variables over time. Corresponding two-sided 95% exact Clopper-Pearson CI.
Hb concentration (g/dL)	From 60 days after last RBC transfusion up to 2 years after exa-cel infusion	Hb concentration (g/dL)	Summarised as continuous variables over time. Corresponding two-sided 95% exact Clopper-Pearson CI.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Changes from baseline in PROs	From 60 days after last RBC transfusion up to 2 years after exa-cel infusion	Definitions are described in section 3.7.2.5 below.	Summarised as continuous variables over time, including dimensional score and total score (if applicable)

Abbreviations: VOC = vaso-occlusive crisis; EAC= Endpoint Adjudication Committee; SCD = sickle cell disease; CI= confidence interval; HbF= fetal hemoglobin; PRO = patient reported outcomes.
* Time point for data collection used in analysis (follow up time for time-to-event measures)

3.7.2 Validity of outcomes

3.7.2.1 VOC-related outcomes

Severe VOCs have highly decremental effects on patient quality of life, and hospitalisations due to VOCs also have impacts on hospital budgets. Any decrease in VOCs and duration of hospitalisation is therefore considered of clinical importance to patients with SCD. Given the clinical relevance of VOCs, and that the VOC-related outcomes are dichotomous, defining a minimum clinical relevant difference is not meaningful.

As to the definition of VOCs in the CLIMB SCD-121 trial, this overlapped with but differed slightly from what has been used in other trials. However, in a post-hoc analysis (based on a previous data-cut), similar results were obtained when using the definition from a different trial; using the CLIMB SCD-121 definition described above, 19 out of 20 patients (95%) met the primary endpoint of freedom from severe VOCs for at least 12 consecutive months (95% CI, 75.1%, 99.9%; P<0.0001). However, when the primary endpoint was analysed using the severe vaso-occlusive event (VOE) definition from the lovotibeglogene autotemcel HGB-206 trial (66), all patients (20/20; 100.0%) were free from severe VOEs for at least 12 consecutive months (95% CI: 83.2%, 100.0%; P<0.0001) (67).

3.7.2.2 Hospitalization related outcomes

Baseline number of inpatient hospitalizations for severe VOCs are calculated on annualized number of hospitalizations for severe VOCs during the 2 years prior to most recent screening. Change (absolute change) from baseline is calculated as Post-baseline value – Baseline value. Relative change from baseline is calculated and expressed in percentage as 100%*(Post-baseline value – Baseline value)/Baseline value.

All inpatient hospitalizations for severe VOCs will be listed, from 2 years prior to enrollment to 2 years after CTX001 infusion. Proportion of subjects free from impatient hospitalization for severe VOCs sustained for at least 12 months (HF12) after CTX001 infusion will be summarized.

A subject will be considered to have met the key secondary efficacy endpoint if he/she has no inpatient hospitalizations for severe VOCs for at least 12 consecutive months. The evaluation starts 60 days after last RBC transfusion for post-transplant support or SCD disease management.

Relative change from baseline in annualized duration of hospitalization for severe VOCs up to 24 months after CTX001 infusion will be summarized. The evaluation starts 60 days after last RBC transfusion for post-transplant support or SCD disease management.

3.7.2.3 Proportion of patients with sustained HbF ≥20%

HbF levels are known to correlate with SCD symptoms. An HbF level of 20% an above is associated with a mild SCD-related symptomatology (68), whereas patients with HbF 30% and above have few, if any, SCD-related complications (69).

3.7.2.4 Hb concentration

Hb concentration is used clinically to determine the presence of anaemia, which is functionally defined as insufficient RBC mass to adequately deliver oxygen to peripheral tissues. Normal Hb concentration varies by age and sex, with a normal range for males 15 years and older ≥13.0 g/dL, and females 15 years and older ≥12.0 g/dL. Anaemia is defined as an absolute reduction in the quantity of Hb (70). Hb levels in people with SCD are typically in the range of 6 – 11 g/dL, resulting in many of the anaemia related symptoms of SCD.

3.7.2.5 PROs

3.7.2.5.1 EuroQoL questionnaires EQ-5D-5L and EQ-5D-Y

The EuroQol Questionnaires EQ-5D-5L and EQ-5D-Y consist of the EQ-5D descriptive system and the EQ VAS. The EQ-5D comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and 5 levels: no problems to extreme problems. The EQ VAS records the patient's self-rated health on a 100-point VAS, endpoints labelled "the best health you can imagine" and "the worst health you can imagine". The child-friendly EQ-5D version (EQ-5D-Y) was introduced by the EuroQol Group in 2009 as a more comprehensible instrument suitable for children and adolescents (71).

MCID for EQ-5D-5L utility scores is estimated at 0.08 points and 0.078 points, respectively for UK and US (72), and for the EQ-5D visual analogue scale (VAS) scores at 7–10 points (73).

3.7.2.5.2 FACT-BMT questionnaire

The Functional Assessment of Cancer Therapy - Bone Marrow Transplantation (FACT-BMT) questionnaire is commonly used in adult patients undergoing bone marrow transplantation and is a self-report questionnaire that includes 2 components: FACT-G which measures general physical, social, family, emotional, and functional well-being and BMTS which measures treatment-specific concerns of bone marrow transplantation. For both components, higher values indicate better health status (74).

The MCID is considered 3 to 7 points for the FACT-G (75, 76, 77, 78) and 2 to 3 points for the BMTS (78, 79).

3.7.2.5.3 PedsQL questionnaire and the PedsQL SCD module

The PedsQL is a brief, standardized, generic assessment instrument that systematically assesses patients' and parents' perceptions of HRQoL in pediatric patients with chronic health conditions using pediatric cancer as an exemplary model. The PedsQL is based on a modular approach to measuring HRQoL and consists of a 15-item core measure of global HRQoL and eight supplemental modules assessing specific symptom or treatment domains. The PedsQL was empirically derived from data collected from 291 pediatric patients with cancer and their parents at various stages of treatment (80).

The PedsQL SCD module is a disease-specific HRQoL measure that comprises nine domains: 1) Pain and Hurt (9 items), 2) Pain Impact (10 items), 3) Pain Management and Control (2 items), 4) Worry I (5 items), 5) Worry II (2 items), 6) Emotions (2 items), 7) Treatment (7 items), 8) Communication I (3 items), and 9) Communication II (3 items) (81). The items are scored on a 5-point Likert scale depending on how much of a problem they have been in the past month (range: 0 – never a problem, 4 – almost always a problem) and the scores are transformed to range between 0 and 100, with better scores indicating higher HRQoL (81). In the CLIMB SCD-121 study, the PedsQL SCD module was used in adolescents in place of the ASQ-Me, which is only validated in adults (82). Adolescent patients who initially started completing the PedsQL SCD module were requested to complete this questionnaire for the duration of the study, rather than switch to ASCQ-Me when they reach 18 years of age (82).

The MCID for PedsQL has been determined to a 4.4 change in the PedsQL 4.0 Total Scale Score for child self-report, while a 4.5 change for parent proxy-report (83).

3.7.2.5.4 Pain scale (11-point NRS)

The NRS is a one-dimensional measure of the intensity of pain in adults and adolescents. The 11-point NRS is a segmented VAS including numbers from 0 to 10, with 0 representing no pain and 10 representing worst possible pain. Each respondent in the CLIMB SCD-121 study was requested to select a whole number on the scale that reflected their pain intensity (82).

The MCID for NRS is 30% or an >1-point reduction (84).

3.7.2.5.5 ASCQ-Me

ASCQ-Me is a disease-specific HRQoL questionnaire that includes multiple domains: the physical impact of SCD (including pain, stiffness, and sleep interference), the impact of SCD on social role (family or social activities), the emotional impact of SCD (health-related anxiety and depression), the severity and frequency of pain episodes, and the SCD medical history checklist. Each score uses the same standardized scale with a mean of 50 and a SD of 10. The score of 50 represents the score of an average patient in the ASCQ-Me field test, which was conducted on 561 SCD patients with varying severity of the disease. Higher ASCQ-Me scores represent better health and scores can be readily interpreted against the benchmark score of 50 (85).

The MCID for ASCQ-Me is considered to be 5 points for all domains (86, 87).

4. Health economic analysis

4.1 Model structure

A de novo economic model was developed to assess the cost-effectiveness of exa-cel vs. SoC in Denmark for patients with SCD with recurrent VOCs who are 12 years of age and older and for whom HSCT is appropriate and a HLA-matched related haematopoietic stem cell donor is not available. In accordance with the guidance manual published by DMC, the analysis was conducted from the Danish limited societal perspective, including direct healthcare costs, patient time, and transportation costs. There is 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 (88, 89).

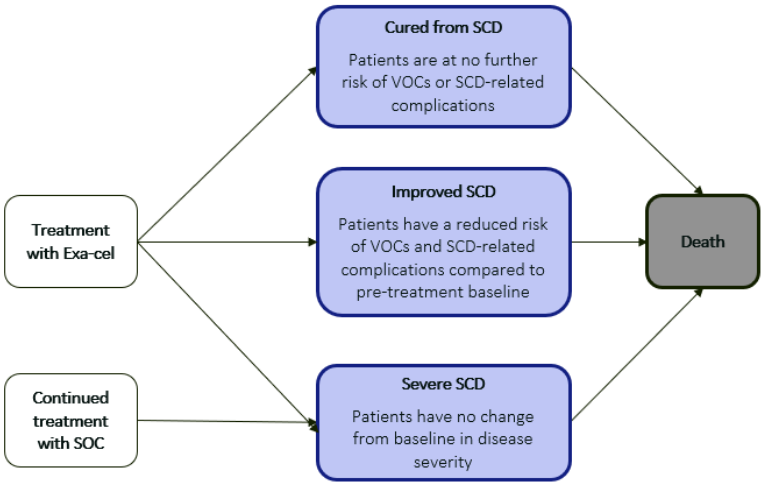
SCD is a chronic disease and is associated with increased risks of complications. The presence of complications in SCD is associated with increased mortality, decreased quality of life, and increased healthcare resource utilisation and costs. The risk of developing SCD-related complications has been shown to be correlated with the frequency of VOCs, a primary clinical outcome among SCD patients. Therefore, a Markov cohort state-transition model, driven by disease status (Cured from SCD, Improved SCD and Severe SCD) as health states, was developed to simulate the natural history and clinical pathways of SCD for the modelled patient population. A diagram of the model structure is shown below (Figure 11).

Patients in the Cured SCD health state are assumed to be at no further risk of VOCs or SCD-related complications. In patients with SCD, end-organ damage linked to complications is due to recurrent VOCs, infarction, and chronic hemolytic anemia. VOCs are directly linked to end-organ damage and early mortality. At health state where VOC=0 (Cured from SCD), no further organ damage is expected to occur and therefore complications are also expected to subside. Exa-cel does not reverse the existing end-organ damage; it is expected to eliminate the symptoms of complications associated with SCD, along with the need for ongoing symptomatic therapy (including hydroxyurea). Biomarker data from the CLIMB SCD-121 trial support the efficacy of exa-cel in preventing further progression of end-organ damage through improvements observed in all haemolysis assessments over time (for up to 24 months), including absolute reticulocyte count, indirect bilirubin, lactate dehydrogenase, and haptoglobin. Similar assumption has been accepted in HTA assessments of other curative therapies, including the NICE assessment of bet-cel in TDT.

Patients in the Improved SCD health state have a reduced risk of VOCs and SCD-related complications compared to pre-treatment baseline. Patients in the Severe SCD health state have no change from baseline in disease severity and risk of VOCs. Risk of SCD-related complications are assumed to be dependent on health state membership. The model includes both chronic and acute complications. Chronic complications are considered permanent conditions that are assumed to last until death once developed (i.e., permanent health states). The chronic complications are assumed to be independent of one another owing to the lack of evidence on joint risk or distributions across complications, therefore, patients may enter multiple chronic complication states during the modelled time horizon. Acute complications occur as transient events that are assumed to last for one month-long model cycle. The SCD-related complications included in the model were selected to represent major clinical events over the course of SCD. The

choice of complications for model inclusion were informed by those used in previous economic models of SCD, published literature and clinical expert opinion. Chronic complications included in the model are chronic kidney disease (CKD), pulmonary hypertension, avascular necrosis, heart failure, neurocognitive impairment, post-stroke, sickle retinopathy, and liver complications (5, 88, 89, 90, 91). Acute complications included in the model are stroke, ACS, acute infection, acute kidney injury or infarction, gallstones, pulmonary embolism, and leg ulcers (5, 88, 89, 91, 92).

Figure 4. Model structure



The model assumes that patients on SOC maintain the baseline frequency of VOCs throughout the model horizon as their treatment does not change. Patients treated with exa-cel have the potential to be cured and achieve a Cure state. Therefore, the model can capture the treatment efficacy of exa-cel and the comparator based on the reduced frequency or absence of VOCs and predict the impact on the development of SCD-related complications.

For exa-cel, only patients who are infused or receive the transplant 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.

Cure status can be achieved among patients with successful engraftment of stem cell therapy (i.e., exa-cel) who achieve 100% VOC absence. At the beginning of each model cycle, patients who remain alive at the end of the previous cycle and are free of chronic complications are at risk of developing the chronic complication and could transition into the corresponding chronic complication state. In each model cycle, patients are also at risk of experiencing acute complications due to SCD, which are modelled as health events occurring independently and concurrently with (or without) chronic complications. Acute complications are assumed to last for only one model cycle and not accumulate. The incidence of acute complications is determined by health state membership per model cycle.

Patients are at risk of death every model cycle. Mortality risk is estimated based on health state, accounting for occurrence of VOCs, acute and chronic complications in each health state. Quality-of-life decrements and healthcare costs associated with VOC, complications and other relevant conditions are included in the model. Other cost components include drug costs, transplant-related costs, blood transfusion and ICT costs, and disease monitoring costs. Both quality-of-life decrements and healthcare costs are aggregated over the modelled lifetime horizon.

The submitted model includes a distributional cost-effectiveness analysis (DCEA). Standard methods of CEA focus exclusively on maximizing total population health, and do not provide decision makers with information about the health inequality impacts of the interventions evaluated (93). In other words, who gains the health benefits within the population. More details may be found in Appendix G.

A lifetime horizon was used because it captures all expected costs and health outcomes of patients over their remaining lifetime following treatment initiation with exa-cel. The cycle length was 1 month. Half-cycle correction was applied to estimate occurrence of health state transitions at the middle of each cycle; however, half-cycle correction was not applied for costs incurred at model entry (e.g., transplant and pre-transplant costs for exa-cel). Annual discount rates of 3.5% and 1.5% were applied to both costs and health outcomes in two parallel base-cases. The parallel base-case with 1.5% discount rate is applied as the 3.5% level has not been validated for net-present value analyses of long-term health-outcomes. The appropriate level for discount rates in assessments of gene-therapies is debated. These interventions come with upfront investment costs that are not discounted, whilst the long-term patient health outcomes become heavily devalued in net present value analyses with high discount rates (94, 95). Consequently, a parallel base-case with a discount rate of 1.5% was considered appropriate for decision making. Furthermore, a scenario with 0% discount-rate was considered in a deterministic sensitivity analysis to further explore the impact of time-discounting.

4.2 Model features

Features of the economic model are included in the table below.

Table 7. Features of the economic model

Model features	Description	Justification
Patient population	Patients with SCD aged 12 years and older with recurrent VOCs for whom a HLA-matched related haematopoietic stem-cell donor is not available	As per the anticipated licensed indication
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (78 years)	A lifetime horizon up until max 100 years of age was selected in the base case to capture cost and outcomes associated to treatment over a patient's lifetime aligned to the methods guide. The time horizon captures all health benefits and costs in line with DMC guidelines.
Cycle length	1 month	In line with the length of treatment cycle and incidence of modelled events and outcomes.

Model features	Description	Justification
Half-cycle correction	Applied	Half-cycle correction was applied to estimate occurrence of health state transitions at the middle of each cycle; however, half-cycle correction was not applied for costs incurred at model entry (e.g., transplant and pre-transplant costs for exa-cel). An annual discount rate of 3.5% was applied to both costs and health outcomes
Discount rate	3.5% year and 1.5%	As per DMC methods guide and justification in section 4.1- the appropriateness of a discount rate of 3.5% in evaluations of gene therapies is debated (96)
Intervention	Exa-cel	Exa-cel is a genetically modified autologous CD34+ cell enriched population that contains human HSPCs edited ex vivo by CRISPR/Cas9 at the erythroid-specific enhancer region of the BCL11A gene. Exa-cel is intended for autologous, one-time, single-dose intravenous use. The minimum recommended dose is 3 × 10^6 CD34+ cells/kg.
Comparator(s)	SOC	Existing clinical management for SCD in Denmark HU/hydroxycarbamide with RBCX transfusions and ICT.
Efficacy inputs	Mean change in VOC frequency	VOC is the landmark complication of SCD and is associated with the occurrence of other complications based on literature. Mean change in VOC is available for exa-cel and comparators.
Utility inputs	Utility for cured SCD Utility for uncomplicated SCD Disutilities for transplant-related events, complications, and other clinical conditions Utility adjustment by age and gender	SCD is associated with quality-of-life decrement over the disease course
Cost inputs	Drug costs, Transplantation-related costs (mobilisation, apheresis, conditioning, and pre-transplant RBCx transfusion costs and other transplantation-	Relevant to the Danish limited societal perspective

Model features	Description	Justification
	related costs), Exchange Blood transfusions and ICT costs, Complication and other condition (infertility, and AEs) costs, Disease monitoring costs, Patient costs	
Other inputs	Cohort inputs Incidence of acute complications Risk of chronic complications Risk of other conditions Mortality	Cohort inputs (patient baseline characteristics) reflect the target population. Incidence of acute complications and risk of chronic complications were based on literature and were associated with health state based on Vertex's Burden of Illness study. Risk of other conditions (e.g., infertility and AEs) was based on literature and was associated with treatment. Mortality was informed by the national life table of Denmark and adjusted by health state.
Outcomes	Life years and QALY	In accordance with DMC guidelines.

Abbreviations: AE=adverse event; ICT = iron chelation therapy; SOC = standard of care; VOC = vaso-occlusive crisis; SCD = sickle cell disease

5. Overview of literature

5.1 Literature used for the clinical assessment

The target population for the indirect treatment comparison (ITC) was based on the population of the CLIMB SCD-121 trial and included patients aged ≥12 years who had severe SCD with recurrent VOCs. An SLR was conducted to identify studies on SCD therapies (Appendix H). To be considered in the ITC, identified studies were required to report a VOC-related outcome, include patients with ages overlapping with CLIMB SCD-121 efficacy data submitted in regulatory filings, and include five or more treated subjects.

Populations treated with SOC were identified from the SOC arms of the HOPE trial (96, 97), the SUSTAIN trial (98), and the NCT01179217 trial (99) trials. A summary of the comparator arms for the ITCs in SCD is summarised in Table 8.

Table 8. Summary of comparators considered feasible for MAICs in SCD

Comparator	Trial	Sample size	Outcomes of interest to the MAIC as reported in respective trials
SOC	HOPE (96, 97)	92	Annualized incidence of VOCs Percentage of patients who had at least 1 VOC during 24-week follow-up
SOC	SUSTAIN (98)	65	Annualized rate of VOCs Number of patients with zero VOCs at 52-week follow-up
SOC	NCT01179217 (99)	78	Number of VOCs through week 48

Abbreviations: MAIC = matching-adjusted indirect comparison; SCD = sickle cell disease; SOC = standard of care; VOC = vaso-occlusive crisis

5.1.1 CLIMB SCD-121 and CTX001-131

Data on exa-cel used in the ITC were derived from the CLIMB SCD-121 trial, an ongoing phase 1/2/3 single-arm, open-label, multi-site, single-dose study investigating the safety and efficacy of exa-cel in patients with a severe form of SCD conducted at 16 sites in the US, Canada, UK, France, Belgium, Germany, and Italy (82, 100, 101).Patients were eligible for participation in CLIMB SCD-121 if they had β^S/β^S, β^S/β^0, or β^S/β^+ genotype, were aged 12to 35 years, were considered eligible for autologous HSCT and had severe SCD defined as experiencing ≥2 VOCs per year during the past 2 years (82, 102). Patients with a 10/10 HLA-matched donor or those with a history of prior HSCT were excluded (82, 101). Please see the trial protocol (82, 102) for a full list of eligibility criteria. The primary efficacy endpoint of CLIMB SCD-121 was the proportion of patients who did not experience a severe VOC for at least 12 consecutive months (VF12) following exa-cel infusion, evaluated from 60 days after last RBC transfusion for post-transplant support or SCD disease management (82, 101). Severe VOC was defined as (82, 101):

- An acute pain event that requires a visit to a medical facility and administration of pain medications or RBC transfusions
- ACS
- Priapism lasting >2 hours and requiring a visit to a medical facility
- Splenic sequestration

The data on exa-cel efficacy used in the ITC were based on the pre-planned second interim analysis of CLIMB SCD-121 data (data cut-off 16 September 2022), at which point 35 patients were treated with exa-cel and 17 were included in the primary analysis set (PES) (100). The PES included patients who were followed for ≥16 months after exa-cel infusion and for ≥14 months after completion of RBC transfusions for post-transplant support or SCD management (100). IPD for patients in the PES were used in this ITC to be consistent with the data submitted to EMA.

CTX001-131 is a multi-center, open-label, study designed to evaluate the long-term safety and efficacy of exa-cel in patients who received exa-cel in CLIMB SCD-121 or in the CLIMB THAL-111 TDT study. All patients who complete or discontinue the parent studies after exa-cel infusion will be asked to participate in this long-term follow-up study (103).

Patients who roll over into the long-term extension study will have follow-up visits every 3 months for the first 3 years, every 6 months in years 4 and 5, and annual visits thereafter for up to 15 years after infusion of exa-cel in the parent study. If the patient is unable or unwilling to come in for a scheduled clinic visit, the visit will be completed by telemedicine, and will include a visit to the patient's home from a home health nurse followed by a conversation between the patient and investigator (i.e., in person, phone, or video conference) within 1 week of the home visit (103).

Patients will be followed-up for a total of up to 15 years after exa-cel infusion including a 2-year follow-up period in the parent study and up to 13 years of follow-up in CLIMB-131 (103).

5.1.2 SUSTAIN

SUSTAIN was a double-blind, randomised, placebo-controlled, phase 2 trial of crizanlizumab in patients with SCD who were aged 16 to 65 years, had β^S/β^S, β^S/β^0, β^S/β^+, β^S/β^c or other genotype, and had experienced 2 to 10 sickle cell-related pain crises, in the year preceding trial enrolment. Patients were randomised in a 1:1:1 ratio to low-dose crizanlizumab (2.5 mg per kg of body weight), high-dose crizanlizumab (5.0 mg per kg) or placebo; this ITC focuses on the comparison against the Food and Drug Administration (FDA)-approved high-dose of crizanlizumab and placebo (i.e., SOC) (104). The trial was conducted at 60 sites in the US, Brazil, and Jamaica and enrolled 198 patients. The primary endpoint was the annual rate of sickle cell-related pain crises (98). Sickle cell-related pain crises, were defined in SUSTAIN as (98) :

- Acute episodes of pain, with no medically determined cause other than a vaso-occlusive event, that resulted in a visit to a medical facility and/or health care professional and analgesic treatment
- ACS
- Hepatic sequestration
- Splenic sequestration
- Priapism

For the purposes of this report, sickle cell-related pain crises as defined in the SUSTAIN trial will be referred to as VOCs. Patients receiving a stable dose of HU therapy were permitted to enrol in SUSTAIN; however, changes to HU dose or initiation of HU in patients not receiving it at baseline were not permitted during the trial's 52-week treatment phase. Patients who were undergoing long-term RBC transfusions were excluded. Of the 198 patients included in SUSTAIN, 65 were randomised to receive placebo (in addition to SOC as described above), hereinafter referred to as SOC in the SUSTAIN trial; 40 (62%) of the 65 patients received HU (98).

5.1.3 HOPE

HOPE was an international, multicentre, phase 3, double-blind, randomised, placebo-controlled trial of voxelotor in patients with SCD who were 12 to 65 years of age, had confirmed sickle cell disease (all variants), had a haemoglobin level between 5.5 and 10.5 g per dL during screening and had 1 to 10 VOCs in the past 12 months (97). Participants were randomized in a 1:1:1 ratio to 1500 mg of voxelotor, 900 mg of voxelotor or placebo (i.e., SOC). The primary end point was the percentage of participants who had a haemoglobin response, defined as an increase from baseline of more than 1.0g per DL at week 24. Secondary endpoints included the annualised incidence rate of VOCs, reported

after both the 24-week treatment period (97) and the 72-week treatment period (96). VOCs were defined in HOPE as a composite of acute painful crisis or ACS (97):

- Moderate to severe pain lasting at least 2 hours
- No explanation other than VOC
- Required oral or parenteral opioids, ketorolac or other analgesics prescribed by a healthcare professional in a medical setting or by telephone
- Episode of ACS.

Participants who were receiving HU at a dose that had been stable for at least 3 months before providing consent were eligible to enrol in HOPE. Participants who were receiving regular RBC transfusions, had a transfusion in the past 60 days, or had been hospitalised for a VOC within 14 days prior to inform consent were excluded.

5.1.4 NCT01179217

NCT01179217 was a phase 3, randomized, placebo-controlled, double-blind, parallel-group trial at 31 sites across the United States in patients who were at least 5 years of age, had received a diagnosis of sickle cell anaemia (β^S/β^S or β^S/β^0) and had at least two pain crises documented in the previous year (99). Patients were randomized in a 2:1 ratio to L-glutamine or placebo (SOC). The primary end point was the number of pain crises through week 48. A pain crisis was defined as:NCT01179217 was a phase 3, randomised, placebo-controlled, double-blind, parallel-group trial at 31 sites across the United States in patients who were at least 5 years of age, had received a diagnosis of sickle cell anaemia (β^S/β^S or β^S/β^0) and had at least two pain crises documented in the previous year (99, 105). Patients were randomized randomised in a 2:1 ratio to L-glutamine or placebo (i.e.,SOC). The primary end point was the number of pain crises through week 48. A pain crisis was defined as:

- Pain leading to treatment with a parenterally administered narcotic in an ER (or outpatient treatment) or during hospitalisation.
- ACS
- Priapism
- Splenic sequestration

For the purposes of this report, pain crises as defined in the NCT01179217 trial will be referred to as VOCs. Patients who were receiving HU at a dose that had been stable for at least 3 months before screening and who intended to continue with that treatment were eligible.

Table 9. Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
CLIMB SCD-121 Vertex Pharmaceuticals Inc. Interim Clinical Study Report. Protocol CTX001-121. 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. 18 December 2022. (100)	CLIMB SCD-121	NCT03745287	Start: 27/11/2018 Completion: 31/10/2024 Data cut-off 15/04/2023	Exa-cel vs SOC in severe SCD
CTX001-131 Vertex Pharmaceuticals Inc. Interim Clinical Study Report. Protocol CTX001-131. A Long-term Follow-up Study of Subjects With β-thalassemia or Sickle Cell Disease Treated with Autologous CRISPR-Cas9 Modified Hematopoietic Stem Cells	CTX001-131	NCT04208529	Start: 20/01/2021 Completion: 09/2039	Exa-cel vs SOC in severe SCD

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
(CTX001). 18 December 2022. (106)				
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. 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. (96, 97)	HOPE	NCT03036813	Start: 12/2016 Completion: 8/10/2019	Exa-cel vs SOC in severe SCD
Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J, et al. Crizanlizumab for the	SUSTAIN	NCT01895361	Start: 07/2013 Completion: 03/2016	Exa-cel vs SOC in severe SCD

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017;376(5):429-39. (98)				
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. (99)	NCT01179217	NCT01179217	Start: 05/2010 Completion: 03/2014	Exa-cel vs SOC in severe SCD

Abbreviations: SCD = sickle cell disease; SOC = standard of care

5.2 Literature used for the assessment of health-related quality of life

A systematic search of MEDLINE and the Cochrane library were made using the Ovid platform, while searches in Embase were conducted using the Elsevier platform. The search period was from the inception of the databases to 6 June 2023, with the exception of conference proceedings, which were hand searched from January 2020 onwards. A full description of the SLR can be found in Appendix I with the inclusion/exclusion criteria for studies reported in Table 104.

In section 10 Health state utility values that are used in the health economic model are described and motivated.

Table 10. Relevant literature included for (documentation of) health-related quality of life

Reference (Full citation incl. reference number)	Health state/ Disutility	Reference to where in the application the data is described/ applied
Disutilities acute complications		

Krol M, Nap A, Michels R, Veraart C, Goossens L. Health state utilities for infertility and subfertility. Reprod Health. May 3 2019;16(1):47. (107)	Infertility	Section 10.2.3
National Institute for Health and Care Excellence. Crizanlizumab for preventing sickle cell crises in sickle cell disease [ID1406] Accessed September 27, 2022. (no longer available online) (88)	VOC	Section 10.2.3
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. Feb 2007;16(1):22-7. (108)	ACS	Section 10.2.3
Jiao B, Basu A, Ramsey S, et al. Health State Utilities for Sickle Cell Disease: A Catalog Prepared From a Systematic Review. Value Health. Feb 2022;25(2):276-287. (109)	Stroke	Section 10.2.3
Bradt P, Spackman E, Synnott PG, et al. Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value. Institute for Clinical and Economic Review, January 23, 2020. Accessed September 27, 2022. https://icer.org/wp-content/uploads/2021/02/ICER_SCD_Evidence-Report_031220-FOR-PUBLICATION.pdf (89)	Acute kidney injury	Section 10.2.3
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. (110)	Pulmonary embolism	Section 10.2.3
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 (111)	Acute infections	Section 10.2.3
National Institute for Health and Care Excellence: Guidelines. Gallstone Disease: Diagnosis and Management of Cholelithiasis, Cholecystitis and Choledocholithiasis. National Institute for Health and Care Excellence (NICE); 2014. (112)	Gallstones	Section 10.2.3
Michaels, J. A., Campbell, W. B., King, B. M., Macintyre, J., Palfreyman, S. J., Shackley, P. & Stevenson, M. D. 2009. A prospective randomised controlled trial and economic modelling of antimicrobial silver dressings versus non-adherent control dressings for venous leg ulcers: the VULCAN trial. *Health Technol Assess,* 13**,** 1-114, iii. (113)	Leg ulcers	Section 10.2.3
Disutilities Chronic complications		
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. Feb 2007;26(2):181-7. (114)	Pulmonary hypertension	Section 10.2.3
Bradt P, Spackman E, Synnott PG, et al. Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value. Institute for Clinical and Economic Review, January 23, 2020. Accessed September 27, 2022. (89)	CKD, Heart failure	Section 10.2.3

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. (110)	Avascular necrosis, Retinopathy, Liver complications	Section 10.2.3
Cherry MG, Greenhalgh J, Osipenko L, 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. (115)	Post-stroke	Section 10.2.3
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. Oct-Dec 2018;32(4):276-283. (116)	Neurocognitive impairment	Section 10.2.3
Treatment related disutilities		
Matza LS, Paramore LC, Stewart KD, Karn H, Jobanputra M, Dietz AC. Health state utilities associated with treatment for transfusion-dependent beta-thalassemia. Eur J Health Econ. 2020;21(3):397-407. (117)	Exa-cel treatment	Section 10.2.3
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. (118)	Graft failure	Section 10.2.3

5.3 Literature used for inputs for the health economic model

A single SLR was conducted to identify published cost-effectiveness studies as well as cost and HCRU (health care resource utilization) studies. The purpose of the SLR was to identify and summarise the economic evaluations and cost burden evidence related to the treatment of 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 haematopoietic stem cell (HSC) donor is not available. Searches were carried out in databases in Embase, MEDLINE, Cochrane, conferences proceedings, and previous HTA submissions. A systematic search of MEDLINE and the Cochrane library were searched using the Ovid platform, while searches in Embase were conducted using the Elsevier platform. A combination of Emtree subject headings (Embase), MeSH (medical subject headings) and free text terms was used to retrieve all the relevant publications. The search period was from the inception of the databases to 10 July 2023, with the exception of conference proceedings, which were hand searched from January 2020 onwards. A full description of the SLR can be found in Appendix J with the inclusion/exclusion criteria for studies in the economic SLR reported in Table 113.

Additionally, targeted literature searches were conducted to identify inputs for mortality, complication risks and infertility prevalence. Relevant literature used for input to the health economic model is presented in in Table 11 below.

Table 11. Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/ estimate	Method of identification	Reference to where in the application the data is described/applied
Mortality			
Caocci G, Orofino MG, Vacca A, et al. Long-term survival of beta thalassemia major patients treated with hematopoietic stem cell transplantation compared with survival with conventional treatment. Am J Hematol. Dec 2017;92(12):1303-1310. (119)	Instant transplant mortality (rate)	Targeted literature review	Section 10.2
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 (120)	SCD-related mortality (SMRs)	Targeted literature review	Appendix J.2.4
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. (121)			
Acute complication risk inputs			
Shah N, Bhor M, Xie L, 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):106-117. (91)	Stroke, Acute chest syndrome, acute infections, gallstones, pulmonary embolism	Targeted literature review	Section 10.2
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. Sep 2016;40(5):295-299. (92)	Acute kidney injury/infarction	Targeted literature review	Section 10.2
Singh A, Minniti C. Leg Ulceration in Sickle Cell Disease: An Early and Visible Sign of End-Organ Disease. 2016. (122)	Leg ulcers	Targeted literature review	Section 10.2
Chronic complications			

Bradt P, Spackman E, Synnott PG, et al. Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value. Institute for Clinical and Economic Review, January 23, 2020. Accessed September 27, 2022. (89)	Chronic kidney disease, Heart failure	Targeted literature review	Section 10.2
Shah N, Bhor M, Xie L, 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):106-117. (91)	Pulmonary hypertension, Avascular necrosis	Targeted literature review	Section 10.2
Cahill CR, Leach JM, McClure LA, et al. Sickle cell trait and risk of cognitive impairment in African-Americans: The REGARDS cohort. EClinicalMedicine. May-Jun 2019;11:27-33. (90)	Neurocognitive impairment	Targeted literature review	Section 10.2
Infertility			
Datta J, Palmer MJ, Tanton C, et al. Prevalence of infertility and help seeking among 15 000 women and men. Hum Reprod. Sep 2016;31(9):2108-18. (123)	Prevalence	Targeted literature review	Section 10.2

6. Efficacy

6.1 Efficacy of exa-cel compared to standard of care for patients with sickle-cell disease

6.1.1 Relevant studies

Relevant studies are presented in Table 12.

Table 12. Overview of study design for studies included in the comparison.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
CLIMB SCD-121 NCT03745287 (124) (125)	Single-arm, open-label, single-dose Phase 1/2/3 study in subjects with severe SCD	Up to 2 years after exa-cel infusion	Patients with severe SCD, defined by: • documented severe SCD genotype, • history of ≥ 2 VOC events per year for the previous two years prior to enrolment, and • eligible for Autologous HSCT as per investigators judgment (n=45)	Single administration of exa-cel by IV infusion following myeloablative conditioning with busulfan	N/A	For a full listing of endpoints, see Appendix A. **Primary efficacy end point:** • Proportion of patients who achieved VF12 **Key secondary efficacy end point:** • Proportion of patients who achieved HF12 **Secondary efficacy end points:** • Severe VOC-free duration for patients who achieved VF12 • Relative reduction from baseline in annualized rate of severe VOCs for patients who did not achieve VF12 • Achieving at least 90%, 80%, 75%, and 50% reduction from baseline in annualised rate of severe VOCs for patients who did not achieve VF12 • Relative reduction from baseline in annualized rate and duration of inpatient hospitalisations for severe VOCs for patients who did not achieve HF12 • Proportion of patients with sustained HbF≥20% for at least 3 months, 6 months, or 12 months • Hb concentration (total Hb and HbF) • Proportion of alleles with intended genetic modification present in peripheral blood and CD34+ cells of the bone marrow. • Change from baseline in reticulocyte count, indirect bilirubin, lactate dehydrogenase, and haptoglobin. • Relative reduction from baseline in number of RBC units transfused for SCD-related indications. • Change from baseline in PROs
CTX001-131 NCT04208529	Prospective cohort study to evaluate the	Up to 15 years after exa-cel infusion	All subjects who complete or discontinue the	No additional intervention to the single	N/A	For a full listing of endpoints, see Appendix A.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
(126)	long-term safety and efficacy of exa-cel in subjects who received exa-cel 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)		parent study (CTX001-111 or CTX001-121 or VX21-CTX001-141 or VX21-CTX001-151) after exa-cel infusion will be asked to participate in this long-term follow-up study.	exa-cel infusion administered in the parent study		**Primary endpoints** are safety endpoints, assessed for up to 15 years post-infusion unless otherwise stated below**:** • New malignancies • New or worsening hematologic disorders (e.g., immune-mediated cytopenia's, aplastic anaemia, primary immunodeficiencies) • All-cause mortality • All SAEs occurring up to 5 years after exa-cel infusion • Exa-cel-related AEs and SAEs **Secondary endpoints** in patients with SCD will be assessed for up to 15 years and include: • Severe VOC • SCD-related transfusions • Total Hb concentration (pre-transfusion) over time • HbF concentration (pre-transfusion) over time Proportion of alleles with intended genetic modification present in peripheral blood leukocytes over time
HOPE (96, 97)	Phase 3, double-blind, randomized, placebo-controlled	72 weeks	Patients 12-65 years with SCD and at 1-10 episodes of VOC in the past 12 months	Voxelotor	Placebo	Primary outcome: • Number of Participants with Increase in Hb >1 g/dL From Baseline to Week 24 Secondary outcomes:

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
	multicenter study					• Annualised VOC Incidence Rate • Percentage Change from Baseline in Haemolysis Measures
SUSTAIN (98)	Phase 2, multicenter, randomized, placebo-controlled, double blind	12 months	Patients 16-65 years of age with SCD with 2-10 sickle-cell related pain crises in the past 12 months	Crizanlizumab	Placebo	Primary outcomes: • Annual Rate of Sickle Cell-related Pain Crises (SCPC) Per Hodges-Lehmann Median (1 year) • Annual Rate of SCPC- Per Standard Median (1 year) Secondary outcomes: • Annual Rate of Days Hospitalised (Key Secondary Endpoint) Per Hodges-Lehmann Median • Time to First SCPC • Time to Second SCPC • Annual Rate of Uncomplicated SCPC Per Hodges-Lehmann Median • Annual Rate of ACS Per Hodges-Lehmann Median • Patient Reported Outcome: Change from Baseline in Pain Severity/Pain Interference Domain from Brief Pain Inventory (BPI) Questionnaire
NCT01179217 (99)	Phase 3, randomized, double-blind, placebo controlled	48 weeks	Patients above 5 years of age with at least 2 episodes of sickle cell crisis	L-glutamine	Placebo	Primary outcome: The Number of Occurrences of Sickle Cell Crises Secondary outcomes: The Number of Hospitalizations for Sickle Cell Pain

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
	multicenter study		within 12 months			The Number of ER/Medical Facility Visits for SCPC The Effect of Oral -L-glutamine on Haematological Parameters The Effect of Oral L-glutamine on Vital Signs

Abbreviations: ASCT = autologous stem cell transplant; SCPC = sickle cell-related pain crises, SCD = sickle cell disease, VOC = vascular occlusion complication.

6.1.2 Comparability of studies

6.1.2.1 Comparability of patients across studies

Due to the single arm nature of the exa-cel pivotal CLIMB SCD-121 trial, ITCs were necessary to generate estimates of comparative effectiveness versus SOC. Relevant comparator studies were identified through an SLR (see Section 5.1 and Appendix H). The ITCs employed unanchored matching-adjusted indirect comparison (MAIC) methodology. Relevant baseline covariates identified as the key effect modifiers and/or prognostic factors were selected as matching variables. In the order of importance, the matching variables were genotype (proportions of patients with β^S/β^S vs non-β^S/β^S genotype), baseline annualised number of VOCs (severe or as defined in the trial), age, sex, and race/ethnicity. Due to the small sample size in the CLIMB SCD-121 PES (N=29), no more than three variables were used for matching, starting with the variables ranked as most important and moving onto lower-ranking variables if a match was not possible. Of note, genotype was not included in matching for any of the MAICs, as only 1 out of 29 patients (3.4%) in the CLIMB SCD-121 PES had the non-β^S/β^S and others are the β^S/β^S genotype. Matching on genotype would result in higher weight to the one non-β^S/β^S genotype patient with a notable reduction in ESS; the results and inferences would have been heavily driven by this patient. The influence of this one patient would be even more apparent as comparator trials (HOPE, SUSTAIN) had more non-β^S/β^S patients. Unadjusted baseline characteristics of CLIMB SCD-121 and the three comparator trials are presented in Table 13. Adjusted values are presented in Section 7.

Table 13. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

Patient characteristics	CLIMB SCD-121 (n=29), exa-cel	SUSTAIN (n=65), SOC	HOPE (n=92), SOC	NCT01179217 (n=78), SOC
Age, mean (SD)	22.2 (6.1)	NR	NR	21.4 (12.4)
Age, median (range)	21 (12-34)	26 (16-56)	28 (12-64)	17 (5-58)
Male, n (%)	16 (55.2)	27 (41.5)	42 (45.7)	33 (42.3)
Annualised number of VOCs at baseline, n (%)				
≤4 (≤5 in NCT01179217)	21 (72.4)	41 (63.1)	NR	62 (79.5)
>4 (>5 in NCT01179217)	8 (27.6)	24 (36.9)	NR	16 (20.5)
Genotype, n (%)				
βs/βs	28 (96.6)	47 (72.3)	74 (80.4)	71 (91.0)
Other	1 (3.4)	18 (27.7)	18 (19.6)	7 (9.0)

Race/ethnicity, n (%)				
Black or African American	26 (89.7)	60 (92.3)	63 (68.5)	73 (93.6)
Other	3 (10.3)	5 (7.7)	29 (31.5)	5 (6.4)

Note: CLIMB SCD-121 data shown here are unadjusted data. For each ITC performed, the CLIMB SCD-121 data was matched and re-weighted on the matching variables. For NCT01179217, the matching variables were: proportion of patients with annualised number of VOCs ≤ 5 vs >5 at baseline, mean age, and sex; for HOPE, the matching variables were: median age, sex, and race; For SUSTAIN the matching variables were: the proportion of patients with annualized number of VOCs ≤ 4 vs >4 at baseline, median age, and sex.
Abbreviations: SD = standard deviation; SOC = standard of care; VOC = vaso-occlusive crisis.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

In line with the expected indication of exa-cel, the target patient population for this assessment consists of Danish patients with severe SCD 12 years and older with recurrent VOCs, for whom HSCT is appropriate and for whom an HLA-matched related haematopoietic stem cell donor is not available. The CLIMB SCD-121 study population is assessed to be comparable with the Danish patients eligible for treatment.

Table 14. Characteristics in the relevant Danish population and in the health economic model

Patient characteristics	Value in Danish population (52)	Value used in health economic model (CLIMB SCD-121)
Age, mean (SD)	22 years	22.2 (6.1) years
Age, median (range)	21 years	21 (12-34) years
Male, n (%)	Around 50%	16 (55.2)
Annualised number of VOCs at baseline, n (%)		
≤4	20	21 (72.4)
>4	8	8 (27.6)
Genotype, n (%)		
βs/βs	28	28 (96.6)
Other	1	1 (3.4)

Abbreviations: SD = standard deviation; VOC = vaso-occlusive crisis

6.1.4 Efficacy – results per CLIMB SCD-121/CTX001-131

6.1.4.1 Data cutoffs and data sets analysed

The study protocol for CLIMB SCD-121 includes 3 interim analyses (IAs) that may be performed following a group sequential testing procedure to allow for early evaluation of efficacy (82). The first IA (IA1) was optional and was not performed. The second IA (IA2) as of the clinical data cut of September 16, 2022, demonstrated transformational, highly consistent, and durable clinical benefit for SCD for the initial Marketing Authorisation Application (MAA). Treatment with exa-cel resulted in robust, clinically meaningful, and

statistically significant improvements in all primary and key secondary efficacy endpoints. Specifically, at IA2 for the initial MAA, Study CLIMB SCD-121 met its primary endpoint of absence of vaso-occlusive crises (VOCs) for at least 12 consecutive months (VF12) and key secondary endpoint of free from inpatient hospitalization for severe VOCs for 12 consecutive months (HF12); following infusion with exa-cel, 16 of 17 (94.1%) subjects in the PES achieved VF12 (95% CI: 71.3%, 99.9%; 1-sided P=0.0001 [against a 50% response rate]) and 17 of 17 (100%) subjects achieved HF12 (95% CI: 80.5%, 100.0%; 1-sided P<0.0001 [against a 50% response rate]).

In this section, updated exa-cel clinical pharmacology, efficacy, and safety data for the pivotal CLIMB SCD-121 study and long-term follow-up (study 131) study are presented as of the 16 April 2023 data cutoff (Day 120 update). This update was performed in response to regulatory authority request and was not pre-specified in the statistical analysis plan (SAP). As of the Day 120 data update (clinical data cut of April 16, 2023), 14 subjects completed Study 121 and 13 patients rolled over to study CTX001-131. One subject discontinued after exa-cel infusion in Study 121 from a death due to COVID-19 infection that resulted in respiratory failure and was not related to exa-cel; no subject has discontinued from Study 131. The overall duration of follow-up (including follow-up in CTX001-131) was up to [redacted] months after exa-cel infusion (127). Results are not reported for the [redacted] patients enrolled in study CTX001-131 separately. The final analysis is planned to be performed once [redacted] patients have reached ≥16 months of post-infusion follow-up, with an efficacy boundary of [redacted] respondents, corresponding to a [redacted]% response rate (127).

Study analysis sets are summarized in Table 15. As of 16 April 2023 (Day 120 update), among the [redacted] enrolled patients, [redacted] discontinued the study before mobilization (due to withdrawal of consent [n=[redacted]], non-compliance [n=[redacted]], and investigator decision [n=[redacted]]) and [redacted] after the start of the mobilization but before conditioning (due to inadequate cell collection [n=[redacted]], withdrawal of consent [n=[redacted]], no longer meeting eligibility criteria for renal function [n=[redacted]], non-compliance [n=[redacted]], and psychological and physical stress [n=[redacted]])(1, 128). A total of [redacted] patients had been treated with exa-cel, and therefore included in the FAS at the Day 120 data cut. Of those, [redacted] patients were included in the PES (1).

Table 15. CLIMB SCD-121 analysis sets (Day 120 update)

Analysis Set	Total number of patients (Day 120 update)
Enrolled Set[a]	[redacted]
Safety Analysis Set[b]	[redacted]
FAS[c]	[redacted]
PES[d]	[redacted]

Abbreviations: FAS = full analysis set; PES = primary efficacy set.
[a] All enrolled patients who signed informed consent and met the eligibility criteria
[b] All patients who started the mobilisation regimen
[c] All patients who received exa-cel infusion
[d] PES included 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. Completion of the (initial) RBC transfusions was determined when all those transfusions for post-transplant support or SCD management had finished followed by 60 days without transfusion. Patients who completed the 24 months of follow-up in the study post exa-cel infusion were included in this set. In addition, patients who died or discontinued the study due to exa-cel-related adverse events and had less than 16 months follow-up post exa-cel infusion, or continuously received RBC transfusions for more than 12 months post exa-cel infusion will also be included in this set.
Source: Exa-cel efficacy and safety update 16 April 2023 (127)

6.1.4.2 VOC related endpoints

6.1.4.2.1 Proportion of subjects achieving VF12 (primary endpoint)

Twenty-nine subjects were evaluable for the primary endpoint (included in PES).

At this updated analysis, following infusion with exa-cel, 96.6% (28 of 29) of the subjects in the PES achieved VF12 (95% CI: 82.2%, 99.9%; 1-sided P <0.0001 [against a 50% response rate] (Table 16). Given that recurrent VOCs lead to significant morbidity and mortality, and that the subjects in the PES had a mean of 3.9 VOCs per year in the previous 2 years at baseline (Table 59), achieving VF12 in 96.6% percent of subjects is highly clinically meaningful. The primary endpoint results were generally consistent across subgroups defined based on annualised rate of VOCs at baseline and age. An additional analysis was also performed in patients with ≥18 months of follow-up, also demonstrating consistent efficacy with the main analysis. One subject (Subject 026) in the PES, who did not achieve VF12 at the time of IA2, had clinical benefit as demonstrated by achieving the stringent key secondary endpoint of HF12, which measures the most severe VOC events (further discussed below in this section). This patient had 7 hospitalisations in the 24-month baseline period prior to exa-cel infusion (

Figure 16). At this updated analysis, Subject 026 has remained free from hospitalization for 23.0 months (1, 127). Results for durability of severe VOC free periods are shown in Appendix B, section B.1.2.1.

Table 16. Overview of CLIMB SCD-121 efficacy results for exa-cel (Day 120 update)

Outcome	Exa-cel (n=29)	95% CI
Proportion of patients achieving VF12, PES, n (%)	28 (96.6%)	82.2% - 99.9%
Proportion of patients achieving HF12, PES, n (%)	29 (100%)	88.1% - 100 %

Abbreviations: HF12 = ; VF12 = VOC-free for at least 12 consecutive months from exa-cel infusion;
Source: Exa-cel efficacy and safety update 16 April 2023 (1, 127)

6.1.4.2.2 Proportion of subjects achieving HF12 (key secondary efficacy endpoint)

Assessment of inpatient hospitalization for VOCs is a highly clinically meaningful endpoint. VOC events are the most common cause of hospitalizations for individuals with SCD (91,

129, 130, 131). The primary efficacy endpoint definition of VOCs is broad and not only includes events treated in a hospital but also those treated in an outpatient clinic or emergency room. In contrast, evaluation of inpatient hospitalization for severe VOCs over time is a stringent efficacy measure and allows assessment of the most severe events associated with the greatest mortality risk and the overall impact of exa-cel treatment (1, 34, 132). At this updated analysis, after exa-cel infusion, 100% of the 29 subjects in the PES were free from inpatient hospitalization for severe VOCs for at least 12 months following exa-cel infusion (HF12) (95% CI: 88.1%, 100.0%; 1-sided P<0.0001 [against a 50% response rate]) (Table 16). Subjects in the PES had a mean (range) of 2.7 (0.5 to 8.5) inpatient hospitalization for severe VOCs per year with a mean (range) duration of 17.4 (2.0 to 64.6) days of inpatient hospitalization per year in the 2 years prior to screening; therefore, all subjects being free from inpatient hospitalization for at least 12 months is highly clinically meaningful. Results for durability of free from inpatient hospitalization for severe VOCs are shown in Appendix B Section B.1.2.2.

6.1.4.3 Other secondary endpoint

Results for Hb and HbF concentration over time, allelic editing, markers for haemolysis, reduction in RBC transfusions and quality of life are shown in Appendices (B.1.3, B.1.4, B.1.5, B.1.6, and B.1.7)

6.1.5 Efficacy – results per SUSTAIN

Only results included in the ITC are presented here. At the end of the 52-week treatment phase, the median annualized rate of VOCs in the intention-to-treat population was 2.98 (IQR: 1.25 – 5.87) in the SOC (placebo) arm. A total of 11 of 65 patients (17%) had zero VOCs at the end of the treatment period in the SOC arm (98).

6.1.6 Efficacy – results per HOPE

Only results included in the ITC are presented here. During the 72-week treatment period, the annualized adjusted incidence rate of VOCs was 2.8 (95% CI: 2.2 – 3.6) in the SOC group (96). The percentage of participants who had at least one VOC during the 24-week study period was 69% in the SOC group (97).

6.1.7 Efficacy – results per NCT01179217

Only results included in the ITC are presented here. Through week 48, the mean (SD) number of VOCs was 3.9 (2.54) in the SOC group (99). Through week 48, the mean (SD) number of VOCs was 3.9 (2.54) in the SOC group (99, 105).

7. Comparative analyses of efficacy

Clinical evidence for standard of care was identified from a systematic literature review (Appendix H). Based on the literature, three indirect treatment comparisons (ITCs) were considered, using data from the control arms of the SUSTAIN trial (98), the HOPE trial (96, 97) and the NCT01179217 trial (99).

7.1.1 Differences in definitions of outcomes between studies

Two VOC-related efficacy outcomes were assessed in the matching-adjusted indirect comparison (MAIC). Definition of VOC reported in all studies are generally similar to that of the CLIMB SCD-121 trial (Table 17). However, there are caveats to consider:

- 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. Note: in SUSTAIN trial, VOC was referred to as SCPC - Sickle Cell-Related Pain Crises.

Table 17. Definition of VOC in SCD studies

Study	Definition
CLIMB-121	Severe VOC is defined as any 1 of the following events: 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 Priapism lasting >2 hours and requiring a visit to a medical facility Splenic sequestration
HOPE	VOC is defined as any 1 of the following documented: Acute painful crisis of moderate to severe pain lasting at least 2 hours (with no explanation other than VOC) Requires oral or parenteral opioids, ketorolac, or other analgesics prescribed by a healthcare professional in a medical setting (hospital, clinic, emergency room) or by telephone Episode of acute chest syndrome (similar ACS criteria as CLIMB) No criteria on splenic sequestration
SUSTAIN	VOC was defined as any 1 of the following events: Acute episodes of pain, with no medically determined cause other than a vaso-occlusive event, that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral nonsteroidal anti-inflammatory drug Acute chest syndrome Hepatic sequestration Priapism Splenic sequestration Note: in SUSTAIN trial, VOC was referred to as SCPC - Sickle Cell-Related Pain Crises

NCT01179217	VOC is defined as any 1 of the following events: Visit to an emergency room/medical facility for acute sickling-related pain which is treated with a parenterally administered narcotic. Medical visits with only oral narcotics will be counted as VOCs so long as oral narcotics are administered during the visit and non-use of parenteral narcotic is clearly documented in the source documentation as a facility policy. Acute chest syndrome Priapism Splenic sequestration

Abbreviation: ACS = acute chest syndrome; IV = intravenous; NSAID = non-steroidal anti-inflammatory; RBC = red blood cell; VOC = vaso-occlusive crisis

7.1.2 Method of synthesis

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. The matching variables ranked by importance were:

- Genotype (proportions of patients with β^S/β^S vs non- β^S/β^S genotype)
- Baseline annualized 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)

Due to the small sample size in the CLIMB SCD-121 PES (N=29), no more than three variables were used for matching based on HTA expert input, starting with the variables ranked as most important and moving onto lower-ranking variables if a match was not possible (133). 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 respective sections. Details of the method of synthesis and the statistical analysis are described in Appendix C.

7.1.3 Results from the comparative analysis

Results from the comparative analysis are summarised in Table 18.

Table 18. Results from the comparative analysis of exa-cel vs. SOC for patients with SCD

Outcome measure	Comparator (SOC)	Exa-cel unweighted (before matching)	Exa-cel re-weighted (after matching)	Result (Rate Ratio [95% CI])
Proportion of subjects VOC-free for 12 months vs SOC as defined in	N=65 16.9% (-,-)	96.6% (82.2, 99.9)	ESS=19 97.1% (81.6, 99.6)	5.7 (3.3, 9.9)

Outcome measure	Comparator (SOC)	Exa-cel unweighted (before matching)	Exa-cel re-weighted (after matching)	Result (Rate Ratio [95% CI])
the SUSTAIN trial				
Proportion of subjects VOC-free for 6 months vs SOC as defined in the HOPE trial	N=91 30.8% (-,-)	N=29 100% (81.1, 100)	ESS=10 100%	3.2 (-,-)
Median annualized VOC rate vs SOC as defined in the SUSTAIN trial	N=65 2.98 (1.25, 5.87)	N=29 0.0 (0.0, 0.0)	ESS=19 0.0 (0.0, 0.0)	NC
Mean annualized VOC rate vs SOC as defined in the HOPE trial	N=91 2.8 (2.2, 3.6)	N=29 0.20 (0.11, 0.39)	ESS=10 0.17 (0.02. 1-18)	0.06 (0.01, 0.43)
Mean rate of VOCs at week 48 vs SOC as defined in the NCT01179217 trial	N=78 3.9 (3.3, 4.5)	N=29 0.17 (-0.1, 0.5)	ESS=27 0.20 (-0.1, 0.5)	0.05 (0.01, 0.26)

Abbreviations: CI, confidence interval; NC, non calculable; SCD, sickle cell disease; SOC, standard of care; VOC, vaso-occlusive crisis.

7.1.4 Efficacy- results per outcome

In the ITC of exa-cel vs SOC in the SUSTAIN trial, the rate ratio was 5.7 (95% CI: 3.3 to 9.9; p<0.0001) indicating that exa-cel resulted in a statistically significant, 5.7-times higher proportion of patients remaining VOC-free for 12 consecutive months compared with SOC as defined in the SUSTAIN trial. The current findings support the superior efficacy of exa-cel and highlight its important clinical benefits in avoiding VOCs. Additional details of the ITC of exa-cel vs SOC in the SUSTAIN trial are described in Appendix C.2.

In the ITC of exa-cel vs SOC in the HOPE trial, the reweighted proportion of patients who were VOC-free for at least 6 consecutive months was 100% for exa-cel compared with 30.8% of patients in the HOPE trial. However, due to small ES, the rate ratio was not

reported. Additional details of the ITC of exa-cel vs SOC in the HOPE trial are described in Appendix C.3.

In the ITC of exa-cel vs SOC in the NCT011179217 trial, the adjusted week 48 mean (SD) VOC rate in patients treated with exa-cel after matching was 0.20 (-0.1, 0.5), compared to 3.9 (3.3, 4.5) in patients treated with SOC in the NCT011179217 trial. The resulting rate ratio was 0.05 (95% CI: 0.01, 0.26; p=0.0003) indicating that exa-cel resulted in a reduction in the mean week 48 rate of VOCs of 95% when compared to SOC as defined in the NCT01179217 trial. Additional details of the ITC of exa-cel vs SOC in the NCT01179217 trial are described in Appendix C.4.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model.

8.1.1 Extrapolation of efficacy data

Patients receiving SOC alone are assumed not to receive additional clinical benefits after model start; therefore, the frequency of VOCs and thereby health state membership is assumed to remain at the baseline level throughout the modelled time horizon. Treatment efficacy of exa-cel is captured by the reduction in VOC frequency. Model inputs of treatment efficacy were informed by the clinical trials CLIMB 121/131 (1, 134, 135).

At baseline, patients were assumed to experience an average of 3.9 VOCs per year. All patients were assumed to have no chronic complications at baseline, as this allows a clean comparison of treatments without the impact of background complication. For patients treated with exa-cel, the treatment efficacy is applied after a treatment phase. The treatment phase includes pre-mobilization, mobilization and apheresis, myeloablative conditioning and infusion, and engraftment. The treatment phase for exa-cel was assumed to last for 12 months, based on the exa-cel clinical trial program. This assumption was considered appropriate by consulted clinicians.

The treatment withdrawal rate was assumed to be 19.0% for exa-cel based on attrition in the CLIMB SCD-121 trial. Of the 58 patients that initiated mobilisation, 11 patients (19.0%) discontinued after starting mobilisation and apheresis and prior to Casgevy administration. Six patients (10.3%) did not achieve the minimum dose. Five patients (8.6%) discontinued due to noncompliance, withdrawn consent, or no longer meeting eligibility requirements (one subject no longer met eligibility criteria for renal function; 1 subject discontinued due to non-compliance; 2 subjects withdrew consent; 1 subject discontinued due to psychological and physical stress) (1). All patients withdrew prior to conditioning. Conditioning is performed in the same step as exa-cel infusion and is only initiated once the edited cells are delivered. This is not spelled out in the SPC because it was considered evident to the reader that patient not infused with Casgevy also did not receive conditioning. Patients who withdraw from treatment before infusion or transplantation are not included in the modelled cohort. The costs of pre-mobilization,

mobilization and apheresis for these patients are included in the model as additional costs in the pre-transplantation cost (1, 134).

The initial engraftment success rate was assumed to be 100% for exa-cel based on treatment experience of 43 patients infused in CLIMB SCD-121. Patients with engraftment failure from exa-cel were assumed not to receive any clinical benefits (i.e., continue experiencing baseline number of VOCs) and continue receiving SOC as per baseline. 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 a potentially curative therapy are receiving additional supporting care including more frequent exchange transfusion to lower risk of VOCs during the treatment phase.

Among modelled patients treated with exa-cel, all of whom achieved engraftment success, 97.1% were assumed to be cured and experience no subsequent VOCs (see Section 7.1.3). This estimate is based on the matched indirect comparison with SOC using the most recent data-cut of the CLIMB SCD-121 trial (see Table 18). The remaining 2.9% 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 (134).

One patient ( ) who achieved the VF12 primary endpoint experienced an acute VOC in the setting of parvovirus B12 infection after 20.2 months of being VOC-free.

Exa-cel patients who are VOC-free for 12 months are assumed to remain VOC-free for a lifetime as exa-cel is a gene edited hematopoietic stem cells (HSC)-based therapy, addressing the underlying pathological mechanism of the disease, for which there is no known mechanism to convert back to a wild-type sequence following CRISPR/Cas9 editing (Vertex Pharmaceuticals Incorporated 2023d). In the most recent data cut of the CLIMB SCD-121/131 clinical trial for patients with SCD treated with exa-cel, at month 24, the mean proportion of edited BCL11A alleles in bone marrow CD34+ hematopoietic stem and progenitor cells (HSPCs) and peripheral blood mononuclear cells was % and %. Patients with SCD also had clinically meaningful increases in HbF and total hemoglobin

levels that occurred early and were sustained over time (134, 136). Current data shows no treatment waning in patients who have up to [redacted] months of follow-up (134).

The benefits of one-time gene therapies are to ameliorate a life-long disease indefinitely and it is expected that the clinical and economic benefits will materialize over the patient's lifetime, as described above in exa-cel's mechanism of action and the anticipated permanence of gene editing. It has not been identified any empirical data or theoretical rationales to support treatment waning over time. Furthermore, Danish experts are aligned that given past experience with stem cell transplantation in this indication, it is not likely that the effect would wane over time if there is sustained effect over 2 years (52). Given the above exa-cel is modelled as a curative treatment.

Table 19. Summary of assumptions associated with extrapolation of VOC frequency

Method/approach	Description/assumption
Data input	CLIMB SCD-121/131, MAIC
Model	Patients cured from SCD do not experience VOC events
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Not applicable
Function with best BIC fit	Not applicable
Function with best visual fit	Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable
Validation of selected extrapolated curves (external evidence)	Not applicable
Function with the best fit according to external evidence	Not applicable
Selected parametric function in base case analysis	Not applicable
Adjustment of background mortality with data from Statistics Denmark	Yes, based on general population mortality provided by DMC
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	Yes, exa-cel patients who are VOC-free for 12 months are assumed to remain VOC-free for a lifetime as exa-cel is a gene edited hematopoietic stem cells (HSC)-based therapy for which there is no known mechanism to

Method/approach	Description/assumption
	convert back to a wild-type sequence following CRISPR/Cas9 editing

Abbreviations: VOC Vaso-occlusive crisis

8.1.2 Calculation of transition probabilities

Among modelled patients treated with exa-cel, all of whom achieved engraftment success, 97.1% were assumed to be cured and experience no subsequent VOCs and thereby transition to the cured status after 12 months. 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 (PES) 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). Probabilities of acute and chronic complications and death were sourced from a Burden of Illness study in patients with SCD conducted by Vertex and are presented in Appendix J. Patients in the SoC arm remained in the Severe SCD state (non-cured) state throughout the simulation and could only transition to the death state. The proportion of patients by health state are presented in Figure 5 and Figure 6.

Table 20. Transitions in the health economic model exa-cel treated patients

Health state (from)	Health state (to)	Description of method	Reference
SCD	Cure	97.1% of patients treated with exa-cel and whom achieved engraftment success transitioned to the cured status after 12 months	CLIMB SCD-121, MAIC
SCD	Severe SCD	2.9%	CLIMB SCD-121

Abbreviation: SCD = Sickle Cell Disease

8.2 Presentation of efficacy data from [additional documentation]

Not applicable

8.3 Modelling effects of subsequent treatments

Subsequent treatment not included, exa-cel is modelled as a potentially curative therapy.

8.4 Other assumptions regarding efficacy in the model

No other assumptions were made.

8.5 Overview of modelled average treatment length and time in model health state

Modelled time in health states without cycle-correction but with adjustment for background mortality of the Danish population are presented in Table 21 and Table 22 respectively.

[redacted]

Table 21 Estimates in the model

	Modelled average time VOC free	Modelled median time VOC free	Observed median from CLIMB-111/131
Exa-cel	Curative therapy, lifelong VOC free	Curative therapy, lifelong VOC free	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 (PES) 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) (134).
SoC	Patients on SoC remain at baseline levels.	Patients on SoC remain at baseline levels.	Not applicable

Abbreviations: VOC vaso-occlusive crisis; SOC = standard of care

The modelled average treatment length and time in model health state is shown in Table 22 below. The initial engraftment success rate was assumed to be 100% for exa-cel based on treatment experience of 43 patients infused in CLIMB SCD-121. Patients with engraftment failure from exa-cel were assumed not to receive any clinical benefits (i.e., continue experiencing baseline number of VOCs) and continue receiving SOC as per baseline. 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 potentially curative therapies are receiving additional supporting care including more frequent exchange transfusion to lower 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 cured and experience no subsequent VOCs.

In Table 22 the modelled average treatment length and time in model health states is described. During the 78-year time horizon patients treated with exa-cel spends a much larger proportion of time alive, since the treatment with exa-cel largely decreases the mortality risk. The decrease in mortality risk is multifaceted since the disease specific SCD

mortality is decreased together with the decrease in acute and chronic complications with their entailed mortality increase. The years alive are also in the cured health state that generates a larger impact on health-related quality of life and lower costs. Figure 5 shows the time spent as cured from SCD in relation to the death health state.

Table 22. Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length, years	Cured, years	Severe SCD, years	Death, years
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]

Figure 5. Exa-cel time in health states over time

[redacted]

Figure 6 below shows the time patient treated with SoC spent in the different health states during the time horizon.

Figure 6. SoC time in health states over time

[redacted]

[redacted]

9. Safety

9.1 Safety data from the clinical documentation

For the FAS, the median follow-up duration after exa-cel infusion was 17.5 months (range: 1.2 to 25.6 months) (1, 138). A total of 13 patients with SCD were enrolled in the long-term follow-up CTX001-131 study (138). The cumulative median (max) follow-up duration for was 17.5 (46.2) months, corresponding to 1.5 (3.8) years (1, 138).

As expected after myeloablation, all patients had at least one AE between exa-cel infusion and Month 24, and all patients had AEs related or possibly related to busulfan and 13 (30.2%) had AEs related or possibly related to exa-cel (Table 23) (138). Sixteen ([redacted]% of) patients experienced an SAE, including [redacted] ([redacted]%) patients who had SAEs related or possibly related to busulfan and no patients with AEs related or possibly related to exa-cel (Table 23) (138). One patient died due to COVID-19 infection which led to respiratory failure (preferred term: respiratory failure) and this death was not considered related to exa-cel (101, 138).

[redacted] (Section 9.1.3) (138).

Safety events at Day 120 update as well as the SOC studies are summarized in Table 23. Note that for NCT01179217, data was sourced from a FDA sponsor resource document (139) due to the lack of granularity in AE data reporting in the original trial (105).

Table 23. Overview of safety events at Day 120 update (FAS); cumulative median (max) follow-up duration: 17.5 (46.2) months

	Exa-cel (N=43) (127)	SOC SUSTAIN (N=62) (98)	SOC HOPE (n=91) (140)	SOC NCT01179217 (n=78+33) (139)	Difference, % (95 % CI)[#]
Number of adverse events, n	NR	NR	NR	1299	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	43 (100)	55 (89)	81 (89)	108 (97.3)	7.6 (3.1, 12.1)

	Exa-cel (N=43) (127)	SOC SUSTAIN (N=62) (98)	SOC HOPE (n=91) (140)	SOC NCT01179217 (n=78+33) (139)	Difference, % (95 % CI)[#]
Number of serious adverse events*, n	NR	NR	NR	411	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	16 (37.2)	17 (27.4)	NR	89 (80.2)	-24.1 (7.9, 40.2)
Number of CTCAE grade ≥ 3 events, n	NR	NR	NR	NR	N/A
Number and proportion of patients with ≥ 1 CTCAE grade 3 events[§], n (%)	[redacted]	NR	24 (26.4)	[redacted]	[redacted]
Number of adverse reactions, n	NR	NR	NR	32	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	13 (30.2)	NR	23 (25.3)	15 (13.5)	5.4 (-9.9, 20.7)
Number and proportion of patients with ≥ 1 drug-related serious adverse event	NR	NR	NR	3 (2.7)	
Number and proportion of patients who had a dose reduction, n (%)	N/A	NR	NR	NR	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	N/A	NR	25 (27)	NR	N/A
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	N/A	NR	7 (8)	NR	N/A

* Patients with AEs related or possibly related to exa-cel. Number of patients with AEs related or possibly related to busulfan was 43 (100%)
[1] Due to the lack of granularity in the reporting of adverse events in the original publication (105), AE data from the NCT01179217 trial (n=78) was extracted from a FDA sponsor briefing document (139). In this report, data was pooled with a phase 2 study by the same sponsor (Study 10478) (n=33).
§ CTCAE v. 5.0 must be used if available.
# Calculation of difference is based on pooled data from the comparator trials
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Event

9.1.1 Serious adverse events

Common SAEs occurring in ≥5% of patients are reported in Table 24. The type and incidence of SAEs were generally consistent with that anticipated due to myeloablative conditioning, autologous HSCT, and the underlying disease (101, 138). No SAEs were considered related to exa-cel (102, 138).

Table 24. Serious adverse events with a frequency of ≥ 5% at Day 120 update; cumulative median (max) follow-up duration: 17.5 (46.2) months

Adverse events	Exa-cel (N=43)		SOC SUSTAIN (N=62)		SOC HOPE (N=91)		SOC NCT01179217 (N=78)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Cholelithiasis, n (%)	[redacted]							
Pneumonia[a], n (%)								
Abdominal pain[a], n (%)								
Constipation[a], n (%)								
Pyrexia[a], n (%)								
Acute chest syndrome								
Sickle cell anaemia with crisis								

[a] AEs described within busulfan SmPC and/or USPI; events were evaluated by matching PT term or similar medical concept.
Source: Exa-cel KRM CTX001-121/131 Day 120 update (138) and Exa-cel efficacy and safety update 16 April 2023 (53)

9.1.2 Engraftment

All 43 patients who received exa-cel achieved neutrophil engraftment before Day 43 (1, 138). Median time to neutrophil engraftment was 27.0 days [redacted]

[redacted] A total of 19 (44.2%) of patients received G-CSF prior to neutrophil engraftment (138). All 43 patients in the FAS achieved platelet engraftment (1, 138). Median time to platelet engraftment was 35.0 days [redacted]

9.1.3 Exa-cel long-term follow-up study (CTX001-131)

Overall, no new safety findings were observed for patients enrolled in the long-term follow-up study. One patient with SCD had an SAE of gastroenteritis norovirus on Study Day 799; the event was considered not related to any study drug and resolved within 4 days (53). No patients had SCD-related complications in the CTX001-131 study (53). No AEs of new malignancies, or new or worsening hematologic disorders, have occurred at any time after exa-cel infusion, including after Month 24 in Study 131 (53). No deaths have occurred during Study 131 (53).

9.2 Safety data from external literature applied in the health economic model

Grade 3+ treatment-related adverse events (AEs) were considered in the model. For patients receiving exa-cel all AEs were assumed to occur at the hospital during the transplant procedure, and thus were captured in transplantation or transplant-related hospitalization disutility and costs. For chronic medications as SOC, recurring AE rates were applied in each model cycle while patients remained on treatment. A monthly rate of any grade 3+ adverse events of 2.19% was applied in the model, based on an average across placebo arms of SAEs in the crizanlizumab trial (98), Grade 3+ AEs in the voxelotor trial (140) and drug related SAEs in the L-glutamine trials (139). Calculations are presented in Section 11.5.

Adverse reactions attributed to mobilisation/apheresis with G-CSF and plerixafor, mobilisation/apheresis with plerixafor only, myeloablative conditioning with busulfan, and exa-cel, respectively, experienced by patients with TDT and SCD in clinical studies with exa-cel are presented in Table 25.

Table 25. Adverse reactions attributed to mobilisation/apheresis in patients with SCD receiving plerixafor (N=58)

System organ class (SOC)	Very common	Common
Blood and lymphatic system disorders		Sickle cell anaemia with crisis
Metabolism and nutrition disorders		Hyperphosphataemia, hypomagnesaemia
Nervous system disorders	Headache	
Respiratory, thoracic and mediastinal disorders		Acute chest syndrome

System organ class (SOC)	Very common	Common
Gastrointestinal disorders	Abdominal pain *, nausea, vomiting	Diarrhoea
Musculoskeletal and connective tissue disorders	Musculoskeletal pain †	Arthralgia
General disorders and administration site conditions		Pain, fatigue

* Abdominal pain included abdominal pain upper. † Musculoskeletal pain included back pain, bone pain, chest pain, neck pain, non-cardiac chest pain, and pain in extremity.

Table 26. Adverse reactions attributed to myeloablative conditioning with busulfan in patients with TDT and SCD (N=97)*

System organ class (SOC)	Very common	Common
Infections and infestations		Pneumonia, sepsis, klebsiella sepsis, oral candidiasis, folliculitis
Blood and lymphatic system disorders	Thrombocytopenia, febrile neutropenia, neutropenia, anaemia, lymphopenia † , leukopenia	Pancytopenia, reticulocytopenia, splenomegaly
Metabolism and nutrition disorders	Decreased appetite, hypokalaemia, hyperphosphatemia, hypomagnesaemia, fluid retention, hypophosphatemia	Hypoalbuminaemia, hypocalcaemia
Nervous system disorders	Headache	Cerebellar haemorrhage, hydrocephalus, peripheral sensory neuropathy, peripheral neuropathy, neuralgia, dysgeusia
Eye disorders		Vision blurred, dry eye
Cardiac disorders		Tachycardia
Vascular disorders		Hypotension, hot flush
Respiratory, thoracic and mediastinal disorders	Epistaxis, oropharyngeal pain	Respiratory failure, idiopathic pneumonia syndrome, hypoxia, dyspnoea, cough

System organ class (SOC)	Very common	Common
Gastrointestinal disorders	Mucositis ‡ , nausea, vomiting, abdominal pain § , diarrhoea, constipation, gastritis	Colitis, dyspepsia, gingival bleeding, gastrooesophageal reflux disease, haematemesis, oesophagitis, dysphagia, gastrointestinal inflammation, haematochezia, mouth ulceration
Hepatobiliary disorders	Venoocclusive liver disease, hyperbilirubinaemia, alanine aminotransferase increased	Aspartate aminotransferase increased, hepatomegaly, gamma-glutamyltransferase increased
Skin and subcutaneous tissue disorders	Pigmentation disorder # , skin exfoliation, alopecia, petechiae, dry skin, rash **	Pruritus, erythema
Musculoskeletal and connective tissue disorders	Musculoskeletal pain ††	Arthralgia
Renal and urinary disorders		Dysuria, haematuria
Reproductive system and breast disorders		Amenorrhoea, intermenstrual bleeding, vulvovaginal pain, dysmenorrhoea, menstruation irregular, premature menopause
General disorders and administration site conditions	Pyrexia, fatigue	Pain
Investigations	Weight decreased	International normalised ratio increased, C-reactive protein increased, weight increased
Injury, poisoning procedural complications		Delayed engraftment, subcutaneous haematoma, skin abrasion, skin laceration

* Frequency is based on the highest incidence from study 111 in patients with TDT or from study 121 in patients with SCD.
† Lymphopenia included CD4 lymphocytes decreased and lymphocyte count decreased.
‡ Mucositis included anal inflammation, mucosal inflammation, pharyngeal inflammation, and stomatitis.
§ Abdominal pain included abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and epigastric discomfort.
# Pigmentation disorder included nail pigmentation, skin hyperpigmentation, and skin hypopigmentation.
** Rash included dermatitis, rash erythematous, rash macular, rash maculo-papular, and rash papular.
†† Musculoskeletal pain included back pain, bone pain, chest pain and pain in extremity.

Table 27. Adverse reactions attributed to exa-cel in patients with TDT and SCD (N=97)*

System organ class (SOC)	Very common	Common
Blood and lymphatic system disorders	Lymphopenia †, ‡	Thrombocytopenia † , neutropenia † , anaemia † , leukopenia †
Immune system disorders		Haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders		Hypocalcaemia †
Nervous system disorders		Headache † , paraesthesia
Cardiac disorders		Tachycardia †
Respiratory, thoracic and mediastinal disorders		Acute respiratory distress syndrome, idiopathic pneumonia syndrome † , epistaxis †
Skin and subcutaneous tissue disorders		Rash †, § , petechiae †
General disorders and administration site conditions		Chills † , pyrexia †
Injury, poisoning procedural complications		Delayed engraftment † , infusion related reactions #

Note: * Frequency is based on the highest incidence from study 111 in patients with TDT or from study 121 in patients with SCD.
† At least one event was also attributed to busulfan myeloablative conditioning.
‡ Lymphopenia included CD4 lymphocytes decreased and lymphocyte count decreased.
§ Rash included dermatitis.
# Infusion related reactions included chills, sinus tachycardia, and tachycardia.

10. Documentation of health-related quality of life (HRQoL)

The EuroQol Quality of Life Scale – 5 dimensions – 5 levels of severity (EQ-5D-5L) was collected in the CLIMB SCD-121/131 trial to measure patients' health-related quality of life (141).

Table 28. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	CLIMB SCD-121/131	Instrument used to elicit health state utility values

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

The study design of study CLIMB SCD-121/131 is described in section 6.1. In the CLIMB SCD-121/131 clinical trial, patients completed patient-reported outcome measures related to their HRQoL, including the EuroQol Questionnaire – 5 dimensions – 5 levels of severity (EQ-5D-5L), and Pediatric Quality of Life Inventory (PedsQL). Utilities for uncomplicated SCD and cured SCD were obtained from analysis of CLIMB SCD-121/131, EQ-5D-5L data (April 2023 data cut), consistent with the preferred measure of HRQoL by the DMC. EQ-5D-5L was measured on patients in the PES aged ≥18 years.

10.1.2 Data collection

In CLIMB SCD-121/131, EQ-5D-5L data were collected at the following time points for the subset of patients in the PES aged ≥18 years (Table 29).

Table 29. Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
12 Months	[redacted]	[redacted]	[redacted]	[redacted]
18 Months	[redacted]	[redacted]	[redacted]	[redacted]
24 Months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRQL health related quality of life

10.1.3 HRQoL results

The results from the latest data cut of the CLIMB SCD-121/ trial show a baseline EQ-5D-5L health utility index score of [redacted] and changes from baseline at 24 months of [redacted], based on Danish value set (Table 30, Figure 7) (72, 134). Table 30 includes EQ-5D-5L values based on Danish value set, for patients treated with exa-cel.

Table 30. HRQoL EQ-5D-5L summary statistics, Danish utility weights

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	23	[redacted]	[redacted]	[redacted]	[redacted]
12 months	23	[redacted]	[redacted]	[redacted]	[redacted]
18 months	16	[redacted]	[redacted]	[redacted]	[redacted]
24 months	15	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRQL health related quality of life

Figure 7. EQ-5D-5L values, based on Danish value set, mean change from baseline through the different data collection time points for patients treated with exa-cel

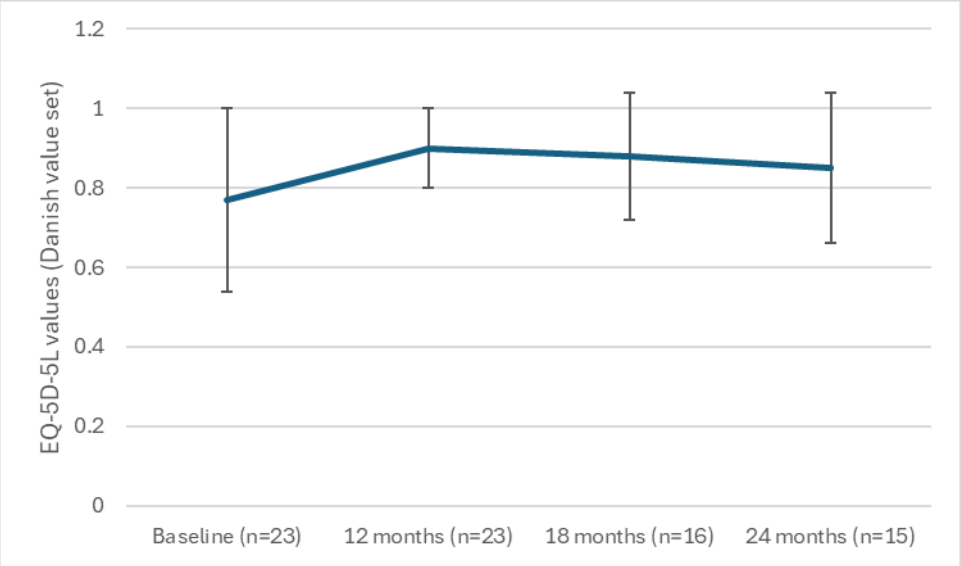


Table 31 and Figure 8 includes EQ5D VAS baseline values of 68.8 and changes from baseline at 24 months of 26.9 (142).

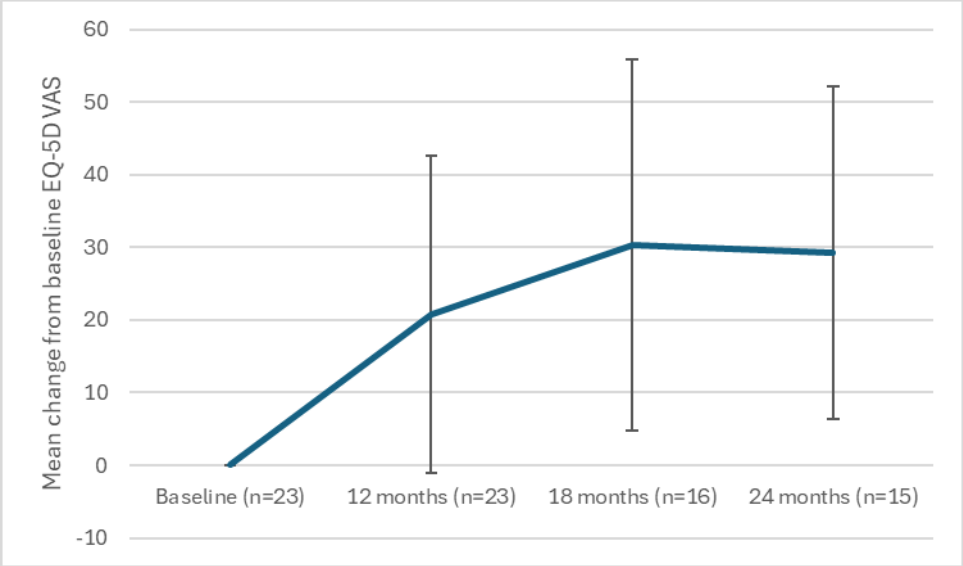
Table 31. EQ5D VAS summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12 months (change)	[redacted]	[redacted]	[redacted]	[redacted]
18 months (change)	[redacted]	[redacted]	[redacted]	[redacted]
24 months (change)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HRQL health related quality of life

Figure 8. EQ-5D VAS values, mean change from baseline through the different data collection time points for patients treated with exa-cel



Note: Baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

The utility input for patients with uncomplicated SCD (SCD in the absence of acute or chronic complications) was assumed to be 0.77 based on the EQ-5D-5L health index score at CLIMB SCD-121 trial baseline (134). The utility input for patients cured from SCD was assumed to be 0.85 based on the change in EQ-5D-5L health index score from baseline to month 24 in the trial (representing an increase of 0.11) (134). 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 (89).

Age adjustment for health state utility values (HSUV) was implemented in the base case analysis according to the DMC guidelines. When calculating the HSUV over time, the multiplicative method was used. The DMC has provided Danish standard values which were used to calculate an index which was be applied to the QALYs over time (143). The age-adjustment was done using the Danish general population utilities stratified by age groups to calculate the age-dependent multipliers. The age-dependent multipliers were then used to adjust the individual's undiscounted utility levels each cycle according to their age.

Table 32. Danish general population utility values stratified by age groups

Age group	Utility values
0-17	1
18-29	0.871
30-39	0.848
40-49	0.834
50-69	0.818
70-79	0.813
80+	0.721

10.2.1.1 Mapping

EQ-5D-5L utility scores were derived using preference weights based on the general Danish population. Mapping was performed based on DMC methods guide for assessing new pharmaceuticals (4), stating that preference weights based on the general Danish population (144) should be used to calculate health-related quality of life. The method used to map utilities is described in Appendix K.

10.2.2 Disutility calculation

Utility decrements due to AEs were sourced from a targeted literature review, including publications and previous HTA submissions (Table 2). Disutilities related to transplantation, infertility, acute complications, and chronic complications were applied to the proportion of the cohort experiencing the relevant events. The disutility per VOC event per month was assumed to be -0.18 based on the NICE submission of crizanlizumab, in which disutility of VOC was reported as -0.46 per event for a duration of 12 days (145, 146). [redacted] This study implies a cumulative disutility of approximately 0.46 over up to 3 weeks following the occurrence of a VOC, which is consistent with previous literature and model values used in previous economic assessments of SCD (145, 146).

Transplantation-related disutilities were informed by published sources. The disutility related to treatment with Exa-cel, in transplant year (-0.11) was based on Matza et al 2020 (117). Matza et al. specifically valued health states relevant to treatment with curative therapies and is thus considered the most relevant to the exa-cel treatment setting. In this study 207 respondents from the general population in England valued eight health state vignettes (developed with clinician, patient, and parent input) in time trade-of interviews (43). This study (49.8% female; mean age = 43.2 years) estimated mean (SD) utilities for the pre-transplant health states of 0.73 (0.25) with oral chelation and 0.63 (0.32) with subcutaneous chelation. The disutility due to engraftment failure (-0.40) was estimated based on the utility difference between patients without graft failure and patients experiencing graft failure (0.55), from a decision analysis model used to compare HSCT with other treatment strategies in SCD (118).

For Exa-cel, the model assumed that disutilities associated with AEs are captured in the transplantation-related disutility. For SOC and chronic medications, 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.

Disutilities due to SCD-related complications were sourced from the literature and are summarized along with all health state utility and disutility inputs in. Similar to mortality risks, in the base-case analysis, disutilities due to VOCs, acute and chronic complications were aggregated using a multiplicative interaction. Disutility related to infertility (-0.06) was sourced from a study utilities in a sample from the Dutch general population (Krol et al. 2019) (107). Disutilities for stroke, pulmonary embolism, avascular necrosis, retinopathy, and liver complications were sourced from studies identified in the SLR and are described in Appendix I (Ojelabi et al., Jiao et al., O'Brien et al). Disutility for acute chest syndrome was based on Lloyd et al., which estimated HRQoL in patients with moderate to severe asthma (108). Disutility for acute kidney injury, heart failure and chronic kidney disease was sourced from ICER's assessment report of Crizanlizumab, Voxelotor, and L-Glutamine (89). Disutility of acute infections was sourced from a prospective cohort study involving 701 patients with severe sepsis (Drabinski et al. 2001) (111). Disutility for gallstone complication was sourced from a clinical guideline for gallstone disease by NICE (112). Disutility of chronic pulmonary hypertension was based on a prospective study investigating HRQoL in patients treated with bosentan (Keogh 2007) (114). Disutility post-stroke was based on a systematic review of clinical effectiveness and cost-effectiveness of primary stroke prevention in children with SCD (Cherry et al. 2012) (115). Disutility of neurocognitive impairment was based on a study comparing HRQoL in adults with normal cognition, mild cognitive impairment and mild stage Alzheimer dementia showing that cognitive difficulties was associated with -0.05 difference in EQ5D vs no cognitive difficulties (Stites 2018) (116).

10.2.3 HSUV results

HSUVs and disutilities for complications and infertility are described in Table 33.

Table 33. Overview of health state utility values and disutilities

	Results [95% CI, SD]	Instrument	Tariff (value set) used	Comments
HSUVs				

	Results [95% CI, SD]	Instrument	Tariff (value set) used	Comments
Uncomplicated SCD	0.77 (0.67, 0.87, 0.23)	EQ-5D-5L	DK	The utility input for patients with uncomplicated SCD (SCD in the absence of acute or chronic complications) was assumed to be 0.77 based on the EQ-5D-5L health index score at CLIMB SCD-121 trial baseline (148)
Cured SCD	0.85 (0.77, 0.93, 0.19)	EQ-5D-5L	DK	The utility input for patients cured from SCD was assumed to be 0.85 based on the change in EQ-5D-5L health index score from baseline to month 24 in the trial (representing an increase of 0.08) (148)
Disutilities, treatment related				
Treatment with Exa-cel, in transplant year	-0.11	EQ-5D-3L	UK	Matza et al 2020 (117)
Graft failure (affects transplantation year)	-0.4	EQ-5D-3L	UK	O'Brien and Hankins 2009 (118)
Disutilities, infertility				
Infertility	-0.06	EQ-5D-3L	UK	Krol 2019 (107)
Disutilities, complications				
VOC	-0.18	EQ-5D-3L	UK	NICE Crizanlizumab STA [ID1406] (88)
Acute chest syndrome	-0.56	EQ-5D-3L	UK	Lloyd 2007 (108)
Stroke	-0.57	EQ-5D-3L	UK	Jiao 2022 (109)
Acute kidney injury	-0.14	EQ-5D-3L	UK	Bradt 2021 (ICER SCD report) (89)
Pulmonary embolism	-0.05	EQ-5D-3L	UK	Ojelabi 2019 (general complications)

	Results [95% CI, SD]	Instrument	Tariff (value set) used	Comments
				(110)
Acute infections	-0.16	EQ-5D-3L	UK	Drabinski 2001 (111)
Gallstones	-0.12	EQ-5D-3L	UK	NICE CG188 (112)
Leg ulcers	-0.11	EQ-5D-3L	UK	Michaels 2009 (113)
Chronic complications				
Pulmonary hypertension	-0.21	EQ-5D-3L	UK	Keogh 2007 (114)
Chronic kidney disease	-0.14	EQ-5D-3L	UK	Bradt 2020 (ICER SCD report) (89)
Avascular necrosis	-0.05	EQ-5D-3L	UK	Ojelabi 2019 (general complications) (110)
Post-stroke	-0.13	EQ-5D-3L	UK	Cherry 2012 (115)
Neurocognitive impairment	-0.05	EQ-5D-3L	UK	Stites 2018 (116)
Retinopathy	-0.05	EQ-5D-3L	UK	Ojelabi 2019 (general complications) (110)
Heart failure	-0.12	EQ-5D-3L	UK	Bradt 2020 (ICER SCD report) (89)
Liver complications	-0.05	EQ-5D-3L	UK	Ojelabi 2019 (general complications) (110)

Abbreviations: VOC Vaso-occlusive crisis

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Section not applicable.

10.3.1 Study design

Section not applicable.

10.3.2 Data collection

Section not applicable.

10.3.3 HRQoL results

Section not applicable.

10.3.4 HSUV and disutility results

Section not applicable.

Table 34. Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable				

Table 35. Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable				

11. Resource use and associated costs

The cost-effectiveness analysis was conducted from a Danish limited societal perspective including patient costs for transportation time and treatment time. Therefore, only direct costs and patient costs based on time and the costs for transportation were considered in the base-case analysis. Scenario analyses present the results when including productivity losses.

11.1 Medicine costs - intervention and comparator

For Exa-cel, the drug acquisition or transplant costs were considered among all patients assigned to the therapy at the beginning of the model. The acquisition cost of exa-cel was assumed to be 14 130 300 DKK. For SOC, dosing schedules were based on product information, when available. Drug acquisition costs for SOC (hydroxyurea) were based on the pharmacy purchase price (AIP) sourced from medicinpriser.dk. Costs of other supportive therapies that are part of SOC were assumed to be negligible and therefore not included in the model. Drug wastage was not considered in the model.

It was assumed that 64% of patients were on hydroxyurea to manage signs and symptoms of SCD at baseline. This was based on the voxelotor and crizanlizumab trials, which reported 64% and 63% of patients using concomitant hydroxyurea, respectively (89, 91, 97). Further, this model input is consistent with that used by the Institute for Clinical and Economic Review in the assessment of chronic medications in the treatment of SCD (89). The proportion of patients receiving deferoxamine (DFO), deferasirox (DFX) and deferiprone (DFP) at baseline was assumed to be 6%, 90% and 4%, respectively, based on a retrospective cohort study monitoring the iron-overload status and chelation of transfused SCD patients (149).

Table 36. Medicine costs used in the model

Pharmaceutical	Strength	Package size	Pharmacy purchase price (DKK)
Exa-cel	Minimum recommended dose is 3 × 10^6 CD34+ cells/kg	N/A	14 130 300
Hydroxyurea	500 mg	100	295
Deferoxamine (DFO)	500 mg	10	526.21
Deferasirox (DFX)	90 mg	90	3112.28
Deferiprone (DFP)	500 mg	100	1718.38
Plerixafor	24	1.2 ml	34 472.86
Busulfan	6mg/ml	8x10 ml	17 089

Abbreviations: DKK= Danish krone; mg = milligrams; ml = milliliters
Source: www.medicinpriser.dk, apotekets indkøbspris
Abbreviations: DFO = desferrioxamine; DFP= deferiprone; DFX = deferasirox

11.2 Medicine costs – co-administration

Not applicable

11.2.1 Transplant related costs

For patients receiving exa-cel, in addition to the treatment/drug costs other costs related to transplant were also considered in the model, including pre-transplant costs, hospitalization/procedure costs, and post-transplant monitoring costs. Pre-transplant costs included both mobilization/apheresis costs and all other transplant preparation costs (e.g., labs, physician visits, transfusions). Costs used in the model are described in Table 37.

Patients assigned to Exa-cel were assumed to receive additional exchange transfusions as a part of the treatment process. Exa-cel mobilization and apheresis process included treatment with plerixafor and hospitalization for harvesting procedure. Then, patients who would be infused with exa-cel received myeloablative conditioning with intravenous busulfan administration and RBC transfusions. Relevant costs were estimated based on resource use and unit costs presented in Table 37.

Patients also require hospitalization for the exa-cel infusion procedure, which was estimated at a cost of DKK 100.181, based on the Danish DRG code 26MP24 (DD572D) Seglcelle talassæmi+(BOQF0) Autolog knoglemarvstransplantation (52).

The model also includes post-transplant monitoring costs for exa-cel. The model assumed 15 years of post-transplant monitoring based on the duration of the open-label extension study following CLIMB SCD-121.

Table 37. Transplant related costs only applicable to exa-cel

Variable	Value	Reference
Pre-transplant costs		
Mobilization HRU		
Mobilization cycles	[redacted]	[redacted]
Plerixafor daily dose (mg/kg)	[redacted]	
Plerixafor length (days)	[redacted]	
Physician visits per cycle	[redacted]	
Mobilization costs		
Plerixafor cost per unit	DKK 34 472.86	Mozobil, 20 mg/ml, 1,2 ml inj.væske, opløsning, Medicinpriser.dk
Plerixafor unit strength (mg)	24	

Hospitalization for harvesting procedure	DKK 3 548	DRG 2024: 30SP04 - Sammedagspakke: UL, flere procedurer, meget kompl. + kompl.
Physician visits	DKK 1 066	Værdisætning af enhedsomkostninger v.1.7 Ledende overlæger/professorer Timeløn 2021
Myeloablation HRU		
Busulfan daily dose (mg/kg)	[redacted]	[redacted]
Myeloablation length (days)	[redacted]	[redacted]
Number of physician visits for transplant eligibility	[redacted]	[redacted]
Myeloablation costs		
Busulfan cost per unit	DKK 2 136	Busulfan "Fresenius Kabi" 6 mg/ml 8 x 10 ml konc.t.inf.væsk.opl. Medicinpriser.dk
Busulfan unit strength (mg)	60	
Cost of each physician visit for transplant eligibility	DKK 1 066	Assume to be the same as outpatient visits
Number of additional transfusions	[redacted]	[redacted]
Pre-transplantation RBC transfusion costs		
Number of exchange transfusion	[redacted]	[redacted]
Total RBC transfusion costs	[redacted]	[redacted]
Additional costs for transplantation		
Hospitalization costs for procedure	DKK 100.181	26MP24 (DD572D)Seglcelle talassæmi+(BOQF0)Autolog

		knoglemarvstransplantation based on KOL interaction (Jan 25)
Post-transplant monitoring		
Number of years of post-transplant monitoring	[redacted]	[redacted]
Monthly post-transplant monitoring cost		
Year 1	DKK 1 117	Takstkort 29A Laboratorieundersøgelser, Blod 21,87 kr, B-hæmoglobin 29,16 + Værdisætning af enhedsomkostninger v.1.7 Ledende overlæger/professorer Timeløn 2021 1066kr
Year 2	DKK 1 117	
Year 3	DKK 1 117	
Year 4	DKK 1 117	
Year 5+	DKK 1 117	

Abbreviations: HRU, healthcare resource utilisation; kg, kilogram; mg, milligram; RBC, red blood cell

11.2.2 Blood transfusion and ICT costs

At baseline, 100% of patients were assumed to receive RBC transfusions, 100% of which also were assumed to receive ICT (89) based on input from clinical expert. 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 cured from SCD. The procedure cost for RBCT was estimated to equal the DRG code 16MA04 (DD561A) Thalassaemia major + (BOQA5) Udskiftningstransfusion. Danish clinical expert estimated that an average of [redacted] bags of blood is needed for each an RBCXT. Unit costs per blood unit were derived from the Blood Bank at Righshospitalet via Danish clinical expert (52). The costing per RBC unit is shown in Table 38. It was assumed that patients with SCD receive [redacted] transfusions per month. Additionally, costs related to ICT were considered based on the type and route of administration of the ICTs (Table 38).

Table 38. Blood transfusion and ICT costs

Activity	Frequency	Unit cost (DKK)	DRG code	Reference
Blood transfusion costs				
Cost per administration	Every 6th week	6 530	16MA04	(DD561A) Thalassaemia major + (BOQA5)Udskiftningstransfusion

Blood cost per unit	[redacted]	[redacted]	[redacted]	[redacted]
Iron chelation costs				
Deferoxamine (DFO), 500 mg, dose 40mg/kg	[redacted]	52.62		(52, 150) Medicinpriser.dk
Administration costs per dose	Per administration	1 989	17MA98	DRG 2024 MDC17 1-dagsgruppe, pat. mindst 7 år
Deferasirox (DFX), 90 mg, 14 mg/kg	Every day	34.58		(151) Medicinpriser.dk
Administration costs per dose	0	0		Zero cost for oral drug
Deferiprone (DFP), 500mg, 75mg/kg	Every day	17.18		(152) Medicinpriser.dk
Administration costs per dose	0	0		Zero cost for oral drug

Abbreviations: DRG = Diagnosis Related Group

11.3 Administration costs

The cost of drug administration was applied to drugs administrated through subcutaneous infusion and transfusion. The DRG2023 code 17MA98 was used to source the cost of administration (Sundhedsdatastyrelsen 2023). More specifically, based on DRG2023 code 17MA98 “MDC17 1-dagsgruppe, pat. mindst 7 år”, a cost of 2005 DKK was assumed for subcutaneous infusion and a cost of 5 901 DKK based on the DRG2023 code 16PR01 “Transfusion af plasma og/eller behandlet blod” to source the cost of administration for transfusions.

Table 39. Administration costs used in the model

Administration type	Frequency	Unit cost DKK	DRG code	Reference
Subcutaneous infusion	5 days every week	1 989	17MA98	DRG 2024: 17MA98 - MDC17 1-dagsgruppe, pat. mindst 7 år

Administration type	Frequency	Unit cost DKK	DRG code	Reference
Transfusion	Approximately every 2nd month	4 218	16PR02	DRG 2024 16PR02 (DD561A) Thalassaemia major+(BOQA0) Blodtransfusion, 4 218 DKK

Abbreviations: DRG = Diagnose related group

11.4 Disease management 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 40). The model assumed a haematological test and the other specified lab tests were performed every third or sixth month (52). Physician visits were assumed to occur every fourth month based on consulted clinical opinion. The Danish clinical expert stated that SCD patients also was monitored with DEXA scan, Urine protein/creatinine ratio testing, glucose tolerance test and hepatitis A+B vaccination. But being treated with exa-cel did not differ these disease management costs and are therefore not included in Table 40 or in the cost effectiveness model. Unit cost per emergency room, inpatient, and outpatient visit, MR T2, echocardiography, fibroscan, retinopathia were based on Danish DRG codes.

Table 40. Disease management costs

Activity	Frequency	Unit cost (DKK)	DRG code	Reference
Lab/test/physician visit frequency				
Haematological tests/labs	[redacted]	N/A	N/A	Danish clinical expert
Renal tests/labs	[redacted]	N/A	N/A	Danish clinical expert
Hepatic tests/labs	[redacted]	N/A	N/A	Danish clinical expert
Lactate dehydrogenase test	[redacted]	N/A	N/A	Danish clinical expert
Foetal haemoglobin lab	[redacted]	N/A	N/A	Danish clinical expert
MR T2 (liver and heart)	[redacted]	N/A	N/A	Danish clinical expert
Echocardiography	[redacted]	N/A	N/A	Danish clinical expert
Retinopathia visit	[redacted]	N/A	N/A	Danish clinical expert

Activity	Frequency	Unit cost (DKK)	DRG code	Reference
Physician visits	[redacted]	N/A	N/A	Danish clinical expert
Unit cost				
Haematological tests/labs	[redacted]	21.87	N/A	2023, Takstkort 29A, Prøvetagning blod
Renal tests/labs	[redacted]	21.87	N/A	2023, Takstkort 29A, Prøvetagning blod
Hepatic tests/labs	[redacted]	21.87	N/A	2023, Takstkort 29A, Prøvetagning blod
Lactate dehydrogenase test	[redacted]	16.00	N/A	Laktatdehydrogenase [LDH];P (U/L), labportal.rh.dk
Foetal haemoglobin lab	[redacted]	57.18	N/A	B-hæmoglobin (fotometer), HONORARTABEL januari 2023
MR T2* (liver and heart)**	[redacted]	5 022	30PR02	DRG 2024:(DD572D)Seglcelle talassæmi + (UXMC80)MR-skanning af hjertet + (UXMD40)MR-skanning af lever (2511 DKK * 2)
Echocardiography	[redacted]	3 543	05PR03	DRG 2024: (DD572D)Seglcelle talassæmi+ (UXUC80C)Transtorakal ekkokardiografi med kontrast
Fibroscan	[redacted]	6 530	16MA04	(DD572D) Seglcelle talassæmi + (DH350)Retinopati og angiopati i retina
Physician visits	Every 4th Month	1 066	N/A	Værdisætning af enhedsomkostninger v.1.7 Ledende overlæger/professorer Timeløn 2021
Total monthly lab/test costs	[redacted]	[redacted]	N/A	[redacted]

*DFO recommended dose is 20-60 mg/kg/day; the midpoint (40 mg/kg/day) was used as base case model input.

Abbreviations: DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox; EPAR: European public assessment report; ICT, Iron chelation therapy; MIMS, Monthly Index of Medical Specialities; NHS, national health services; NICE, National Institute for Health and Care Excellence; RBC, red blood cell; SCD, sickle cell disease; STA: single technology appraisal, MR, Magnetic Resonance.
*Applied to patients with SCD; not applied for patients cured from SCD beginning after treatment phase: Monitoring costs is the difference in HRU in cured SCD and patients with SCD based on Danish clinical expert response.

11.5 Costs associated with management of adverse events

Costs for adverse events (AE) for exa-cel, are captured in transplantation or transplantation-related hospitalization costs, as those AEs were assumed to occur during the procedure hospitalization. AE costs for SOC were estimated based on monthly rates of recurring AEs, 2.19% per month.

The monthly adverse event rate for standard of care was calculated by averaging the adverse event rates of patients in the placebo arms of the pivotal trials of crizanlizumab, voxelotor, and L-glutamine. In the crizalizumab pivotal trial, 17 patients out of the 62 patients in the placebo arm experienced at least 1 serious adverse event (98). Converting this from a probability into an annual rate gives us an annual rate of 32.05% and, assuming these occur equally across all weeks of the 52 week follow-up, we calculate a 2.67% monthly AE rate. Vinchinsky et al. 2019 describes the voxelotor pivotal trial, where 24 of the 91 placebo patients experienced a grade 3+ treatment related adverse event (140). Converting this once again to an annual rate and adjusting to account for the 36.4 week median follow-up time we calculate a 3.64% monthly AE rate. Finally, the L-glutamine sponsor briefing document reports that in their trial 3 out of 111 placebo arm patients experienced drug-related severe adverse events (139) (note that this document was used rather than the original NCT01179217 publication due to the availability of more granular data. However, in this report, data was pooled with a smaller phase 2 study, resulting in a higher n, see Table 23). Using the 48-week follow-up we can calculate a monthly rate of 0.25%. Averaging these three values results in a monthly AE rate of 2.19% for placebo patients across these trials, which was then used as a proxy for the standard of care monthly grade 3+ AE rate.

The cost of a grade 3+ AE was assumed to be equal to the cost of a single physician visit based on Værdisætning af enhedsomkostninger v.1.7 Ledende overlæger/professorer Timeløn 2021 see Table 41. The cost per cycle equals 23.00 DKK (2.19%*1066 DKK).

Table 41. Cost associated with management of adverse events

Variable	DRG code	Unit cost/DRG tariff (DKK)
Treating a grade 3+ AE, affects 2.19% of patients per cycle	Værdisætning af enhedsomkostninger v.1.7 Ledende overlæger/professorer Timeløn 2021	1 066

Abbreviations: AE = adverse events

11.6 Subsequent treatment cost

Not applicable, no subsequent treatment is modelled.

Table 42. Medicine costs of subsequent treatments

Medicine	Strengths	Package size	Pharmacy purchase price (DKK)	Relative dose intensity	Average duration of treatment

Not applicable

11.7 Patient costs

Patient costs were estimated by the time spent due to administration and visits and transportation costs (round trip) (52). Patient costs were sourced from the DMC's guidance (Medicinrådet 2022 Værdisætning af enhedsomkostninger v.1.7). The costs and resource use applied in the analysis are presented in Table 43.

Table 43. Patient costs used in the model

Activity	Time spent	Unit cost (DKK)
Visit or drug administration	[redacted]	203 per hour
Round trip		149.2 per round trip

Abbreviations: DKK= Danish krone

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

11.8.1 Complication and other condition costs

The event cost per acute complication and the monthly cost of chronic complications were estimated based on Danish DRG 2023 codes and published literature (Table 44). 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 6 333 DKK based on DRG 2023 16MA04, (DD570) Seglcelleanæmi med krise).

Table 44. The event cost per acute complication and the monthly cost of chronic complications

Complication	Unit cost/DRG tariff (DKK)	DRG code
Acute complication costs (cost per event)		
VOC	6 530	DRG 2024, 16MA04, (DD570) Seglcelleanæmi med krise)

Complication	Unit cost/DRG tariff (DKK)	DRG code
Acute chest syndrome	35 426	Assumption being similar to pneumonia disease: DRG gruppe 04MA14 (DJ110) Influenza med lungebetændelse uden påvist influenzavirus
Stroke	44 492	DRG 2024 01MA05, DI619) Hjerneblødning UNS
Acute kidney injury	49 298	DRG 2024, 11MA01, Akutte medicinske nyresygdomme uden dialyse og uden plasmaferese
Pulmonary embolism	33 516	DRG 2024 04MA04, (DI260) Lungeemboli med akut cor pulmonale),
Acute infections	46 094	DRG 2024, 18MA08, Andre infektioner eller parasitære sygdomme
Gallstones	24 496	DRG 2024 07MA13, (DK805) Galdesten uden kolangitis eller kolecystitis)
Leg ulcers	58 089	DRG 2024, 09MA06, Kroniske sår i huden
Chronic complication costs (monthly cost per complication)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: DRG, Diagnose related group. * Calculation shown in Appendix

12. Results

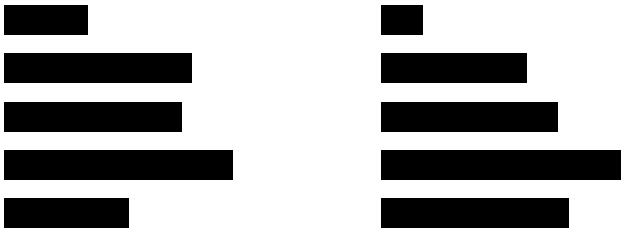
12.1 Base case overview

Base case settings for the model are presented in the table below.

Table 45. Base case overview

Feature	Description
Comparator	SoC
Type of model	Markov model
Time horizon	78 years (lifetime)
Treatment line	N/A exa-cel is a gene therapy (the HSCT option is ruled out following unsuccessful search for an available HLA-matched donor)
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in study CLIMB-111 (reference). Danish population weights were used to estimate health-state utility values. Frequency of VOC (mean per month) CLIMB-111
Costs included	Drug and transplant costs Hospitalization costs for exa-cel procedure Post-transplant monitoring costs Blood transfusion costs Iron chelation therapy costs Acute complication costs VOC costs Chronic complication costs Monitoring/lab costs AE costs Fertility preservation costs Transportation costs Annual discount rates of 3.5% and 1.5% were applied to both costs and health outcomes in two parallel base-cases
Dosage of medicine	Based on weight
Average time on treatment	Intervention: N/A Comparator: 78 years
Inclusion of waste	No

Average time in model health state



Abbreviation: SoC = standard of care, VOC vaso-occlusive crisis, SCD= sickle cell disease, AE = adverse events,

12.1.1 Base case results

Base case results are presented in the table below. Patients treated with exa-cel experienced a substantial reduction in the number of VOCs over the lifetime horizon and the lifetime burden of acute and chronic complications of SCD is projected to be lower in patients treated with stem cell therapies than in those receiving SOC. The results show a cost-effective treatment for a patient population with a great unmet need. The selected discount rates are defined based on DMC's handbook and a parallel scenario with a discount-rate level found to be more appropriate for gene-therapies with a high upfront investment cost and a transformational effect on patients' lives.

Table 46. Base case results, discounted estimates, DKK

	3.5 % discount rate			1.5 % discount rate		
	Exa-cel	**SoC**	**Difference**	**Exa-cel**	**SoC**	**Difference**
Drug or transplant costs (DKK)						
Mobilisation, apheresis, conditioning, and pre-treatment lab costs (DKK)						
Hospitalization costs for procedure (exa-cel) (DKK)						
Post-transplant monitoring costs (DKK)						
Blood transfusion costs (DKK)						

Iron chelation therapy costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute complication costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic complication costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring /lab costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fertility preservation costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient time and transportation costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs						
Cured / uncomplicated SCD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Complication disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Incremental cost per QALY gained (ICER)	**DKK 123 628**	**Dominant**

12.2 Sensitivity analyses

Various sensitivity analyses were conducted to explore the main areas of uncertainty within the model, including parameter uncertainty and structural uncertainty.

12.2.1 Deterministic sensitivity analyses

The DSA results indicate that the model was robust to most parameter changes [redacted]

Table 47. One-way sensitivity analyses results, the top ten most impactful parameters

Parameters	Change (lower – upper bound CI)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case with 3.5% disc. rate			[redacted]	[redacted]	[redacted]
Demographics					
Age (years) ± 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
Baseline clinical characteristics					
Frequency of VOC (mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameters		Change (lower – upper bound CI)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
per month) ± 95% CI						
Patients with baseline RBCX transfusion (%) ± 20%						
Efficacy						
Patients cured after treatment - Exa-cel (%) ± 20%						
Base utility						
Uncomplicated SCD utility ± 95% CI						
Cured SCD utility ± 95% CI						
Costs						
Blood transfusion costs						
Iron chelation costs						
Discount rate						
3.5% and 1.5% fixed discount rate						

Parameters	Change (lower – upper bound CI)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]					

Abbreviations: ICER = incremental cost-effectiveness ratio; CI = confidence intervals, DKK = Danish krone, DMC = Danish Medicines Council; VOC vaso-occlusive crisis, SCD= sickle cell disease; NICE = The National Institute for Health and Care Excellence; DMC = Danish Medicines Council

Results of the DSA are displayed in a tornado diagram, which present the 20 model inputs that most influence the ICER (discounted cost per QALY gained) for SOC.

Figure 9. Top 20 DSA and scenario analysis results of ICER exa-cel vs SOC

[redacted]

Table 48 shows the results from scenario analyses. Results were most sensitive to the baseline age, cost per blood unit, VOCs at baseline and discount rate. Exa-cel was the dominant strategy when taking productivity losses into consideration.

Table 48. Scenario analyses results

Scenarios	Incremental costs (DKK)	Incremental QALYs	ICER (DKK/QALY)
[redacted]			

[redacted]

Abbreviations: SMR = standardized mortality rate; DCEA = distributional cost-effectiveness analysis; DKK = Danish krone

12.2.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was conducted to simultaneously vary multiple parameters, based on their distributions, and re-estimate model outputs. A Monte-Carlo simulation with 1,000 iterations was conducted. In each iteration, key efficacy, utility, and cost inputs were randomly drawn from the specified distributions to inform the possible range of the inputs. The results were presented as a cost-effectiveness scatter plot and a cost-effectiveness acceptability curve comparing exa-cel with SoC. Both graphs display results for both the base CEA and equity-weighted results from the DCEA. All the model parameters that were varied in the PSA and their associated distributions are summarized in appendix G. Whenever available, the standard error (SE) of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability, the SE for each parameter was assumed as 20% of the mean value.

The probabilistic ICERs per QALY gained for exa-cel versus SoC were similar to the base-case deterministic results. Results of the PSA are displayed in incremental cost-effectiveness scatterplots, which present the variability in incremental costs and incremental QALYs over 1,000 iterations of the PSA. For exa-cel all analysis are in the first quadrant of the scatterplot, indicating that exa-cel is consistently more effective and more costly versus SoC in all iterations.

Table 49. Probabilistic sensitivity analysis results, based on 3.5% discount rate

Comparator	Mean QALY	Mean cost (DKK)	ICER (DKK/QALY)
Exa-cel	[redacted]	[redacted]	
SoC	[redacted]	[redacted]	
Incremental cost and QALY of Exa-cel vs SoC	[redacted]	[redacted]	
ICER per LY			[redacted]
ICER per QALY			[redacted]

Abbreviations: SoC = standard of care; ICER = incremental cost-effectiveness ratio; LY = life years; QALY = quality adjusted life years; DKK = Danish krone

The cost effectiveness acceptability curve in [redacted] shows that at the WTP of 1 000 000 DKK the probability of exa-cel being cost effective is 100%.

Figure 10. Cost effectiveness plane exa-cel vs standard of careEAC

[redacted]

[redacted]

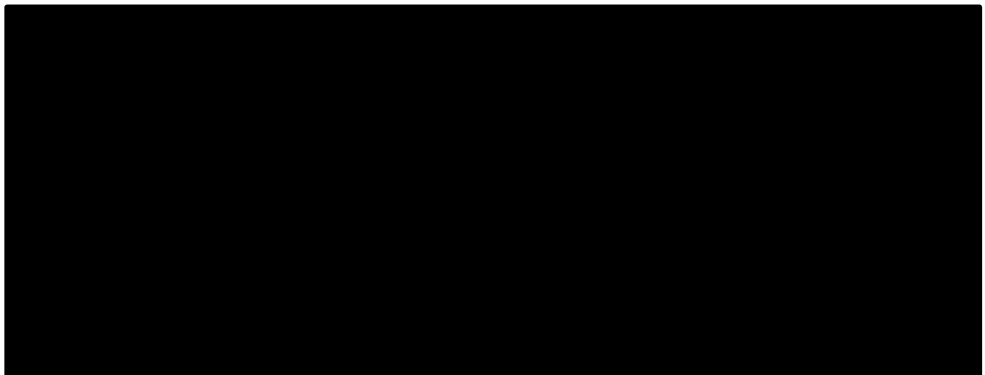
Figure 11 presents the cost-effectiveness plane, which shows that all of the 1,000 iterations were in the North-East quadrant. This means that exa-cel resulted in more QALYs and higher costs compared to SoC.

Figure 11. Cost effectiveness plane exa-cel vs standard of care

[redacted]

Figure 12 includes a convergence plot for the estimated mean. This is an iteration plot of ICER as a function of the number of PSA simulations needed for the outputs of interest to be considered to have converged i.e., the mean ICER has stabilised to within the specified accuracy of the deterministic ICER. In this case approximately a hundred PSA simulations was needed (157).

Figure 12. Convergence plot for the estimated mean (DKK)



13. Budget impact analysis

Based on Danish clinical expert opinion the prevalence and incidence [redacted] The numbers presented in Table 50 represent the number of patients expected to be treated in a scenario when exa-cel is introduced and one scenario when exa-cel is not introduced. Table 51 shows the budget impact if exa-cel is recommended and one scenario if exa-cel is not recommended.

Table 50. Number of new patients expected to be treated over the next five-year period if the pharmaceutical is introduced

	2024	2025	2026	2027	2028
	Recommendation				
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Non-recommendation				
Exa-cel	0	0	0	0	0
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC = standard of care

Table 51. Expected budget impact of recommending the pharmaceutical for the indication (DKK)

	2024	2025	2026	2027	2028
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC = standard of care

With the scenario of exa-cel being recommended it is important to show the budget impact of exa-cel treatment after 5 years. [redacted]

Table 52. Number of new patients expected to be treated over the next six to ten years (2029-2033) if the pharmaceutical is introduced (adjusted for market share)

	2029	2030	2031	2032	2033
			Recommendation		
Exa-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Exa-cel	0	0	0	0	0
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC = standard of care

Figure 13. Budget impact per year, over a ten-year period with exa-cel

Figure 14. Expected budget impact of recommending the pharmaceutical for the indication

14. List of experts

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Appendix A. Main characteristics of studies included

Table 53. Main characteristic of CLIMB SCD-121

Trial name: CLIMB SCD-121	NCT03745287
Objective	The purpose of the study is to evaluate the safety and efficacy of a single-dose of autologous CRISPR/Cas9 modified CD34+ HSPCs (exa-cel) in patients with severe SCD. CRISPR/Cas9 editing of autologous CD34+ HSPCs at erythroid lineage-specific enhancer of BCL11A is intended to disrupt BCL11A gene expression selectively in erythroid cells and consequently increase γ-globin expression in patients with SCD.
Publications – title, author, journal, year	de la Fuente J, Locatelli F, Frangoul H, Corbacioglu S, Wall D, Cappellini M, de Montalembert M, Kattamis A, Lobitz S, Rondelli D, Sheth S, Steinberg M, Walters M, Bobruff Y, Simard C, Song Y, Zhang L, Sharma A, Imren S, Hobbs B, Grupp S. 5612617 EFFICACY AND SAFETY OF A SINGLE DOSE OF EXAGAMGLOGENE AUTOTEMCEL FOR TRANSFUSION-DEPENDENT-THALASSEMIA AND SEVERE SICKLE CELL DISEASE. Hemasphere. 2023 Apr 10;7(Suppl):2-3.
Study type and design	CLIMB SCD-121 is a phase 1/2/3 single-arm, open-label, multi-site, single-dose study. For each patient, the study is conducted in four stages, including 1) screening and pre-mobilization, 2) mobilization, autologous CD34+ stem cell collection, exa-cel manufacture and disposition, 3) myeloablative conditioning and exa-cel infusion, and 4) follow-up through engraftment and for up to 2 years after exa-cel infusion (with up to 15 years of follow-up provided in the long-term CTX001-131 study) Patients enrolled in CLIMB SCD-121 will be eligible to roll over into long-term follow-up Study CTX001-131, evaluating the long-term safety following exa-cel infusion for up to 15 years (126)
Sample size (n)	45 (estimated)
Main inclusion criteria	Patients eligible for CLIMB SCD-121 have the βS/βS, βS/β0, or βS/β+ genotype, are aged 12–35 years, and have severe SCD defined as experiencing ≥2 severe VOCs per year during the past 2-years. Patients are required to be eligible for autologous HSCT but have no HLA-matched related donor (Section 6.4.1.3) (Vertex Pharmaceuticals Inc, 21 May 2021). **Inclusion Criteria:** Diagnosis of severe sickle cell disease as defined by: Documented severe sickle cell disease genotype History of at least two severe vaso-occlusive crisis events per year for the previous two years prior to enrolment

Trial name: CLIMB SCD-121	NCT03745287
	Eligible for autologous stem cell transplant as per investigators judgment
Main exclusion criteria	**Exclusion Criteria:** An available 10/10 human leukocyte antigen (HLA)-matched related donor Prior hematopoietic stem cell transplant (HSCT) Clinically significant and active bacterial, viral, fungal, or parasitic infection
Intervention	Exa-cel is a genetically modified autologous CD34+ cell enriched population that contains human HSPCs edited by CRISPR/Cas9 at the erythroid-specific enhancer region of the BCL11A gene. Exa-cel is provided as a single-dose dispersion for infusion intended for one-time use only. The finished product is composed of one or more vials, with each vial containing 4-13 x 10^6 cells/mL CD34+ HSPCs suspended in cryopreservative medium. The minimum recommended dose of exa-cel is 3 × 10^6 CD34+ cells/kg
Comparator(s)	N/A
Follow-up time	Follow-up through engraftment and for up to 2 years after exa-cel infusion (with up to 15 years of follow-up provided in the long-term CTX001-131 study)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary outcome measures:** Proportion of subjects who have not experienced any severe vaso-occlusive crisis (VOC) for at least 12 consecutive months (VF12) [Time frame: From 60 days after last RBC transfusion up to 2 years after exa-cel infusion] Proportion of subjects with engraftment (first day of three consecutive measurements of absolute neutrophil count [ANC] ≥500/µL on three different days) [Time frame:within 42 days after exa-cel infusion] Time to engraftment [Time frame: From exa-cel infusion up to 2 years after exa-cel infusion] Frequency and severity of collected adverse events (AEs) [From screening to 2 years after exa-cel infusion] Incidence of transplant-related mortality (TRM) within 100 days after exa-cel infusion [Time frame: Within 100 days after exa-cel infusion] Incidence of TRM within 1 year after exa-cel infusion [Time frame: Within 1 year after exa-cel infusion] All-cause mortality [Time frame: 2 years after mobilization] **Secondary outcome measures:**

Trial name: CLIMB SCD-121	NCT03745287
	Proportion of subjects free from inpatient hospitalization for severe VOCs sustained for at least 12 months (HF12)[Time frame: From 60 days after last RBC transfusion up to 2 years after exa-cel infusion]
	Proportion of subjects who have not experienced any severe VOC for at least 9 consecutive months (VF9) any time after exa-cel infusion [Time frame: From 60 days after last RBC transfusion up to 2 years after exa-cel infusion]
	Proportion of subjects with 90 percent (%), 80%, 75% or 50% reduction in annualized rate of severe VOCs [Time frame:60 days after last RBC transfusion up to 2 years after exa-cel infusion]
	Relative change from baseline in annualized rate of severe VOCs [Time frame: From 60 days after last RBC transfusion up to 2 years after exa-cel infusion]
	Duration of severe VOC free in subjects who have achieved VF12 [Time frame: From 60 days after last RBC transfusion up to 2 years after exa-cel infusion]
	Relative Change from baseline in rate of inpatient hospitalization for severe VOCs [Time frame: From 60 days after last RBC transfusion up to 2 years after exa-cel infusion]
	Relative change from baseline in annualized duration of hospitalisation for severe VOCs [Time frame: From 60 days after last RBC transfusion up to 2 years after exa-cel infusion]
	Proportion of subjects with sustained HbF ≥20% for at least 3 months [Time frame: From 60 days after last RBC transfusion up to 2 years after exa-cel infusion]
	Proportion of subjects with sustained HbF ≥20% for at least 12 months [Time frame: From 60 days after last RBC transfusion up to 2 years after exa-cel infusion]
	Proportion of subjects with sustained HbF ≥20% for at least 6 months [Time frame: From 60 days after last RBC transfusion up to 2 years after exa-cel infusion]
	Change in number of units of RBC transfused for SCD-related indications [Time frame: 6 months up to 2 years after exa-cel infusion]
	HbF concentration over time [Time frame: 1 month up to 2 years after exa-cel infusion]
	Hb concentration over time [Time frame: From the time of exa-cel up to 2 years after exa-cel infusion]
	Change from baseline in indirect bilirubin over time [Time frame: From baseline (pre-infusion) up to 2 years after exa-cel infusion]
	Change from baseline in reticulocyte count over time [Time frame: From baseline (pre-infusion) up to 2 years after exa-cel infusion]
	Change from baseline in haptoglobin over time [Time frame:From baseline (pre-infusion) up to 2 years after exa-cel infusion]
	Change from baseline in lactate dehydrogenase over time [Time frame: From baseline (pre-infusion) up to 2 years after exa-cel infusion]

Trial name: CLIMB SCD-121	NCT03745287
	Proportion of alleles with intended genetic modification present in peripheral blood leukocytes over time [Time frame:1 month up to 2 years after exa-cel infusion] Proportion of alleles with intended genetic modification present in CD34+ cells of bone marrow over time [Time frame:6 months up to 2 years after exa-cel infusion] Change in patient-reported outcome (PRO) over time assessed using weekly pain-scale (11-point numerical rating scale [NRS]) [Time frame:3 months up to 2 years after exa-cel infusion] Change in PRO over time assessed using EuroQol quality of life scale (EQ-5D-5L) [Time frame: 3 months up to 2 years after exa-cel infusion] Change in PRO over time assessed using EQ-5D-Youth (EQ-5D-Y) [Time frame:3 months up to 2 years after exa-cel infusion] Change in PRO over time assessed using functional assessment of cancer therapy-bone marrow transplant (FACT-BMT) questionnaire [Time frame: 3 months up to 2 years after exa-cel infusion] Change in PRO over time assessed using adult sickle cell quality of life measurement system (ASCQ-Me) [Time frame:3 months up to 2 years after exa-cel infusion] Change in PRO over time assessed using paediatric quality of life inventory (PedsQL) [Time frame:3 months up to 2 years after exa-cel infusion] Change in PRO over time assessed using PedsQL sickle cell disease module [Time frame: 3 months up to 2 years after exa-cel infusion]
Method of analysis	Intention to treat
Subgroup analyses	Planned subgroup analyses for the primary endpoint included analyses by Age at screening (≥12 to <18 and ≥18 to ≤35 years of age) Genotype (βS/βS and non-βS/βS) Sex and an analysis in the subgroup of patients with ≥3 VOCs per year for the prior 2 years at baseline.
Other relevant information	CLIMB SCD-121 is still ongoing

Abbreviations: VOC = vaso-occlusive crisis; RBC = red blood cell; TI6/12 = transfusion independence for at least 6/12 consecutive months; SD = standard deviation, PRO = patient reported outcomes; HbF = fetal hemoglobin

Table 54. Main characteristic of CTX001-131

Trial name: CTX001-131	NCT04208529
Objective	This is a multi-site, observational study to evaluate the long-term safety and efficacy of exa-cel in subjects who received exa-cel in Study CTX001-111 (NCT03655678) or VX21-CTX001-141 (transfusion-dependent β-thalassemia [TDT] studies) or Study CTX001-121

Trial name: CTX001-131	NCT04208529
	(NCT03745287) or VX21-CTX001-151 (severe sickle cell disease [SCD] studies; NCT05329649). The primary objective of the long-term CTX001-131 study is to evaluate long-term safety up to 15 years following exa-cel infusion in patients who received a single-dose of exa-cel for treatment of TDT or SCD (103). Evaluation of long-term efficacy in this population constitutes a secondary objective of the study (103).
Publications – title, author, journal, year	N/A
Study type and design	A prospective cohort study. All subjects who complete or discontinue the parent study (CTX001-111 or CTX001-121 or VX21-CTX001-141 or VX21-CTX001-151) after exa-cel infusion will be asked to participate in this long-term follow-up study. Patients who roll over into the long-term extension study will have follow-up visits every 3 months for the first 3 years, every 6 months in years 4 and 5, and annual visits thereafter for up to 15 years after infusion of exa-cel in the parent study (103). If the patient is unable or unwilling to come in for a scheduled clinic visit, the visit will be completed by telemedicine, and will include a visit to the patient's home from a home health nurse followed by a conversation between the patient and investigator (i.e., in person, phone, or video conference) within 1 week of the home visit (103). Patients will be followed-up for a total of up to 15 years after exa-cel infusion including a 2-year follow-up period in the parent study and up to 13 years of follow-up in CLIMB-131 (103).
Sample size (n)	
Main inclusion criteria	Inclusion criteria: Subjects (or his or her legally appointed and authorized representative or guardian) must sign and date informed consent form (ICF) and, where applicable, an assent form Subjects must have received exa-cel infusion in a parent study
Main exclusion criteria	No exclusion criteria
Intervention	No additional intervention to the exa-cel administered in the parent study
Comparator(s)	N/A
Follow-up time	Up to 15 years post exa-cel infusion
Is the study used in the health economic model?	Yes

Trial name: CTX001-131	NCT04208529
Primary, secondary and exploratory endpoints	Consistent with the primary objective, primary endpoints of the study are safety endpoints, assessed for up to 15 years post-infusion (except for SAEs, as noted below) (103): New or worsening hematologic disorders [up to 15 years post exa-cel infusion] All-cause mortality [up to 15 years post exa-cel infusion] Serious adverse events (SAEs) [up to 5 years post exa-cel infusion] exa-cel-related AEs [up to 15 years post exa-cel infusion] **Secondary outcome measures:** Hemoglobin (Hb) concentration over time [up to 15 years post exa-cel infusion] HbF concentration over time [up to 15 years post exa-cel infusion] Proportion of alleles with intended genetic modification present in peripheral blood over time [up to 15 years post exa-cel infusion] Change in patient-reported outcome (PRO) over time in subjects ≥18 years of age assessed using EuroQol quality of life scale (EQ-5D-5L) for subjects from study CTX001-111 and study CTX001-121 only [up to 5 years post exa-cel infusion] Change in PROs over time in subjects ≥18 years of age assessed using functional assessment of cancer therapy-bone marrow transplant (FACT-BMT) questionnaire for subjects from study CTX001-111 and study CTX001-121 only [up to 5 years post exa-cel infusion] Change in PROs over time in subjects <18 years assessed using EQ-5D-Youth (EQ-5D-Y) [up to 5 years post exa-cel infusion] Change in PROs over time in subjects <18 years assessed using pediatric quality of life inventory (PedsQL) Core [up to 5 years post exa-cel infusion] Proportion of subjects who have not experienced any severe vaso-occlusive crises (VOC) for at least 12 consecutive months (VF12) [From 60 days after last RBC transfusion up to 15 years post-exa-cel infusion] Proportion of subjects with SCD free from inpatient hospitalization for severe VOCs sustained for at least 12 months (HF12) [From 60 days after last RBC transfusion up to 15 years post-exa-cel infusion] Proportion of subjects with at least 90 percent (%), 80%, 75% or 50% reduction in annualized rate of severe VOCs [From 60 days after last RBC transfusion up to 15 years post-exa-cel infusion] Relative change from baseline in annualized rate of severe VOCs [From 60 days after last RBC transfusion up to 15 years post-exa-cel infusion] Duration of severe VOC free in subjects who have achieved VF12 [From 60 days after last RBC transfusion up to 15 years post exa-cel infusion] Relative change from baseline in rate of inpatient hospitalizations for severe VOCs [From 60 days after last RBC transfusion up to 15 years post-exa-cel infusion]

Trial name: CTX001-131	NCT04208529
	Relative change from baseline in annualized duration of hospitalization for severe VOCs [From 60 days after last RBC transfusion up to 15 years post-exa-cel infusion] Proportion of subjects with sustained HbF ≥20% for at least 3 months [From 60 days after last RBC transfusion up to 15 years post-exa-cel infusion] Proportion of subjects with sustained HbF ≥20% for at least 6 months [From 60 days after last RBC transfusion up to 15 years post-exa-cel infusion] Proportion of subjects with sustained HbF ≥20% for at least 12 months [From 60 days after last RBC transfusion up to 15 years post-exa-cel infusion] Change in volume of RBCs transfused for SCD-related indications over time [Up to 15 years post exa-cel infusion] Change from baseline in reticulocytes/erythrocytes over time [From baseline up to 15 years post exa-cel infusion] Change from baseline in lactate dehydrogenase (LDH) over time [From baseline up to 15 years post exa-cel infusion] Change from baseline in haptoglobin over time [From baseline up to 15 years post exa-cel infusion] Change from baseline in total bilirubin over time [From baseline up to 15 years post exa-cel infusion] Change from baseline in indirect bilirubin over time [From baseline up to 15 years post exa-cel infusion] Change in SCD-specific PROs over time in subjects ≥18 years of age assessed using adult sickle cell quality of life measurement system (ASCQ-Me) (subjects from Study 121 only) [Up to 5 years post exa-cel infusion] Change in SCD-specific PROs over time in subjects <18 years of age assessed using PedsQL SCD module [Up to 5 years post exa-cel infusion] Change in PRO over time assessed using 11-point numerical rating scale (NRS) [Up to 5 years post exa-cel infusion] Change in PROs over time assessed using Wong Baker FACES pain scale [Up to 5 years post exa-cel infusion] Change in PROs over time using face, legs, activity, cry, consolability (FLACC) behavioural pain scale [Up to 5 years post exa-cel infusion]
Method of analysis	Intention to treat
Subgroup analyses	Planned subgroup analyses for the primary endpoint included analyses by age at screening (≥12 to <18 and ≥18 to ≤35 years of age), genotype (βS/βS and non-βS/βS), sex, and an analysis in the subgroup of patients with ≥3 VOCs per year for the prior 2 years at baseline.

Abbreviations: VOC = vaso-occlusive crisis; RBC = red blood cell; TI6/12 = transfusion independence for at least 6/12 consecutive months; SD = standard deviation, PRO = patient reported outcomes; HbF = fetal hemoglobin

Table 55. Main characteristic of SUSTAIN

Trial name: SUSTAIN	NCT01895361
Objective	The purpose of this study was to determine whether the investigational drug SelG1 when given to sickle cell disease patients either taking or not taking hydroxyurea was effective in preventing or reducing the occurrence of pain crises. SelG1 prevents various cells in the bloodstream from sticking together. By stopping these cell-cell interactions, SelG1 may prevent small blood vessels from becoming blocked and therefore reduce the occurrence and severity of pain crises. Other effects of SelG1 was evaluated, as well as the safety of the drug and how long it stayed in the blood stream.
Publications – title, author, journal, year	Ataga, K. I., Kutlar, A., Kanter, J., Liles, D., Cancado, R., Friedrisch, J., Guthrie, T. H., Knight-Madden, J., Alvarez, O. A., Gordeuk, V. R., Gualandro, S., Colella, M. P., Smith, W. R., Rollins, S. A., Stocker, J. W. & Rother, R. P. 2017. Crizanlizumab for the prevention of pain crises in sickle cell disease. *New England Journal of Medicine,* 376**,** 429-439. (98)
Study type and design	A Phase II, Multicenter, Randomized, Placebo-Controlled, Double-Blind, 12-Month Study
Sample size (n)	198
Main inclusion criteria	Sickle Cell Disease (HbSS, HbSC, HbSβ^{o}-thalassemia, or HbSβ^{+}-thalassemia) If receiving hydroxyurea or erythropoietin, treatment must have been prescribed for at least 6 months, with the dose stable for at least 3 months Between 2 and 10 sickle cell-related pain crises in the past 12 months Age 16 Years to 65 Years
Main exclusion criteria	On a chronic transfusion program or planning on exchange transfusion during the study Hemoglobin <4.0 g/dL Planned initiation, termination, or dose alteration of hydroxyurea during the study Receiving chronic anticoagulation therapy (e.g. warfarin, heparin) other than aspirin
Intervention	Crizanlizumab 5.0 or 2.5 mg/kg i.v. E4W,
Comparator(s)	Placebo (i.v. E4W)
Follow-up time	1 year
Is the study used in the health economic model?	No

Trial name: SUSTAIN	NCT01895361
Primary, secondary and exploratory endpoints	Primary outcomes: Annual Rate of Sickle Cell-related Pain Crises (SCPC) Per Hodges-Lehmann Median (1 year) Annual Rate of Sickle Cell-related Pain Crises (SCPC) - Per Standard Median (1 year) Secondary outcomes: Annual Rate of Days Hospitalized (Key Secondary Endpoint) Per Hodges-Lehmann Median Time to First Sickle Cell-related Pain Crisis Time to Second Sickle Cell-related Pain Crisis Annual Rate of Uncomplicated Sickle Cell-related Pain Crisis Per Hodges-Lehmann Median Annual Rate of Acute Chest Syndrome Per Hodges-Lehmann Median Patient Reported Outcome: Change From Baseline in Pain Severity/Pain Interference Domain From Brief Pain Inventory (BPI) Questionnaire
Method of analysis	ITT
Subgroup analyses	Concomitant hydroxyurea use Categorized history of crisis frequency Sickle cell disease genotype
Other relevant information	

Table 56. Main characteristic of HOPE

Trial name: HOPE	NCT03036813
Objective	The key purpose for the study is to establish efficacy and safety of voxelotor as compared with placebo.
Publications – title, author, journal, year	Vichinsky, E., Hoppe, C. C., Ataga, K. I., Ware, R. E., Nduba, V., El-Beshlawy, A., Hassab, H., Achebe, M. M., Alkindi, S., Brown, R. C., Diuguid, D. L., Telfer, P., Tsitsikas, D. A., Elghandour, A., Gordeuk, V. R., Kanter, J., Abboud, M. R., Lehrer-Graiwer, J., Tonda, M., Intondi, A., Tong, B. & Howard, J. 2019. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. *New England Journal of Medicine,* 381**,** 509-519 (97) Howard, J., Ataga, K. I., Brown, R. C., Achebe, M., Nduba, V., El-Beshlawy, A., Hassab, H., Agodoa, I., Tonda, M. & Gray, S. 2021. 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. *The Lancet Haematology,* 8**,** e323-e333. (96)
Study type and design	A Phase 3, Double-blind, Randomized, Placebo-controlled, Multicenter Study
Sample size (n)	449
Main inclusion criteria	Male or female study participants with sickle cell disease Participants have had at least 1 episode of vaso-occlusive crisis (VOC) in the past 12 months. Age 12 to 65 years Hemoglobin (Hb) ≥5.5 and ≤10.5 g/dL during screening For participants taking hydroxyurea (HU), the dose of HU (mg/kg) must be stable for at least 3 months prior to signing the ICF.
Main exclusion criteria	More than 10 VOCs within the past 12 months that required a hospital, emergency room or clinic visit Patients who are receiving regularly scheduled blood (RBC) transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) or have received a RBC transfusion for any reason within 60 days of signing the ICF Hospitalized for sickle cell crisis or other vaso-occlusive event within 14 days of signing the ICF (i.e., a vaso-occlusive event cannot be within 14 days prior to signing the ICF) Hepatic dysfunction characterized by alanine aminotransferase (ALT) >4 × upper limit of normal Severe renal dysfunction (estimated glomerular filtration rate at the Screening visit; calculated by the central laboratory) <30 mL/min/1.73 m^2 or on chronic dialysis
Intervention	Voxelotor 1500 or 900 mg orally once daily
Comparator(s)	Placebo

Trial name: HOPE	NCT03036813
Follow-up time	72 weeks
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	Primary outcome: Number of Participants With Increase in Hb >1 g/dL From Baseline to Week 24 Secondary outcomes: Annualized Vaso-Occlusive Crisis (VOC) Incidence Rate Percentage Change From Baseline in Hemolysis Measures Percentage Change From Baseline in Hemolysis Measures Percentage Change From Baseline in Hemolysis Measures Percentage Change From Baseline in Hemolysis Measures
Method of analysis	ITT
Subgroup analyses	NR

Table 57. Main characteristic of NCT01179217

Trial name: NCT01179217	NCT01179217
Objective	To evaluate the efficacy of oral L-glutamine as a therapy for sickle cell anemia and sickle ß0-thalassemia as evaluated by the number of occurrences of sickle cell crises.
Publications – title, author, journal, year	Niihara, Y., Miller, S. T., Kanter, J., Lanzkron, S., Smith, W. R., Hsu, L. L., Gordeuk, V. R., Viswanathan, K., Sarnaik, S. & Osunkwo, I. 2018. A phase 3 trial of l-glutamine in sickle cell disease. *New England Journal of Medicine,* 379**,** 226-235. (99, 105)
Study type and design	Phase 3, prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter study
Sample size (n)	230
Main inclusion criteria	Patient is at least five years of age. Patient has been diagnosed with sickle cell anemia or sickle ß°-thalassemia (documented by hemoglobin electrophoresis). Patient has had at least two documented episodes of sickle cell crises within 12 months of the screening visit. If the patient has been treated with an anti-sickling agent within three months of the screening visit, the therapy must have been continuous for at least three months with the intent to continue for the duration of the study. Patient or the patient's legally authorized representative has given written informed consent. If the patient is a female of child-bearing potential, she agrees to avoid pregnancy during the study and is willing and agrees to practice a recognized form of birth control during the course of the study (e.g. barrier, birth control pills, abstinence).
Main exclusion criteria	Patient has a significant medical condition that required hospitalization (other than sickle cell crisis) within two months of the screening visit. Patient has prothrombin time INR > 2.0. Patient has serum albumin < 3.0 g/dl. Patient has received any blood products within three weeks of the Screening Visit. Patient has uncontrolled liver disease or renal insufficiency. Patient is pregnant or lactating or has the intention of becoming pregnant during the study (if female and of child-bearing potential). Patient is currently taking or has been treated with any form of glutamine supplement within 30 days of the screening visit.

Trial name: NCT01179217	NCT01179217
	Patient has been treated with an experimental anti-sickling medication/ treatment within 30 days of the screening visit (with the exception of hydroxyurea in pediatric patients). Patient is currently taking or has been treated with an investigational drug within 30 days of the screening visit (with the exception of hydroxyurea in pediatric patients). Patient is currently enrolled in an investigational drug or device study and/or has participated in such a study within 30 days of the screening visit. There are factors that would, in the judgment of the investigator, make it difficult for the patient to comply with the requirements of the study.
Intervention	L-glutamine (0.3 g/kg orally, twice daily)
Comparator(s)	Placebo
Follow-up time	48 weeks
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	Primary outcome: The Number of Occurrences of Sickle Cell Crises Secondary outcomes: The Number of Hospitalizations for Sickle Cell Pain The Number of Emergency Room/Medical Facility Visits for Sickle Cell Pain The Effect of Oral -L-glutamine on Hematological Parameters The Effect of Oral L-glutamine on Vital Signs The Effect of Oral L-glutamine on Hematological Parameters
Method of analysis	ITT
Subgroup analyses	Hydroxyurea use Sex Age

Appendix B. Efficacy results per study

B.1 CLIMB SCD-121/CTX001-131

Table 58. Results per study – CLIMB SCD-121 and CTX001-131

Results of CLIMB SCD-121 and CTX001-131 (NCT03745287 and NCT04208529)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients VOC-free for at least 12 consecutive months (VF12)	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Calculations made on the PES (day 120 data-cut)	

Results of CLIMB SCD-121 and CTX001-131 (NCT03745287 and NCT04208529)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
VOC-free duration, months, mean (range)	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Calculations made on patients VOC-free in the PES (day 120 data-cut)	
Proportion of patients hospitalization free for 12 consecutive months (HF12)	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Calculations made on PES (day 120 data-cut)	

Results of CLIMB SCD-121 and CTX001-131 (NCT03745287 and NCT04208529)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Hb levels at 3, 6, 12, and 24 months post exa-cel infusion, FAS, g/dL mean (SD)	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Calculations made on FAS (day 120 data-cut, including CTX001-131)	
HbF levels at 3 . 6. 12, and 24 months post exa-cel infusion, FAS, g/dL mean (SD)	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Calculations made on FAS (day 120 data-cut, including CTX001-131)	

Results of CLIMB SCD-121 and CTX001-131 (NCT03745287 and NCT04208529)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of RBCs expressing HbF at 3, 6, 12, and 24 months post exa-cel infusion, FAS, % (SD)	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Calculations made on FAS (day 120 data-cut, including CTX001-131)	

B.1.1 CLIMB SCD-121 baseline characteristics

Table 59: Baseline Characteristics (Study 121 PES and FAS)

Baseline Characteristics	PES N = 29	FAS N = 43
Genotype, n (%)		
β^S/β^S	[redacted]	[redacted]
β^S/β^0	[redacted]	[redacted]
β^S/β^+	[redacted]	[redacted]
HbF (g/dL)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
HbF (%)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Total Hb (g/dL)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Annualized rate of severe VOCs		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]

Min, max	[redacted]	[redacted]
Annualized rate of inpatient hospitalizations for severe VOCs		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Annualized duration of inpatient hospitalizations for severe VOCs (days)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Annualized units of RBCs transfused for SCD–related indications		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Indirect bilirubin (µmol/L)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Haptoglobin (g/L)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Lactate dehydrogenase (U/L)		

n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Weight (kg)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Hydroxyurea, n (%)		
N	[redacted]	[redacted]
Yes	[redacted]	[redacted]

Abbreviations: EAC: Endpoint Adjudication Committee; FAS: Full Analysis Set; Hb: hemoglobin; HbF: fetal hemoglobin; max: maximum; min: minimum; N: total sample size; n: size of subsample; NA: not available; 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 mobilization unless specified otherwise. Baseline severe VOCs, inpatient hospitalizations for severe VOCs, and RBC transfusions were based on the 2 years before the most recent screening. For hemolysis markers, reticulocytes, and indirect bilirubin, if these are multiple measurements before mobilization, the most recent one prior to the start of exchange transfusions was used. If it was missing, then the most distant from the last exchange transfusion prior to that measurement and still before the start of mobilization was used. Subjects with Gilbert's syndrome were excluded from the summary of indirect bilirubin. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included. Hb measurements were from central laboratories. Annualized rate = total number of events/number of years. Annualized duration = total duration of events/number of years. Annualized units = total units/number of years. One year = 365.25 days. For hemolysis markers, values with "below detectable limit" are considered as 0.

Sources: Study 121/Table 14.1.4.1 and Table 14.1.4.2 (data cutoff date of 16 April 2023)

B.1.2 VOC-related endpoints (additional tables and figures)

Table 60. Subgroup analysis for the primary efficacy endpoint of VF12 in the PES (Day 120 update)

Subgroup	Statistics	N	Proportion	95% CI
Age group	Age ≥12 and <18 years	[redacted]	[redacted]	[redacted]
	Age ≥18 and ≤35 years	[redacted]	[redacted]	[redacted]
Baseline VOCs	≥3 VOCs per year	[redacted]	[redacted]	[redacted]
Follow-up duration	≥18 months of follow-up	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; PES = primary efficacy set; VOC = vaso-occlusive crisis.

Source: Exa-cel efficacy and safety update 16 April 2023 (127)

B.1.2.1 Extended Durability of Severe VOC Free Period: Duration of Severe VOC Free (Secondary Endpoint)

As of the data cutoff date (16 April 2023), for the 28 subjects in PES who achieved VF12, the mean (SD) VOC free duration was 20.7 (7.1) months, including the follow-up in Study 131. Twenty seven of 28 (96.4%) subjects who achieved VF12 remained VOC free for the duration of follow-up in Studies 121 and 131, up to 43.6 months after exa-cel infusion (Table 61, Figure 15) demonstrating the durability of treatment effect. One subject (Subject 005) achieved VF12 and was VOC free for ~22.7 months after exa-cel infusion, then had a single event adjudicated as a VOC by the Endpoint Adjudication Committee (EAC) in the setting of parvovirus infection and has subsequently been VOC free for ~10.4 months.

Table 61: Summary of Severe VOC Free Duration for Subjects Who Achieved VF12 (Study 121 PES; Studies 121 and 131 [SCD]PES)

Category	Studies 121 and 131 Total N = 29
Subjects who achieved VF12, N1	[redacted]
Duration of severe VOC free for subjects who achieved VF12 (months)	
N	[redacted]
Mean (SD)	[redacted]
Median	[redacted]
Min, max	[redacted]

Sources: Exa-cel efficacy and safety update 16 April 2023 (127)
EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; N: total sample size; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease; VF12: absence of any severe VOCs for at least 12 consecutive months after exa-cel infusion; VOC: vaso-occlusive crises
Notes: The post exa-cel infusion follow-up periods in both Studies 121 and 131, if any, are included in this analysis. The evaluation of the severe VOC free duration in subjects who achieved VF12 started 60 days after the last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of the initial RBC transfusions for post-transplant support or SCD management. Duration of severe VOC free (months) = (the day before the start date of the first severe VOC after achieving VF12 or the data cutoff date or the end of study date whichever was earlier – the start date of VF12 + 1)/30. If there were multiple severe VOC free periods, the longest severe VOC free period was used in the summary. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included in the analysis.

Figure 15: Historical and after exa-cel severe VOCs and severe VOC free duration among patients in the FAS (studies 121 and 131, Day 120 update)

[redacted]

B.1.2.2 Extended Durability of Free from Inpatient Hospitalization for Severe VOCs (secondary endpoint)

In Study 121, 41 of 43 subjects 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 41 subjects, 40 subjects were free from inpatient hospitalization for VOCs after exa-cel infusion through the duration of follow-up in Studies 121 and 131 for mean (range) of 16.2 (1.3 to 43.6) months, starting 60 days after the last RBC transfusion (

Figure 16) and [redacted] (1, 127).

Figure 16: Duration free from inpatient hospitalisation for severe VOC among patients in the FAS (studies 121 and 131, Day 120 update)

[redacted]

[redacted]

B.1.3 Total Hb and HbF Concentration Over Time (Secondary Endpoints)

Hematologic stability (stable total Hb, HbF and F-cell levels) was achieved at Month 4 and maintained for the duration of follow-up. Increases in total Hb and HbF occurred early and were maintained over time from Month 6 through Month 42, demonstrating durability of response (Table 13). In the FAS, mean (SD) total Hb levels were 12.0 (1.5) g/dL at Month 3 and were subsequently maintained at ≥12 g/dL over the duration of follow-up (Figure 17, Table 62). HbF levels were 4.5 (1.4) g/dL at Month 3, increased to 5.5 (1.4) g/dL at Month 6, and were maintained at >5 g/dL thereafter (Table 62). [redacted]

Figure 17. Summary of Total Hb (g/dL) and HbF (g/dL) Over Time (Studies 121 and 131 [SCD]FAS)

[redacted]

Notes: Mean values are plotted in the line, mean + SE and mean – SE values are plotted as bars at each visit. The numbers of subjects 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 mobilization in Study 121. Analysis visit was used in the figure.

Figure 18: Hb fractionation over time among patients in the FAS (studies 121 and 131, Day 120 update)

Results observed in the PES were similar to those seen in the FAS (128, 158). Mean (SD) total Hb levels were 12.1 (1.3) g/dL at Month 3 and were maintained with mean ≥11.1 g/dL from Month 6 onward.

Figure 19. Total Hb and HbF over time for individual patients in the FAS (studies 121 and 131, Day 120 update)

[redacted]

[redacted]

Figure 20: Total Hb and HbF over time for individual patients in the FAS (studies 121 and 131, Day 120 update)

[redacted]

[redacted]

Figure 21: Hb fractionation over time among patients in the PES (studies 121 and 131, Day 120 update)

[redacted]

[redacted]

Figure 22: Proportion of Hb comprised by HbF over time among patients in the FAS (studies 121 and 131, Day 120 update)

Figure 23: Proportion of circulating RBCs expressing HbF (F-cells) over time among patients in the FAS (studies 121 and 131, Day 120 update)

Figure 24: Proportion of circulating RBCs expressing HbF (F-cells) over time among patients in the PES (studies 121 and 131, Day 120 update)

Table 62: Hb and HbF levels and proportion of F-cells over time among patients in the FAS and PES (studies 121 and 131, Day 120 update)

Visit	Statistics	FAS				PES			
		Hb (g/dL)	HbF (g/dL)	HbF (% of Hb)	F cells (%)	Hb (g/dL)	HbF (g/dL)	HbF (% of Hb)	F cells (%)
Baseline	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mean (SD)	[redacted]							

Abbreviations: FAS = full analysis set; Hb = hemoglobin; HbF = fetal hemoglobin; PES = primary efficacy set; SD = standard deviation.
Source: [redacted]

B.1.4 Proportion of alleles with intended genetic modification

The proportion of alleles with the intended genetic modification (allelic editing) in the CD34+ cells of the bone marrow and in peripheral blood over time are indicative of the durable engraftment of edited LT-HSCs and reflect the permanent nature of the intended edit.

Figure 25. Peripheral blood allelic editing (%) over time among patients in the FAS (studies 121 and 131, Day 120 update)

Figure 26. Bone marrow allelic editing (%) over time among patients in the FAS (studies 121 and 131, Day 120 update)

[redacted]

Results with regards to peripheral blood and bone marrow editing were similar in the PES.

Table 63. Proportion of alleles with intended genetic modification present in CD34+ cells of the bone marrow and peripheral blood over time among patients in the FAS and PES (studies 121 and 131, Day 120 update)

Visit	Statistics	FAS		PES	
		Bone marrow allelic editing (%)	Blood allelic editing (%)	Bone marrow allelic editing (%)	Blood allelic editing (%)
Baseline	n	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	n	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	n	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	n	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	n	[redacted]	[redacted]	[redacted]	
	Mean (SD)	[redacted]	[redacted]	[redacted]	
Month 24	n	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FAS = full analysis set; PES = primary efficacy set; SD = standard deviation
Source: : Exa-cel efficacy and safety update 16 April 2023 (127)

B.1.5 Hemolysis biomarkers

[redacted]

B.1.6 Reduction in RBC transfusions

[redacted]

B.1.7 EQ-5D-5L

The EQ-5D-5L assesses an adult subject's health status in a standardized way, is widely used in multiple diseases, and consists of 2 parts: the EQ-5D-5L descriptive system and the EQ VAS. The mean EQ-5D-5L health utility scores at baseline 0.77 were lower than the average Danish general population scores (0.87), indicating health-related quality of life impairment prior to exa-cel infusion. Clinically meaningful improvements in EQ-5D-5L were observed from Month 6 onward, with the mean (SD) change from baseline at Month 24 with a score of scores of 0.08 points.

At baseline, mean (SD) EQ-5D-5L utility index scores in CLIMB THAL-121 were reported to be greater than the average Danish population score (0.87 points). Despite the near normal baseline scores, positive changes in EQ-5D-5L utility scores were observed over time, indicating improvement in overall health status after exa-cel infusion. These results indicate an impressive improvement in overall health status after exa-cel infusion, even exceeding general population norms, that was sustained through follow-up (Table 64). EQ VAS scores demonstrated substantial improvement at Month 6 onward, with the mean (SD) change from baseline at Month 24 of 29.3 (22.9) points, far exceeding the MCID for EQ VAS of 7 to 10 points (73), indicating early and meaningful improvement in subjects' self-rated health status.

Table 64: Summary of EQ-5D-5L Scores and Change from Baseline for Subjects ≥18 and ≤35 Years of Age (PES)

Visit	Statistic	EQ VAS	US Health Utility Score	UK Health Utility Score
Baseline	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]
Month 3	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]
Change at Month 3	n	[redacted]	[redacted]	[redacted]

	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]
Month 6	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]
Change at Month 6	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]
Month 12	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]
Change at Month 12	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]
Month 18	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]
Change at Month 18	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]

	Min, max	[redacted]	[redacted]	[redacted]
Month 24	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]
Change at Month 24	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]

Source: Exa-cel efficacy and safety update 16 April 2023 (127)
Abbreviations: EQ-5D-5L: EuroQol Quality of Life Scale – 5 dimensions – 5 levels of severity; N: number of subjects; n: size of subsample; PES: Primary Efficacy Set
Note: The PES included 23 subjects ≥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 mobilization.

B.2 SUSTAIN

Table 65. Results per study – SUSTAIN

Results of SUSTAIN (NCT01895361)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median annualized rate of VOCs at end of the 52 w treatment phase	Crizanlizumab	67	1.63 (IQR: 0.00 – 3.97)	N/A	N/A	N/A	N/A	N/A	N/A		(98)
	SOC	65	2.98 (IQR: 1.25 – 5.87)								
Proportion of patients with zero VOCs at the end of the treatment period (52 w)	Crizanlizumab	67	27 (36%)	N/A	N/A	N/A	N/A	N/A	N/A		(98)
	SOC	65	11 (17%)								

B.3 HOPE

Table 66. Results per study – HOPE

Results of HOPE (NCT03036813)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Annualized adjusted incidence rate of VOCs	voxelotor		2.4 (1.8 – 3.1)	N/A	N/A	N/A	N/A	N/A	N/A		(96, 97, 159)
	SOC		2.8 (2.2 – 3.6)								
Proportion of participant who had at least one VOC during the 24-week study period	Voxelotor		67%	N/A	N/A	N/A	N/A	N/A	N/A		(97)
	SOC		69%								

B.4 NCT01179217

Table 67. Results per study – NCT01179217

Results of NCT01179217 (NCT01179217)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Mean number of VOCs	L-glutamine		3,2 (SD 2.24)	N/A	N/A	N/A	N/A	N/A	N/A		(99, 105)
	SOC		3.9 (SD 2.54)								

Appendix C. Comparative analysis of efficacy

Table 68. Comparative analysis of studies comparing Exa-cel to SOC for patients with SCD

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Proportion of patients VOC-free at 12 months	CLIMB SCD-121/CTX001-131 SUSTAIN	NA	NA	NA	Rate ratio: 5.5	3.1, 9.6	<0.0001		No
Mean rate of VOCs through week 48	CLIMB SCD-121/CTX001-131 NCT01179217	NA	NA	NA	Rate ratio: 0.06	0.01, 0.28	0.0003		No

Note: only outcomes of the MAIC that were calculable are included in the table.

C.1 Method of synthesis

C.1.1 Matching variables used of ITC vs SOC

C.1.1.1 Matching variables used of ITC of exa-cel vs SOC in the SUSTAIN trial

The following three variables were matched on for the ITC versus the SUSTAIN trial: the proportion of patients with annualized number of VOCs ≤ 4 vs >4 at baseline, median age, and sex. The SUSTAIN publication reported median rather than mean age; in order to match on age, a new intermediate categorical variable was created as patients aged ≥ versus patients aged < than the median age in SUSTAIN (98).

C.1.1.2 Matching variables used of ITC of exa-cel vs SOC in the HOPE trial

The following three variables were matched on for the ITC versus the HOPE trial: median age, sex, and race (97). The HOPE publication reported median rather than mean age; in order to match on age, a new intermediate categorical variable was created as patients aged ≥ median (versus patients aged < median age) in HOPE (97), so that the target for matching is to achieve a proportion of 50% for this intermediate categorical variable.

C.1.1.3 Matching variables used of ITC of exa-cel vs SOC in the NCT01179217 trial

The following three variables were matched on for the ITC versus the NCT01179217 trial: the proportion of patients with annualized number of VOCs ≤ 5 vs >5 at baseline, mean age, and sex.

C.1.1.4 Statistical analysis and weights applied

Using the MAIC methodology proposed by Signorovitch et al. (160), an individual patient i from the CLIMB SCD-121 trial was re-weighted using the propensity score weight wi to align with the matching variables' aggregate summary statistics at baseline as reported for each comparator. For patients treated with exa-cel, descriptive statistics of the matching variables before and after matching were summarized alongside the aggregate summary statistics from the comparator trial.

For the binary outcomes of either VF12 or VF6, after applying wi to each patient treated with exa-cel, a re-weighted percentage of patients achieving VF12 was calculated based on the equation below:

$$\hat{\boldsymbol{y}} = \frac{\sum_i \boldsymbol{y_i} * \boldsymbol{w_i}}{\sum_i \boldsymbol{w_i}} \quad (\boldsymbol{y_i} = 0 \; or \; 1)$$

where y_i denotes the achievement (yes/no) of VF12 and $\hat{y}$ the re-weighted percentage of patients achieving VF12, estimated using PROC GENMOD with patient weights entered through the WEIGHT option. Standard errors (SE) were calculated using a robust sandwich estimator.

Event rate endpoints included annualized rate of VOC and adjusted Week 48 rate of VOCs. The method of calculating the re-weighted event rate varied depending on the comparator, in order to be consistent with the method used in the comparator's trial.

For the comparison to the HOPE trial, applying w_i to each exa-cel subject, the re-weighted group-level annualized rate of VOCs was calculated through the following equation:

$$\hat{\boldsymbol{y}} = \frac{\sum_i e_i * w_i}{\sum_i \mathrm{t}_i * w_i} \times 365.25$$

where e_i and t_i denote the number of VOCs and the exposure time (in days) for i-th patient, respectively.

For the comparison to the SUSTAIN trial, first, individual-level annualized rate was calculated for each exa-cel subject as:

$y_i = \frac{e_i}{t_i} \times 365.25; i = 1, \cdots, n$,

Where e_i and t_i denote the number of VOCs and the exposure time (in days) for i-th patient, respectively. The re-weighted group median of individual-level annualized rates was subsequently identified by ordering patients by their annualized VOC rate y_i to obtain the ordered pair of y_i and w_i, calculating the half of the total weight as $m_w = \frac{1}{2}\sum_{i=1}^{n} w_i$, $i = 1, \cdots, n$. If $w_1 > m_w$, then y_1 was the weighted median. If $\sum_{i=1}^{k} w_i = m_w$, then $\frac{1}{2}(y_k +$ y_{k+1}) was the weighted median. Otherwise finding $k, 1 \le k \le n$ such that $\sum_{i=1}^{k} w_i < m_w < \sum_{i=1}^{k+1} w_i$. Then, y_{k+1} was the weighted median.

For the comparison to the NCT01179217 trial, first individual-level adjusted Week 48 rate was calculated for each exa-cel subject as:

$y_i = \frac{e_i}{t_i} \times 336;\ i = 1, \cdots, n\ \ y_i = \frac{e_i}{t_i} \times 365.25 i = 1, \cdots, n,$ where e_i and t_i denote the number of VOCs and the exposure time (in days) for *i*-th patient. The re-weighted group mean of annualized rate adjusted Week 48 rate of VOC was calculated as:

$$\hat{\boldsymbol{y}} = \frac{\sum_i \boldsymbol{y_i} * \boldsymbol{w_i}}{\sum_i \boldsymbol{w_i}}$$

Histograms of weights generated by the MAIC are presented in below.

Figure 27. Histogram of Weights Generated by MAIC of Exa-Cel CTX-001 for Voxelotor Trial Primary Efficacy Set

Figure 28. Histogram of Weights Generated by MAIC of Exa-Cel CTX-001 for Standard of Care in Voxelotor Trial Primary Efficacy Set

Figure 29. Histogram of Weights Generated by MAIC of Exa-Cel CTX-001 for Crizanlizumab Trial Primary Efficacy Set

Figure 30. Histogram of Weights Generated by MAIC of Exa-Cel CTX-001 for Standard of Care in Crizanlizumab Trial Primary Efficacy Set

Figure 31. Histogram of Weights Generated by MAIC of Exa-Cel CTX-001 for L-glutamine Trial Primary Efficacy Set

Figure 32. Histogram of Weights Generated by MAIC of Exa-Cel CTX-001 for Standard of Care in L-glutamine Trial Primary Efficacy Set

C.1.1.5 Comparison for binary outcomes

For the indirect treatment comparisons of re-weighted exa-cel percentage versus comparator's percentage as extracted from the literature, rate ratios (RR) were calculated as follows:

$$\text{Rate ratio} = \frac{\text{Re-weighted exa-cel percentage}}{\text{Comparator's percentage as extracted from study literature}}$$

Z Statistics were calculated, and p values (two-sided) and 95% CI were reported.

C.1.1.6 Comparison for event rate outcomes

For the indirect treatment comparisons of re-weighted exa-cel rate versus rates in the HOPE and NCT01179217 trial, as extracted from the literature, rate ratios were calculated as following.

Comparison to HOPE trial:

$$\text{Rate ratio} = \frac{\text{Re-weighted group-level annualized rate of VOC in exa-cel}}{\text{Comparator's group-level rate as extracted from study literature}}$$

Comparison to NCT01179217 trial:

$$\text{Rate ratio} = \frac{\text{Re-weighted group mean of individual-level adjusted Week 48 rate of VOC in exa-cel}}{\text{Comparator's group mean of individual-level Week 48 rate as extracted from study literature}}$$

Comparison to the SUSTAIN trial:

Re-weighted group median of individual-level annualized rate of VOC was presented for exa-cel. Median of individual-level annualized rate of VOC based on 52-week follow-up was extracted from the SUSTAIN trial. No rate ratio was calculated for the comparisons to the SUSTAIN trial.

For all comparisons, if the effective sample size (ESS) was <5 for exa-cel group after re-weighting, no formal comparisons were made. If the proportion of VF12 or VF6 was 100% or 0% for either exa-cel trial or comparator trial data, no formal statistical comparison was conducted, and 95% CI and p-values will not be presented for the RR. In addition, a 95% CI will not be presented for a value of 100% in the re-weighted analysis. If an event rate (either annualized rate or (adjusted) Week 48 rate of VOC) is zero for either exa-cel trial or comparator, no formal statistical comparison was conducted.

C.2 ITC of exa-cel vs SOC in the SUSTAIN trial

C.2.1 Outcomes used of ITC of exa-cel vs SOC in the SUSTAIN trial

The following endpoints were selected for the ITC versus SOC in the SUSTAIN trial.

- Percentage of patients who were VOC-free for at least 12 months.
  - This was based on the existing CLIMB SCD-121 endpoint of VF12 (82) and the percentage of patients VOC-free at 52-week follow up in SUSTAIN (98). For the comparison to SOC in SUSTAIN, the re-weighted percentage of VF12 was calculated for CLIMB SCD-121.
- Annualized rate of VOCs throughout follow-up period.
  - In SUSTAIN, the group median of the annualized rate of VOC based on 52-week follow-up was reported (98). For the comparison to SOC in SUSTAIN, first individual-level annualized rates were calculated for each subject in CLIMB SCD-121, then the re-weighted group median of the individual-level annualized rate of VOCs was calculated.

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 (82). In SUSTAIN, the evaluation started on Day 1 of treatment (98).

C.2.2 Summary of baseline characteristics

Several differences were noted before matching in baseline characteristics between the 65 SOC-treated patients in the SUSTAIN trial and the 29 exa-cel-treated patients from the CLIMB SCD-121 PES (Table 69). Of the 29 exa-cel patients, 96.6% were genotype β^s/β^s in comparison to 72.3% in the SOC-treated patients in the SUSTAIN trial. Before matching, exa-cel patients had moderately higher proportion of males (13.7% higher) and fewer patients with an annualized number of >4 VOCs (9.3% lower) than SOC-treated patients in the SUSTAIN trial. Genotype could not be used for matching, as indicted above, nearly all patients in the CLIMB SCD-121 PES were β^s/β^s (homozygous). Race was also not used for the matching; however, the proportion of Black patients was similar between SOC and exa-cel both before and after matching (2.1% more Black patients in SOC-treated arm after matching). Matching resulted in an exa-cel effective sample size (ESS) of 19.

Table 69. Baseline characteristics of patients included in the MAIC vs SOC as defined in the SUSTAIN trial

Variable	SOC (N=65)	Exa-cel unweighted (before matching) (N=29)	Exa-cel re-weighted (after matching) (ESS=19)
Genotype, n (%)			
β^s/β^s	47 (72.3)	[redacted]	[redacted]
Other	18 (27.7)	[redacted]	[redacted]
Annualized number of VOCs at baseline, n (%)			
≤4	41 (63.1)	[redacted]	[redacted]
>4	24 (36.9)	[redacted]	[redacted]
Age			
Mean (SD)	Not reported	[redacted]	[redacted]
Median (range)	26 (16–56)	[redacted]	[redacted]
≥26, n (%)		[redacted]	[redacted]
<26, n (%)		[redacted]	[redacted]
Sex, n (%)			
Male	27 (41.5)	[redacted]	[redacted]
Race, n (%)			
Black or African American	60 (92.3)	[redacted]	[redacted]
Other	5 (7.7)	[redacted]	[redacted]

Abbreviations: ESS = effective sample size; SD = standard deviation; VOC = vaso-occlusive crisis
Matching variables bolded. Integer population (n) values are not available for re-weighted summary statistics after matching.

C.2.3 Proportion of patients VOC-free at 12 months

The re-weighted proportion of patients who did not experience a VOC for at least 12 consecutive months for exa-cel was 97.1% (95% CI: 81.6 to 99.6) 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 70) (98). The resulting rate ratio was 5.7 (95% CI: 3.3 to 9.9; p<0.0001) indicating that exa-cel resulted in a statistically significant, 5.7-times higher proportion of patients remaining VOC-free for 12 consecutive months compared with SOC as defined in the SUSTAIN trial.

Table 70. Proportion of subjects VOC-free for 12-months, exa-cel vs SOC as defined in the SUSTAIN trial

	SOC (N = 65)	Exa-cel unweighted (before matching) (N = 29)	Exa-cel re-weighted (after matching) (ESS = 19)
Proportion (95% CI)	16.9% (-, -)	[redacted]	[redacted]
Rate Ratio (95% CI)			[redacted]
***P* value**			[redacted]

Abbreviations: CI = confidence interval; ESS = effective sample size; SOC = standard of care; VOC = vaso-occlusive crisis

C.2.4 Median annualized VOC rate

The group median of (individual-level) annualized VOC rate in patients treated with SOC in the SUSTAIN trial was 2.98 (interquartile range [IQR]: 1.25 to 5.87) (98). The corresponding rate in patients treated with exa-cel was 0 (IQR 0 to 0), both before and after matching. The current findings support the superior efficacy of exa-cel and highlight its important clinical benefits in avoiding VOCs.

Table 71. Median annualized rate of VOCs, exa-cel vs SOC as defined in the SUSTAIN trial

	SOC (N = 65)	Exa-cel unweighted (before matching) (N = 29)	Exa-cel re-weighted (after matching) (ESS = 19)
Median Annualized Rate of VOCs (IQR)	2.98 (1.25-5.87)	[redacted]	[redacted]
Rate Ratio (95% CI)			[redacted]
***P*-value**			[redacted]

Abbreviations: ESS = effective sample size; IQR = inter-quartile range; NC = not calculated; SOC = standard of care; VOC = vaso-occlusive crisis

C.3 ITC of exa-cel vs SOC in the HOPE trial

C.3.1 Outcomes used of ITC of exa-cel vs SOC in the HOPE trial

The following endpoints were selected for the ITC versus voxelotor and SOC in the HOPE trial:

- Percentage of patients who were VOC-free for at least 6 months in the HOPE trial (VF6):
  - For the comparison it was presumed that the 33% of the voxelotor group and the 31% in the SOC group who did not have at least one VOC were VOC-free during the 24-week treatment period (97).
- Percentage of patients who were severe VOC-free for at least 6 months in CLIMB SCD-121.
  - As the HOPE trial reports the percentage of patients who had at least one VOC during the 24-week treatment period, it was necessary to derive the proportion of patients who were VOC-free for at least 6 consecutive months in CLIMB SCD-121, and then the re-weighted percentage was calculated for the ITC.
- Annualized rate of VOCs throughout follow-up period.
  - The annualized rate of VOCs during the 72-week treatment period was reported in the long-term follow-up of the HOPE trial (96).
  - For the comparison to voxelotor and the SOC in HOPE, the re-weighted group-level annualized rate of VOCs was calculated for 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 (82). In HOPE, the evaluation started on Day 1 of treatment (97).

C.3.2 Summary of baseline characteristics

Baseline characteristics before matching between the 92 SOC-treated patients in the HOPE trial and the 29 exa-cel-treated patients from the CLIMB SCD-121 PES are presented in Table 72. Genotype was not used for matching, as nearly all [redacted] patients in the CLIMB SCD-121 PES were β^s/β^s (homozygous); in the HOPE trial, the proportion of patients in the SOC arm who were β^s/β^s (homozygous) was 80.4%. Annualized number of VOCs was also not used for matching as more than 40% patients reported 1 VOC per year at baseline in the HOPE trial while all patients enrolled in CLIMB SCD-121 reported more than 1 VOC per year at baseline. It is worth noting, compared to patients enrolled in CLIMB SCD-121, patients receiving SOC in the HOPE trial had a lower annualized number of VOCs at baseline. Differences in certain baseline characteristics were noted: exa-cel patients were younger vs. the SOC in HOPE (median age of 21 vs. 28), and a higher proportion of exa-cel patients were male and of Black / African American race (55.2% vs 45.7% and 89.7% vs 68.5%, respectively). Matching resulted in an exa-cel ESS of 10.

Table 72. Baseline characteristics of patients included in the MAIC vs SOC as defined in the HOPE trial of voxelotor

Variable	SOC (N=92)	Exa-cel unweighted (before matching) (N=29)	Exa-cel re-weighted (after matching) (ESS=10)
Genotype, n (%)			
β^S/β^S	74 (80.4)	[redacted]	[redacted]
Other	18 (19.6)	[redacted]	[redacted]
Annualized number of VOCs at baseline, n (%)			
=1	39 (42.4)	[redacted]	[redacted]
>1	53 (57.6)	[redacted]	[redacted]
Age			
Mean (SD)	Not reported	[redacted]	[redacted]
Median (range)	28 (12–64)	[redacted]	[redacted]
≥28, n (%)		[redacted]	[redacted]
<28, n (%)		[redacted]	[redacted]
Sex, n (%)			
Male	42 (45.7)	[redacted]	[redacted]
Race, n (%)			
Black or African American	63 (68.5)	[redacted]	[redacted]
Other	29 (31.5)	[redacted]	[redacted]

Abbreviations: ESS = effective sample size; SD = standard deviation; VOC = vaso-occlusive crisis
Matching variables bolded. Integer population (n) values are not available for re-weighted summary statistics after matching.

C.3.3 Proportion of patients VOC-free at 6 months

The re-weighted proportion of patients who did not experience a VOC for at least 6 consecutive months for exa-cel was [redacted] compared with 30.8% of patients who were VOC-free at 24-week follow-up reported in the HOPE trial (97). The resulting rate ratio was [redacted] (95% CI not calculated) indicating that exa-cel resulted in a statistically significant, [redacted] times higher proportion of patients remaining VOC-free for 12 consecutive months when compared with those treated with SOC in the HOPE trial.

Table 73. Proportion of subjects who remained VOC-free for 6-months, exa-cel vs SOC as defined in the HOPE trial

	SOC (N = 91)	Exa-cel unweighted (before matching) (N = 29)	Exa-cel re-weighted (after matching) (ESS = 10)
Proportion (95% CI)	30.8% (-, -)	[redacted]	[redacted]
Rate Ratio (95% CI)			[redacted]
***P* value**			[redacted]

Abbreviations: CI = confidence interval; ESS = effective sample size; NC = not calculated; SOC = standard of care; VOC = vaso-occlusive crisis

C.3.4 Mean annualized VOC rate

The group mean of (individual-level) annualized VOC rate in patients treated with SOC in the HOPE trial was 2.8 (95% CI: 2.2 to 3.6); the corresponding rate in patients treated with exa-cel was [redacted] after matching (Table 74). The resulting rate ratio was [redacted] indicating that exa-cel resulted in a [redacted] reduction in the mean annualized rate of VOCs compared to SOC as defined in the HOPE trial of voxelotor.

Table 74. Mean annualized rate of VOCs, exa-cel vs SOC as defined in the HOPE trial

	SOC (N = 91)	Exa-cel unweighted (before matching) (N = 29)	Exa-cel re-weighted (after matching) (ESS = 10)
Mean Annualized Rate of VOCs (95% CI)	2.8 (2.2-3.6)	[redacted]	[redacted]
Rate Ratio (95% CI)			[redacted]
***P*-value**			[redacted]

Abbreviations: CI = confidence interval; ESS = effective sample size; NC = not calculated; SOC = standard of care; VOC = vaso-occlusive crisis

C.4 ITC of exa-cel vs SOC in the NCT01179217 trial

C.4.1 Outcomes used of ITC of exa-cel vs SOC in the NCT01179217 trial

The following endpoint was selected for the ITC versus L-glutamine and SOC in the NCT01179217 trial:

- Rate of VOCs throughout follow-up period.
  - In NCT01179217, the mean number of VOCs through week 48 was reported (99). In NCT01179217, the mean number of VOCs through week 48 was reported (99, 105).
  - For the comparison to L-glutamine and SOC in the NCT01179217 trial, first individual-level adjusted Week 48 rate for each subject in CLIMB SCD-121 were

calculated, then the re-weighted group mean of individual-level adjusted Week 48 rate of VOCs was calculated.

C.4.2 Summary of baseline characteristics

Baseline characteristics before matching between the 78 SOC-treated patients in the NCT01179217 trial and the 29 exa-cel-treated patients from the CLIMB SCD-121 PES are presented in Table 75. Genotype was not used for matching, however, the proportion of β^s/β^s (homozygous) patients was similar in the CLIMB SCD-121 PES [redacted] and SOC-treated patients in the NCT01179217 (91.0%). Race was not used for matching, however, the proportion of Black patients was similar between SOC and exa-cel both before and after matching. Small differences in certain baseline characteristics were noted: exa-cel patients were older vs. the SOC arm in NCT01179217 (median age of 21 vs. 17). Matching resulted in an exa-cel ESS of 27.

Table 75. Baseline characteristics of patients included in the MAIC vs SOC as defined in the NCT01179217 trial of L-glutamine

Variable	SOC (N=78)	Exa-cel unweighted (before matching) (N=29)	Exa-cel re-weighted (after matching) (ESS=27)
Genotype, n (%)			
β^s/β^s	71 (91.0)	[redacted]	[redacted]
Other	7 (9.0)	[redacted]	[redacted]
Annualized number of VOCs at baseline, n (%)			
≤5	62 (79.5)	[redacted]	[redacted]
>5	16 (20.5)	[redacted]	[redacted]
Age			
Mean (SD)	21.4 (12.4)	[redacted]	[redacted]
Median (range)	17 (5-58)	[redacted]	[redacted]
Sex, n (%)			
Male	33 (42.3)	[redacted]	[redacted]
Race, n (%)			
Black or African American	73 (93.6)	[redacted]	[redacted]
Other	5 (6.4)	[redacted]	[redacted]

Abbreviations: ESS = effective sample size; SD = standard deviation; SOC = standard of care; VOC = vaso-occlusive crisis
Matching variables bolded. Integer population (n) values are not available for re-weighted summary statistics after matching.

C.4.3 Proportion of patients VOC-free

No data was reported in the NCT01179217 trial on the proportion of patients who remained VOC-free.

C.4.4 Mean rate of VOCs through Week 48

The mean (SD) rate of VOCs through week 48 in patients treated with SOC in the NCT01179217 trial was 3.9 (2.5) (99). The corresponding adjusted Week 48 mean (SD) rate in patients treated with exa-cel after matching was [redacted]. The resulting rate ratio was [redacted] indicating that exa-cel resulted in a reduction in the mean week 48 rate of VOCs of [redacted] when compared to SOC as defined in the NCT01179217 trial.

Table 76. Week 48 mean rate of VOCs, exa-cel vs SOC as defined in the NCT01179217 trial

	SOC (N = 78)	Exa-cel unweighted (before matching) (N = 29)	Exa-cel re-weighted (after matching) (ESS = 27)
Week 48 Mean Rate of VOCs (SD)	3.9 (2.5)	[redacted]	[redacted]
Rate Ratio (95% CI)			[redacted]
***P*-value**			[redacted]

Abbreviations: CI = confidence interval; ESS = effective sample size; SD = standard deviation; SOC = standard of care; VOC = vaso-occlusive crisis

C.5 Conclusions of MAIC analyses

The results of these MAIC analyses found that exa-cel had superior efficacy versus all included comparators. When considering patients who were VOC-free at 12-months, exa-cel resulted in statistically significant higher proportions versus SOC, with up to 5.7-times (versus SOC as defined in the SUSTAIN trial). In addition, rate of VOCs rate was lower after exa-cel infusion in all comparisons, supporting the superior clinical efficacy of exa-cel.

It should be noted that the comparisons included may have underestimated the efficacy of exa-cel, as matching on genotype was not feasible for all comparisons. [redacted] In contrast, the proportion of patients with the HbSS genotype ranged from 72.3% in the SOC arm of the SUSTAIN trial to 91.0% of patients in the SOC arm of the NCT01179217 trial (97, 98, 99). Further, the SUSTAIN and HOPE trials were open to patients with genotypes typically associated with less severe SCD manifestations (97, 98, 161).

Limitations of the analysis include the small exa-cel ESS, resulting from the relatively small sample size of the CLIMB SCD-121 PES (N=29). HTA expert input recommended a maximum of three matching variables for each MAIC. While the comparisons against the three included trials were deemed feasible, given the differences in matching variables in HOPE versus CLIMB SCD-121 before matching, a large reduction in the ESS was noted following matching. Not all outcomes of interest were available for all comparisons: 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 annualized rate of VOC as reported in the HOPE trial was adjusted for baseline hydroxyurea use, age, and geographic region.

Overall, the MAIC findings support the overwhelming efficacy of exa-cel compared to SOC in SCD, resulting in higher proportions of patients who are VOC-free and a reduction in the rate of VOCs.

Appendix D. Extrapolation

This Appendix has not been populated with regards to extrapolation as there is no time to event data in this submission. Instead, the derivation for incidence of acute complications and risk of chronic complications is described.

D.1 Extrapolation of effect measures

D.1.1 Data input

Not applicable.

D.1.2 Model

N/A no time to event data.

D.1.3 Proportional hazards

N/A no time to event data.

D.1.4 Evaluation of statistical fit (AIC and BIC)

N/A no time to event data.

D.1.5 Evaluation of visual fit

N/A no time to event data.

D.1.6 Evaluation of hazard functions

N/A no time to event data.

D.1.7 Validation and discussion of extrapolated curves

N/A no time to event data.

D.1.8 Adjustment of background mortality

In accordance with DMC guidelines. Adjustment to Danish general population mortality has been implemented.

D.1.9 Adjustment for treatment switching/cross-over

N/A no time to event data.

D.1.10 Waning effect

No treatment waning of treatment effect is considered, Exa-cel is considered to be a potentially curative therapy.

D.1.11 Cure-point

12 months after the treatment phase individuals are modelled to be cured from SCD.

D.2 Derivation for incidence of acute complications and risk of chronic complications

Among patients with SCD receiving SOC or chronic medication, the incidence of acute complications and the risk of chronic complications were estimated based on the number of VOCs occurring in the model cycle. In the literature, the incidence/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 incidence of acute complications or the risk of chronic complications were then derived as a weighted average of incidence/risk between patients with the VOC number as zero and patients with VOC occurrence. The equation was as below.

$$Incidence\ or\ risk\ in\ overall\ patient\ population\ with\ and\ without\ VOC\ occurrence = Proportion\ of\ patients\ with\ VOC\ number\ as\ 0 \times Incidence\ or\ risk\ when\ VOC\ number\ as\ 0 + Proportion\ of\ patients\ with\ VOC\ occurrence \times Inidence\ or\ risk\ when\ VOC\ occurs$$

The incidence/risk in patients with the VOC number as zero was derived based on the literature, where the following parameters were reported - the incidence/risk in the overall patient population with and without VOC occurrence, the proportion of patients with VOC occurrence, and the HR or of incidence when VOC occurs. It is derived using the equation above and the ones below.

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

$$I_0 = Incidence\ (rate)\ when\ VOC\ number\ as\ 0$$

$$I_V = Incidence\ (rate)\ when\ VOC\ occurs$$

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

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

$$I_V = I_0 \times HR$$

$$I_V = -LN(1 - 1/(EXP(-I_0)/(OR \times (1 - EXP(-I_0))) + 1))$$

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

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

Appendix E. Serious adverse events

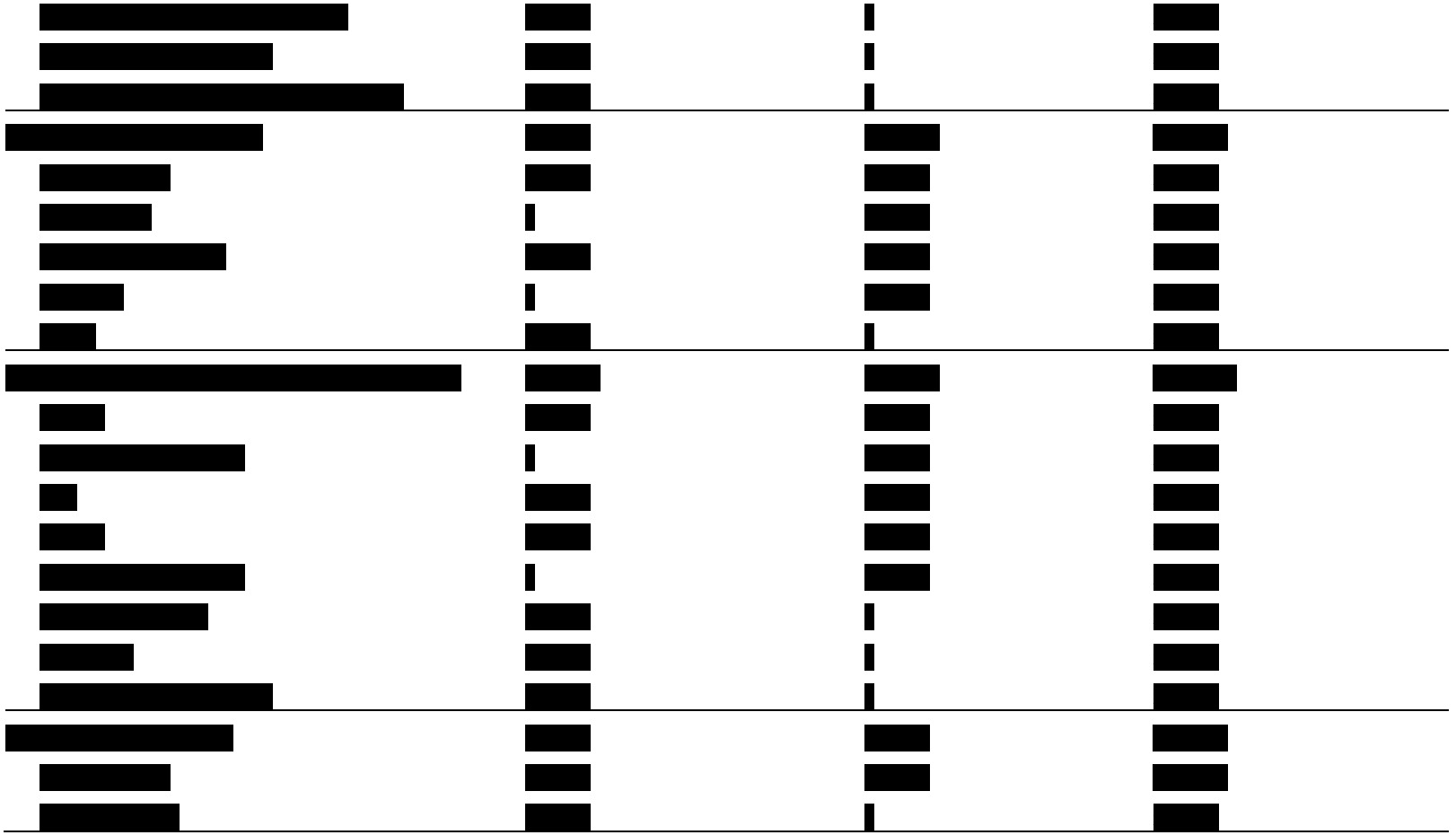
Table 77. Serious adverse events occurring in ≥2 patients in the FAS (Day 120 update)

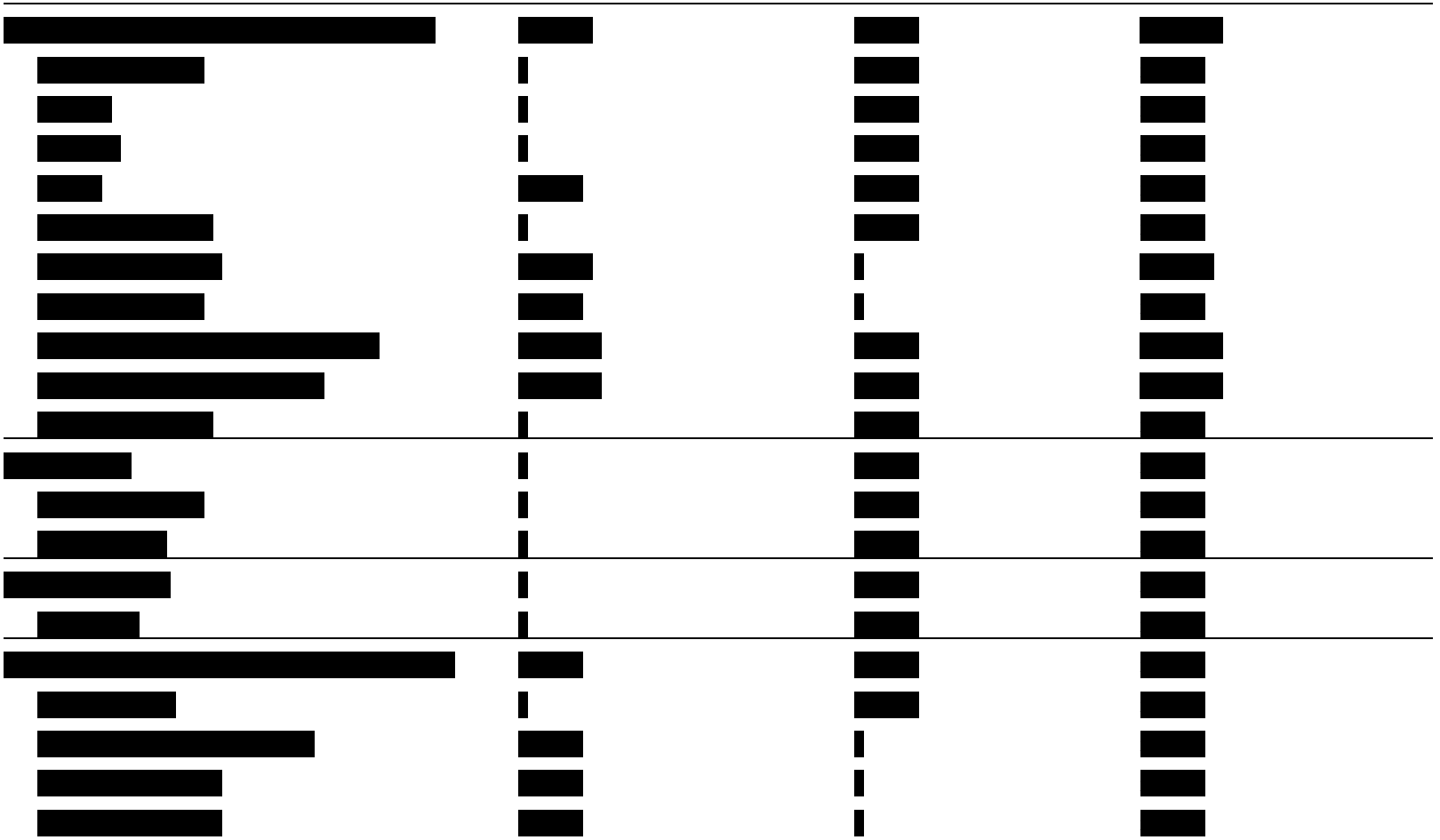
Preferred term	SAEs Exa-cel to M24[a]
Evaluable patients, N1	[redacted]
Patients with any SAEs	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

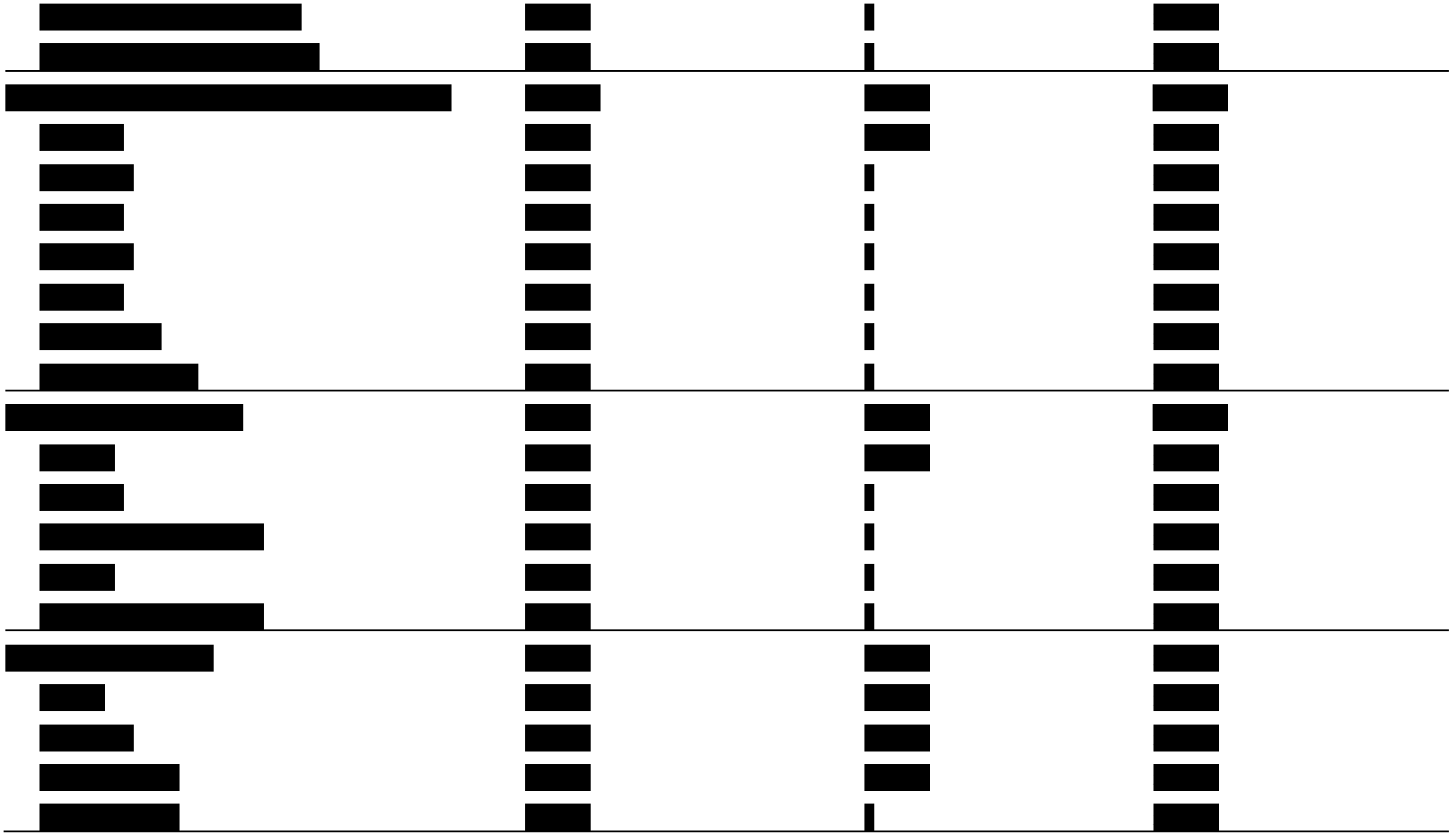
Abbreviations: FAS = full analysis set; M = month; N1 = number of patients in the safety analysis set who were on or after the start date of each study interval; SAE = serious adverse event.
[a] Study intervals: Exa-cel to M24: Day of exa-cel infusion to M24 visit or end of study visit.
[b] AEs described within busulfan SmPC and/or USPI; events were evaluated by matching PT term or similar medical concept
Source: Exa-cel KRM CTX001-121/131 Day 120 update (158) and Exa-cel efficacy [redacted] (127, 134)

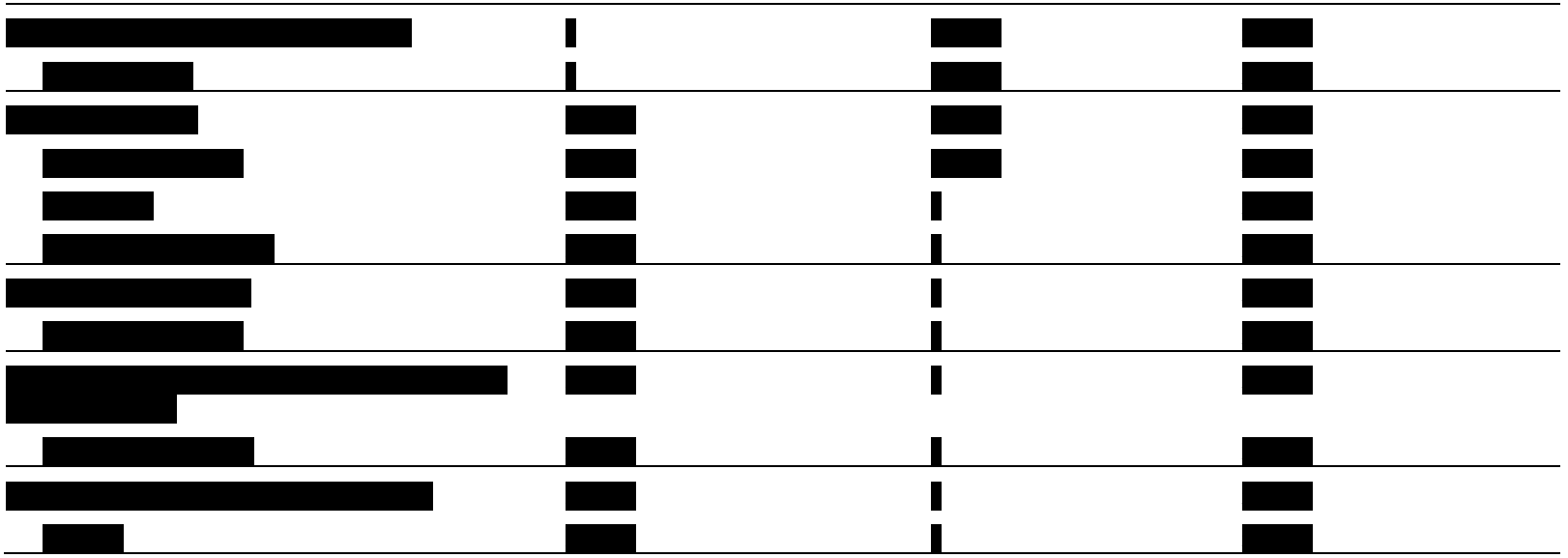
Table 78: Serious Adverse Events by System Organ Class and Preferred Term Before and After CTX001 Infusion and Overall Safety Analysis Set

System Organ Class Preferred Term	ENROLL to <CTX001 N = 58 n (%)	CTX001 to M24 N = 58 n (%)	ENROLL to M24 N = 58 n (%)
Evaluable subjects, N1	[redacted]	[redacted]	[redacted]
Subjects with any SAEs	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]









- MedDRA version 26.0.
- Evaluable subjects, N1: The number of subjects in the Safety Analysis Set who are on or after the start date of each study interval. Percentages are calculated as n/N1*100.
- When summarizing number and percentage of subjects for each study interval, a subject with multiple events within a category and study interval is counted only once in that category and study interval.
- Study intervals: ENROLL to <CTX001: Enrollment to the day before CTX001 infusion; CTX001 to M24: Day of CTX001 infusion to Month 24 visit or end of study visit; Enroll to M24: Enrollment to Month 24 visit or end of study visit.
- Table is sorted in descending order of frequency of the CTX001 to M24 column by SOC, and by PT within each SOC.

Appendix F. Health-related quality of life

Other PRO related results are included below.

Table 79. Summary of FACT-BMT scores and change from baseline for patients ≥18 and ≤35 Years of Age in the PES (Day 120 data cut)

Visit	Statistics	FACT-BMT Total Score	FACT-G Total Score	BMTS	FACT-G Subscores			
					[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

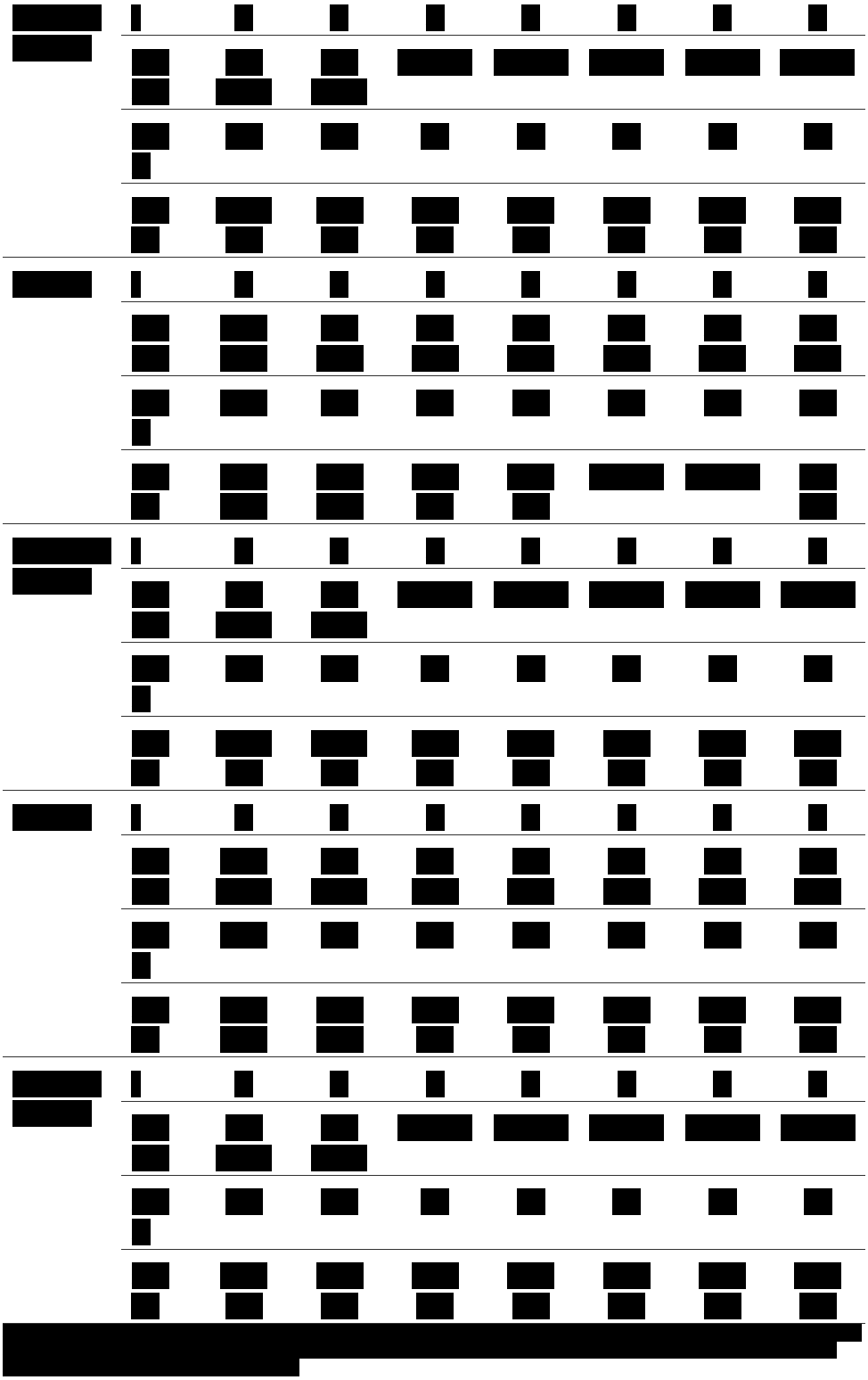


Table 80. Summary of EQ-5D-5L scores and change from baseline for patients ≥18 and ≤35 Years of Age in the PES (day 120 data cut)

Visit	Statistic	EQ VAS	US Health Utility Score	UK Health Utility Score
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

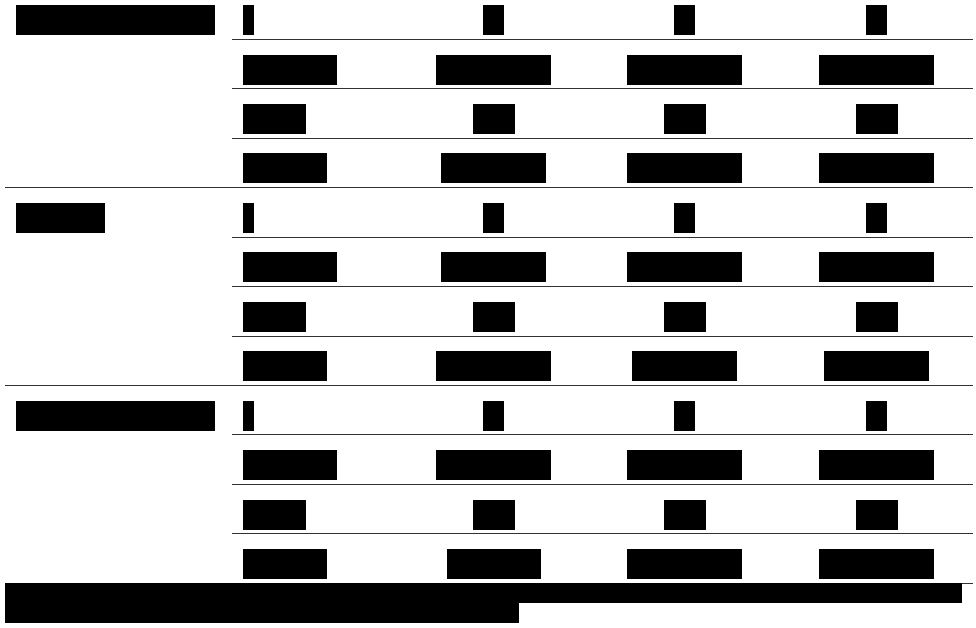


Table 81. Summary of ASCQ-Me scores and change from baseline for patients ≥18 and ≤35 years of age in the PES (Day 120 data cut)

Visit	Statistic	Emotional Impact Standardized Score	Pain Impact Standardized Score	Social Functioning Impact Standardized Score	Stiffness Impact Standardized Score	Sleep Impact Standardized Score	Pain Episode Frequency Standardized Score	Pain Episode Severity Standardized Score
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change at Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]							
	[redacted]							
Change at month 12	[redacted]							
	[redacted]							
	[redacted]							
	[redacted]							
Month 18	[redacted]							
	[redacted]							
	[redacted]							
	[redacted]							
Change at month 18	[redacted]							
	[redacted]							
	[redacted]							
	[redacted]							
Month 24	[redacted]							
	[redacted]							
	[redacted]							
	[redacted]							
Change at month 24	[redacted]							

Figure 33. NRS for subjects ≥18 and ≤35 years of age at screening over time Primary Efficacy Set

Table 82. Detailed change in pain NRS score for patients ≥18 and ≤35 years of age in the PES (Day 120 update)

Visit	Statistic	Total N=23	Change from Baseline N=23
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]
Month 6	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]
Month 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]
Month 18	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]
Month 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]

Table 83. Summary of PedsQL Scores and change from baseline at each visit for subjects ≥12 and <18 years of age at screening PES (day 120 data cut)

Visit	Statistic	Emotional Functioning Score	Physical Functioning Score	Psychosocial Health Summary Score	School Functioning Score	Social Functioning Score	Total score
Baseline	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]
Month 3	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]
Change at month 3	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]					
Month 6	n	[redacted]					
	Mean (SD)	[redacted]					
	Median	[redacted]					
	Min, max	[redacted]					
Change at month 6	n	[redacted]					
	Mean (SD)	[redacted]					
	Median	[redacted]					
	Min, max	[redacted]					
Month 12	n	[redacted]					
	Mean (SD)	[redacted]					
	Median	[redacted]					
	Min, max	[redacted]					
	n	[redacted]					

Change at month 12	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min, max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	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]
Change at month 18	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]

Table 84. Summary of EQ-5D-Youth scores and change from baseline at each visit for subjects ≥12 and <18 years of age at screening PES (day 120 data cut)

Visit	Statistic	EQ VAS
Baseline	n	
	Mean (SD)	
	Median	
	Min, max	
Month 3	n	
	Mean (SD)	
	Median	
	Min, max	
Change at month 3	n	
	Mean (SD)	
	Median	
	Min, max	
Month 6	n	
	Mean (SD)	
	Median	
	Min, max	
Change at month 6	n	
	Mean (SD)	
	Median	
	Min, max	
Month 12	n	
	Mean (SD)	
	Median	
	Min, max	
Change at month 12	n	
	Mean (SD)	
	Median	
	Min, max	
Month 18	n	
	Mean (SD)	
	Median	
	Min, max	

Change at month 18	n	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Min, max	[redacted]

Abbreviations: SD= standard deviation

Appendix G. Probabilistic sensitivity analyses

G.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to simultaneously vary multiple parameters, based on their distributions, and re-estimate model outputs. A Monte-Carlo simulation with 1,000 iterations was conducted. In each iteration, key efficacy, utility, and cost inputs were randomly drawn from the specified distributions to inform the possible range of the inputs. The results were presented as a cost-effectiveness scatter plot and a cost-effectiveness acceptability curve comparing exa-cel with each comparator. [redacted]

Table 85. Overview of parameters in the PSA

Parameters	Point esimate	Lower bound	Upper bound	Probability distribution
Cohort inputs				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Clinical inputs				
[redacted]				
Complication risk inputs				
[redacted]				
[redacted]				
[redacted]				

[redacted]				
[redacted]				
[redacted]				
[redacted]				
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[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Cost inputs				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility inputs				
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality inputs				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

G.2 Distributional cost-effectiveness analysis

A DCEA is a framework that provides this information regarding equity in the distribution of costs and health benefits of an intervention (162). The DCEA uses additional evidence to the standard CEA to model and to evaluate equity impacts and trade-offs. It is therefore useful whenever a decision is expected to have different consequences for different groups of people within the population, such as the present submission.

There is already an acceptance for considering differences based on levels of severity, or for orphan diseases in standard practice. The key aspect of a DCEA that distinguishes it from other standard weighting methods such as NICE’s severity modifier is that it provides information about distributional consequences; that is, differences in the benefits and burdens of alternative decisions across different subpopulations according to their socioeconomic status.

Accordingly, a DCEA was built on top of the CEA model described in Section 4.1. The DCEA evaluates how adoption of exa-cel would affect the current differences in quality-adjusted life expectancy (QALE) between socio-economic groups. The model utilises an aggregate

approach, which relies on the results from the existing CEA, to reflect how the health benefits from the intervention in TDT are distributed among the population (163). In addition, the DCEA uses an indirect equity weighted framework, which uses information about the baseline and final health distributions and the decision maker's aversion to health inequality to also create weighted results, where the resultant ICER is adjusted to reflect aversion to health inequality. The methodology employed in this model are based on those published by the University of York (162).

Hence, the DCEA produces two outcomes which can be considered in addition to the ICER from the CEA– a change in the slope index of inequality (SII) and a weighted ICER. The SII measures the difference in health status (in this case, QALEs) between the most and least deprived portions of a population. The model uses the index of multiple deprivation (IMD) to segment the population. IMD is a standard measurement of deprivation which aggregates and weights area-based information regarding the following domains: income, employment, education, health, crime, barriers to housing and services, and living environment. IMD is a relative measure, and used to segment the population into quintiles, 1 representing the most deprived segment of the population and IMD 5 representing the least deprived. Thus, the IMD model is a proxy for overall deprivation which can be unequally experienced by ethnic groups, but the domains included in the measure are not themselves connected with ethnicity. Again, SCD is of relevance for this method in that the condition disproportionally affects subgroups of the Danish population.

The difference in QALEs is calculated by first splitting the incremental QALYs, as calculated by the CEA, into IMD group according to the proportion of patients with TDT who are represented in each IMD category. These QALYs are then added to the QALEs of the general population, which is also segmented into IMD group. The change in SII is then derived by comparing the distribution of QALEs across IMD groups pre- vs post-intervention. This change in SII reports whether adoption of exa-cel increases or decreases health inequality and the magnitude of that effect and can be used alongside the non-weighted ICER to present equity and cost-effectiveness.

The decision makers' aversion to health inequality and the general populations' QALEs are used to calculate equity weights which are applied to the incremental QALYs and costs from the CEA to calculate an equity weighted ICER. The Atkinson's social welfare function is used to calculate the equity weights which represent the amount to which society places additional value on health outcomes for the most deprived group (IMD 1) compared to the least deprived group (IMD 5). The weight for IMD 5 group (least deprived) is set at 1.0, and the weights increase for lower IMD groups, representing increased value in treating the more deprived groups. The equity weights are applied to the apportioned cost and the QALYs for each IMD group, and then are combined based on the distribution of IMD groups in the TDT population to compute an equity weighted ICER.

15.1.1.1 General population inputs

The DCEA requires both the size of the general population (i.e., the national population) and the size of the eligible treatment population. The QALE and proportion of the general population in each IMD group was sourced from a published UK study, which combined utility estimates from the Health Survey for England and mortality data from the Office of National Statistics (164). Another key input required to calculate the equity weighted ICER is the Atkinson inequality aversion parameter, represented by ϵ. This value represents the decision maker's aversion to health inequality. In a traditional CEA, which does not evaluate health inequality, the value of ϵ is 0, meaning that the decision maker is only concerned with the maximum health benefit for the population. An increasing value for ϵ

represents an increasing willingness to accept lower net health for the whole population in exchange for decreased health inequality, i.e, an increase in health concentrated among those in the quintiles representing higher levels of social deprivation. The base case value in the global model (ϵ=11) is sourced from a study which performed an online survey of the general English population (n=244) in order to specifically elicit aversion parameters. In the UK population (given the QALEs by IMD group noted above), an Atkinson inequality aversion parameter of 11 results in the following weight values applied to health benefits and costs: [redacted] for IMD 5 (least deprived), [redacted] for IMD 4, [redacted] for IMD 3, [redacted] for IMD 2, and [redacted] for IMD 1 (most 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.

Table 86. DCEA general population inputs

Variable	Value	Reference
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: Index of multiple deprivation (IMD)

15.1.1.2 Treatment population inputs

DCEA inputs for the exa-cel treated population are contained in Table 20. The proportion of the eligible TDT treatment population in each IMD group is based on [redacted]

The model includes inputs for health opportunity cost shares, which represents how much more or less a health care decision will affect an IMD group. was assumed to be a 'flat' (equally distributed across IMD groups). Given the progressive tax system and nationalised health insurance funding pool which characterises the UK health system, it is reasonable to assume that opportunity costs are shared proportionately across the population. Thus, in the base case, the burden of opportunity-cost is assumed to be proportional and shared in an equitable manner (i.e., [redacted]% for each for the five IMD groups).

It is assumed that [redacted]% of eligible patients utilize exa-cel. Finally, the market shares of currently available treatment options are used to weight the impact different treatments have on the change in SII. In the base case model, it is assumed that [redacted] patients ([redacted]%) are on SOC alone.

Table 87. DCEA treatment population inputs

Variable	Value	Reference
Eligible treatment population distribution		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Current market share

[redacted]	[redacted]	[redacted]

Abbreviations: IMD = Index of multiple deprivation, SoC= Standard of Care

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

We performed a SLR following standard methods outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) (167), Cochrane guidelines (168) and the UK National Institute for Health and Care Excellence (NICE) guidelines (169). We employed a comprehensive search strategy across multiple bibliographic databases (Table 88).

Table 88. Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	OvidSP®	No limit	May 10, 2022
Medline	OvidSP®	No limit	May 10, 2022
CENTRAL	OvidSP®	No limit	May 10, 2022

Databases: The search was conducted on May 10, 2022. The SLR followed standard methods outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA), Cochrane guidelines, and the UK NICE guidelines for the following databases using the OvidSP® platform:

- MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Medline® Daily, Medline and Versions®
- EMBASE®
- Cochrane Central Register of Controlled Trials

The search was subsequently updated in July 2023. For the updated clinical SLR, due to a change in database subscription, two search strategies were developed for the Embase and Ovid databases, using the initial search strategy from the original clinical SLR. The Embase search strategy was performed in the Embase database (hosted by Elsevier), whilst the searches for MEDLINE and Cochrane were conducted using the Ovid platform.

Table 89. Other sources included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Not applicable as no other sources where included			

In addition to the bibliographic databases, websites of the three conferences were searched (the most recent two years only as abstracts from prior meetings are indexed in EMBASE).

Table 90. Conference material included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
The European Hematology Association (EHA)	https://ehaweb.org/	2 years	May 10, 2022
The European Society for Blood and Marrow Transplantation (EBMT)	https://www.ebmt.org/	2 years	May 10, 2022
American Society of Hematology (ASH)	https://www.hematology.org/	2 years	May 10, 2022

The bibliographies of four recently published reviews on the related topic area were reviewed as another method to identify relevant studies. Reviews were flagged during title and abstract screening and identified from manual searches.

Study screening was carried out in two phases: (a) title/abstract screening and (b) full-text screening. Both steps were covered by two independent reviewers, with a third reviewer used to resolve any discrepancies. The inclusion and exclusion criteria for studies was pre-specified based on the PICOS approach (Population, Interventions, Comparators, Outcomes, Study design). The risk of bias assessment was performed using the NICE checklist for RCTs, while the Downs and Black checklist was used to assess single-arm studies.

H.1.1 Search strategies

The search strategy was based on a combination of free text words, indexing terms (e.g., Excerpta Medica database [EMBASE] subject heading [EMTREE] or Medical Subject Headings [MESH] terms) and their relationship using Boolean terms (e.g., 'and', 'or', 'not'). Complete search strategies for the bibliographic databases searched are included in Table 93

Table 91. Search strategy table for MEDLINE® and Cochrane using Ovid updated in July 2023 (ran on 01/07/2023)

#	Search String	Results
1	exp hemoglobin S/ or exp Sickle Cell Disease/ or anemia, sickle cell/ or hemoglobin, sickle/ or Sickle cell disease.mp. or (sickle cell* adj3 (disease* or anemia* or anaemia*)).ti,ab. or (hemoglobinopath* or haemoglobinopath*).ti,ab. or ((hemoglobin* or haemoglobin*) adj1 SC*).ti,ab. or (sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	38,624
2	(crispr* OR "Clustered Regularly Interspaced Short Palindromic Repeat*").ti,ab. or exp exagamglogene autotemcel/ or exp CRISPR-Cas Systems/ or exp Clustered Regularly Interspaced	39,129

	Short Palindromic Repeats/ or (CTX001 or "CTX 001" or CTX-001).mp.	
3	exp Zynteglo/ or exp betibeglogene autotemcel/ or (Zynteglo or betibeglogene autotemcel or beticel or beti-cel or LentiGlobin).mp.	29
4	exp crizanlizumab/ or (crizanlizumab or critznlizumab or Adakveo).mp.	92
5	exp voxelotor/ or (Voxelotor or Oxbryta or GBT440 or "GBT 440" or GBT-440).mp.	148
6	exp glutamine/ or (glutamine or L-Glutamine or L Glutamine).mp.	52,116
7	Hydroxyurea/ or (hydroxycarbamide or hydroxyurea or Hydrea or Droxia or Siklos).mp.	13,444
8	(stem adj3 cell adj3 transplant*).ti,ab. or (hematopoietic adj3 transplant*).ti,ab. or exp Stem Cell Transplantation/ or (((allogenic or allogeneic) adj (stem or transplantation)) or alloSCT or allo-SCT).ti,ab. or (haploidentical adj (transplant* or donor)).ti,ab.	123,027
9	exp thrombocyte transfusion/ or exp Erythrocyte transfusion/ or Blood Transfusion/ or exp Leukocyte transfusion/ or Platelet transfusion/ or Plasma exchange/ or ((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj3 (transfus* or infus* or therap*)).ti,ab.	137,402
10	(Deferoxamine or Desferal or Deferasirox or Exjade or Jadenu or Deferiprone or Ferriprox).mp. or exp iron chelation/ or (Iron chelat* or FeAsc or ferrous- ascorbate complex).ti,ab.	16,600
11	exp placebo/ or exp medical care/ or (best medical care or supportive care or BSC).ti,ab.	22,242
12	or/2-11	395,414
13	1 and 12	6,570
14	exp Prospective Studies/ OR exp Random Allocation/ or exp Adaptive Clinical Trial or exp Randomized controlled trials as Topic/ or Randomized Controlled Trial/ or Clinical Trial/ or Controlled clinical trial/ or Multicenter study/ or Prospective study/ or Phase 1 clinical trial/ or Phase 2 clinical trial/ or Phase 3 clinical trial/ or Phase 4 clinical trial/ or exp randomization/ or (randomi?ed controlled trial$ or rct).tw. or (random$ adj2	2,051,734

	allocat$).tw. or ((singl$ or doubl$ or tripl$) adj (blind$3 or mask$3)).ti,ab. or placebo$.ti,ab.	
15	(animal* not human*).mp. or (animal/ not (animal/ and human/)) or (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/)	9,641
16	(news or comment or editorial or note or case reports).pt. or (historical article/ or case report/ or editorial/)	18,518
17	14 not (15 or 16)	2,051,408
18	13 and 17	916
19	Limit 18 to English language, Date: 11 May 2022 to till date	64

Table 92. Search strategy for Embase® using Elsevier updated in July 2023 (ran on 01/07/2023)

#	Search String	Results
1	'hemoglobin s'/exp OR 'sickle cell disease'/exp OR 'anemia, sickle cell'/de OR 'hemoglobin, sickle'/de OR 'sickle cell disease' OR ('sickle cell*' NEAR/3 (disease* OR anemia* OR anaemia*)) OR hemoglobinopath*:ti,ab OR haemoglobinopath*:ti,ab OR (((hemoglobin* OR haemoglobin*) NEAR/1 sc*):ti,ab) OR 'sickle haemoglobin' OR 'sickle hemoglobin' OR 'sickle anaemia' OR 'sickle anemia'	59,984
2	(crispr*:ti,ab OR 'clustered regularly interspaced short palindromic repeat*':ti,ab OR 'exagamglogene autotemcel'/exp OR 'crispr-cas systems'/exp OR 'clustered regularly interspaced short palindromic repeats'/exp OR ctx001 OR 'ctx 001')	65,287
3	('zynteglo'/exp OR 'betibeglogene autotemcel'/exp OR zynteglo OR 'betibeglogene autotemcel' OR beticel OR 'beti cel' OR lentiglobin)	255
4	'crizanlizumab'/exp OR crizanlizumab OR critznlizumab OR adakveo	368
5	'voxelotor'/exp OR voxelotor OR oxbryta OR gbt440 OR 'gbt 440'	418
6	glutamine/exp OR (glutamine OR L-Glutamine OR 'L Glutamine')	89,422
7	Hydroxyurea/de OR (hydroxycarbamide OR hydroxyurea OR Hydrea OR Droxia OR Siklos)	33,643

8	(deferoxamine OR desferal OR deferasirox OR exjade OR jadenu OR deferiprone OR ferriprox OR 'iron chelation'/exp OR 'iron chelat*':ti,ab OR feasc:ti,ab OR 'ferrous- ascorbate complex':ti,ab)	32,142
9	(((stem NEAR/3 cell NEAR/3 transplant*):ti,ab) OR ((hematopoietic NEAR/3 transplant*):ti,ab) OR 'stem cell transplantation'/exp OR (((allogenic OR allogeneic) NEXT/1 (stem OR transplantation)):ti,ab) OR allosct:ti,ab OR 'allo- sct':ti,ab OR ((haploidentical NEXT/1 (transplant* OR donor)):ti,ab))	224,986
10	('thrombocyte transfusion'/exp OR 'erythrocyte transfusion'/exp OR 'blood transfusion'/de OR 'leukocyte transfusion'/exp OR 'platelet transfusion'/de OR 'plasma exchange'/de OR (((blood OR erythrocyte* OR 'red cel*' OR 'red blood cell*' OR rbc*) NEAR/3 (transfus* OR infus* OR therap*)):ti,ab))	268,885
11	('placebo'/exp OR 'medical care'/exp OR 'best medical care':ti,ab OR 'supportive care':ti,ab OR bsc:ti,ab)	1,721,703
12	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	2,378,332
13	#1 AND #12	18,642
14	'prospective studies'/exp OR 'random allocation'/exp OR 'adaptive clinical trial or exp randomized controlled trials as topic' OR 'randomized controlled trial'/de OR 'clinical trial'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'prospective study'/de OR 'phase 1 clinical trial'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'randomization'/exp OR 'randomi$ed controlled trial?':ti,ab OR rct:ti,ab OR ((random? NEAR/2 allocat?):ti,ab) OR (((singl? OR doubl? OR tripl?) NEXT/1 (blind?3 OR mask?3)):ti,ab) OR placebo?:ti,ab	2,666,337
15	(animal? NOT human? OR ('animal'/de NOT ('animal'/de AND 'human'/de)) OR 'animal'/de OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'nonhuman'/de)	10,021,777
16	('news' OR 'comment' OR 'note' OR 'case reports' OR 'historical article' OR 'case report' OR 'editorial')	5,128,963
17	#15 OR #16	14,780,695
18	#14 NOT #17	2, 303,749
19	#13 and #18	2,460
20	limit #19 to English language, Date: 11 May 2022 to till date	232

Table 93: Search strategy table for Embase®, MEDLINE® and Cochrane using Ovid in May 2022 clinical SLR (ran on 10/05/2022)

No.	Query	Results
1	exp hemoglobin S/ or exp Sickle Cell Disease/ or anemia, sickle cell/ or hemoglobin, sickle/ or Sickle cell disease.mp. or (sickle cell* adj3 (disease* or anemia* or anaemia*)).ti,ab. or (hemoglobinopath* or haemoglobinopath*).ti,ab. or ((hemoglobin* or haemoglobin*) adj1 SC*).ti,ab. or (sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	94,696
2	(crispr* or "Clustered Regularly Interspaced Short Palindromic Repeat*").ti,ab. or exp exagamglogene autotemcel/ or exp CRISPR-Cas Systems/ or exp Clustered Regularly Interspaced Short Palindromic Repeats/ or (CTX001 or "CTX 001" or CTX-001).mp.	81,731
3	exp Zynteglo/ or exp lovotibeglogene autotemcel/ or (Zynteglo or lovotibeglogene autotemcel or lovocel or lovo-cel or LentiGlobin).mp.	219
4	exp crizanlizumab/ or (crizanlizumab or critznlizumab or Adakveo).mp.	356
5	exp voxelotor/ or (Voxelotor or Oxbryta or GBT440 or "GBT 440" or GBT-440).mp.	440
6	exp glutamine/ or (glutamine or L-Glutamine or L Glutamine).mp.	133,265
7	Hydroxyurea/ or (hydroxycarbamide or hydroxyurea or Hydrea or Droxia or Siklos).mp.	45,382
8	(stem adj3 cell adj3 transplant*).ti,ab. or (hematopoietic adj3 transplant*).ti,ab. or exp Stem Cell Transplantation/ or (((allogenic or allogeneic) adj (stem or transplantation)) or alloSCT or allo-SCT).ti,ab. or (haploidentical adj (transplant* or donor)).ti,ab.	335,443
9	exp thrombocyte transfusion/ or exp Erythrocyte transfusion/ or Blood Transfusion/ or exp Leukocyte transfusion/ or Platelet transfusion/ or Plasma exchange/ or ((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj3 (transfus* or infus* or therap*)).ti,ab.	381,422
10	exp iron chelation/ or (Iron chelat* or FeAsc or ferrous-ascorbate complex).ti,ab. or (Deferoxamine or Desferal or Deferasirox or Exjade or Jadenu or Deferiprone or Ferriprox).mp.	46,601
11	exp placebo/ or exp medical care/ or (best medical care or supportive care or BSC).ti,ab.	1,526,254
12	or/2-11	2,488,730
13	1 and 12	24,032
14	exp Prospective Studies/ or exp Random Allocation/ or exp Adaptive Clinical Trial/ or exp Randomized controlled trials as Topic/ or Randomized Controlled Trial/ or Clinical Trial/ or Controlled clinical trial/	5,445,295

No.	Query	Results
	or Multicenter study/ or Prospective study/ or Phase 1 clinical trial/ or Phase 2 clinical trial/ or Phase 3 clinical trial/ or Phase 4 clinical trial/ or exp randomization/ or (randomi?ed controlled trial$ or rct).tw. or (random$ adj2 allocat$).tw. or ((singl$ or doubl$ or tripl$) adj (blind$3 or mask$3)).ti,ab. or placebo$.ti,ab.	
15	(animal$ not human$).mp. or (animal/ not (animal/ and human/)) or (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/)	16,193,710
16	(news or comment or editorial or note or case reports).pt. or (historical article/ or case report/ or editorial/)	8,491,923
17	14 not (15 or 16)	4,875,471
18	13 and 17	3,826
19	limit 18 to english language	3,775
20	MEDLINE = 819 Embase = 2,583 Cochrane = 373	FINAL NUMBER TO SCREEN = 2,914

H.1.2 Systematic selection of studies

Search and selection were carried out in two phases: (a) title and abstract screening and (b) full text screening. In both phases, dual review was applied. The inclusion and exclusion criteria for each indication are presented in Table 94. The criteria are presented according to the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Study design) framework.

Table 94. Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	SCD patients and aged ≥12 years	Patients without SCD Paediatric SCD patients (aged <12 years) Studies that enrolled only special populations including pregnant women or individuals undergoing surgery
Intervention	Exa-cel (CTX001)[1]	Not applicable
Comparators	Lovotibeglogene autotemcel, lovo-cel [Zynteglo, LentiGlobin] Crizanlizumab [Adakveo] Voxelotor [Oxbryta] L-glutamine [Endari] (not approved in EU) Hydroxycarbamide (hydroxyurea) [Hydrea, Droxia] Allogeneic stem cell transplantation, including alternate donor transplantation (matched sibling/related donor, matched unrelated donor, mismatched unrelated donor, mismatched related donor/haploidentical) and source of donor (bone marrow, cord blood, peripheral blood) Red blood cell transfusions (RBCT) and other types of transfusions (simple/exchange) Iron chelation therapy (ICTs): deferoxamine [Desferal], deferasirox [Exjade and Jadenu], deferiprone [Ferriprox] (and combinations of ICTs) Placebo + best medical care	Other treatments
Outcomes	Primary endpoint[1] Sickle cell crisis/ VOC (frequency, severity, and duration in one event) Secondary endpoints Pain Hemoglobin (Hb) response (e.g., total hemoglobin concentration over time	Any other outcomes not listed in the inclusion criteria

	including Hb fractionation, i.e., HbS, HbF, other transgene Hb) Hospital admission, including emergency department (ED) and nurse visits SCD complications (e.g., stroke, acute chest syndrome, organ damage) Anaemia symptoms Adverse events Mortality Health-related quality of life and other patient-reported outcomes Engraftment times: OS, EFS, TRM, graft failure rates, aGVHD, cGVHD (curative therapies only) Change in number of blood transfusions for SCD-related indications (e.g., frequency, RBC units) Use of concomitant medicines (i.e., pain medication use)	
Time	Initial SLR: From inception to 10 May 2022 SLR update: From 11 May 2022 to 1 July 2023	SLR update: articles published before 11 May 2022
Study design	Randomized controlled trials (RCTs) Single-arm trials	Commentaries and letters Systematic and non-systematic reviews Study protocols with no results
Language restrictions	English language publications only	Studies published in language other than English

[1] Primary efficacy outcome: vaso-occlusive event-free (as per definition in CLIMB 121)
[2] Primary efficacy outcome: transfusion-independence (as per definition in CLIMB 111)

H.1.2.1 Screening process

After excluding duplicate citations across the bibliographic databases, records were imported into the DistillerSR® platform for screening.

Step 1 – Title and abstract review: All unique records identified from the searches were screened based on the predefined PICOTS criteria described above. Two reviewers independently screened titles and abstracts and classified each record as either 1) exclude or 2) continue to full-text review. Any discrepancy between reviewers was resolved by a third reviewer. A third reviewer also confirmed the classifications for all studies marked for full-text review and from a sample of exclusions. Furthermore, we used artificial intelligence technology to screen all excluded records and assign each a probability of likelihood for inclusion. Any study with a probability ranking over 85% was rescreened. These quality control (QC) measures, in addition to searching conferences and references

of review articles, provide transparent and robust identification of eligible studies. All publications included at the end of this stage were obtained for Step 2.

Step 2 – Full-text review: We retrieved the full-text articles for all relevant studies identified from title and abstract screening. We followed the same process as with title and abstract screening. Two reviewers assessed all full-text reports based on the predefined PICOTS criteria and classified each study 1) to exclude or 2) to include. A third reviewer resolved discrepancies and confirmed the classifications made by the two reviewers for all studies marked as include and from a sample of exclusions. Records excluded after review of the full-text report were documented, along with a clear justification for their exclusion.

H.1.2.2 Study prioritization for indirect treatment comparison feasibility assessment

Those studies that met the PICOTS criteria after full-text review were included in the SLR. References reporting on the same trial (i.e., the same set of patients) were linked such that data collection and analysis was study-based. All studies included after completion of the full-text review were prioritized for relevancy for conducting an indirect treatment comparison (ITC) with exa-cel trial data for TDT and SCD by two independent reviewers. Discrepancies were checked against the source document and was resolved by consensus. Prioritization criteria included the following:

- Study population included subjects with ages corresponding to the CLIMB trial study populations included in BLA and MAA regulatory submissions based on the primary efficacy set (PES) (i.e., TDT studies with a mean or median age below 12 years, SCD studies with a mean or median below 18 years, or TDT and SCD studies with a mean or median age above 35 years were not eligible for ITC assessment)
- Study investigated an established comparator treatment (i.e., early experimental treatments were not eligible for ITC assessment)
- Study reported the primary endpoint (VOCs for SCD and transfusion-related outcome for TDT) and baseline characteristics of the population included in the reported primary endpoint
- Study included a minimum of 5 treated subjects
- Treatment corresponded to the FDA-approved dose (e.g., not dose-escalation study)
- Current standard-of-care available to study participants was sufficiently similar to present day (e.g., individuals had SCD treatment options including hydroxyurea and TDT treatment options including transfusion and iron chelation therapy)

Studies in which data for study population characteristics and/or outcomes were not available were not eligible for ITC assessment. We completed data extraction and risk of bias assessments for all studies that were prioritized for the ITC assessment.

H.1.2.3 Data collection and synthesis

Extraction of data from the studies prioritized for the ITC assessment was conducted using a standardized data extraction template developed and piloted based on an existing validated IQVIA template. The data extraction workbook was designed in Excel to capture key data from studies and for ease of use in summarizing data (semi-automation of histograms, formatted to develop R friendly data files).

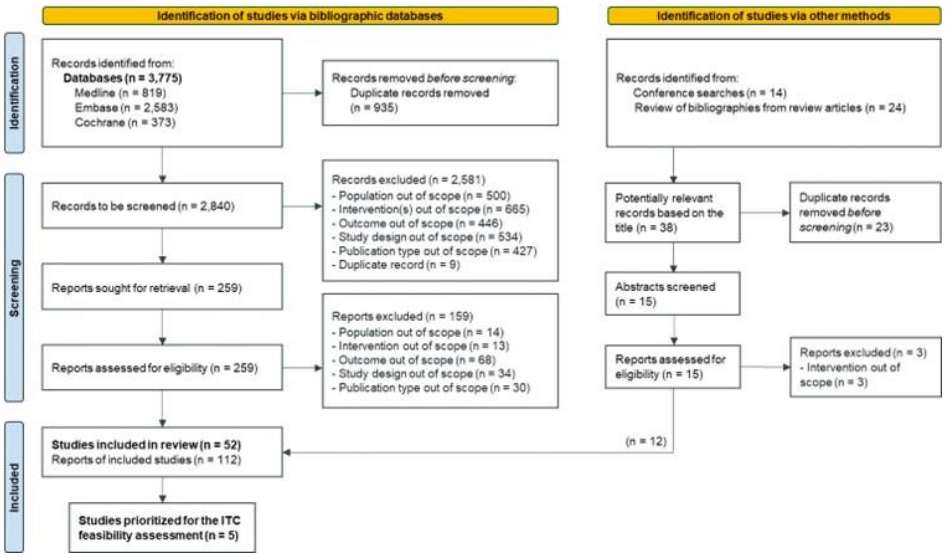
For each study, information on key methodological characteristics, selection criteria, study population/patient characteristics, and results were extracted. Data extraction was conducted by two investigators independently. Discrepancies were checked against the source document by a third reviewer. Web Plot Digitizer was used to digitize and extract data presented only as an image or graphic.

The data extracted from each study can be provided upon request. Where relevant, baseline characteristics reported by categories were extracted as proportions (number and percentage) and continuous variables were extracted using the mean and standard deviation (SD) or median and range. Continuous outcomes were reported using the mean and SD, standard error (SE), or other reported measure of variance where applicable. Binary outcomes were reported as the proportion of patients with the event over the total number of patients (numerator and denominator). If alternative measures were reported in the study, the relevant measures were calculated where possible.

H.1.3 Results of the SLR

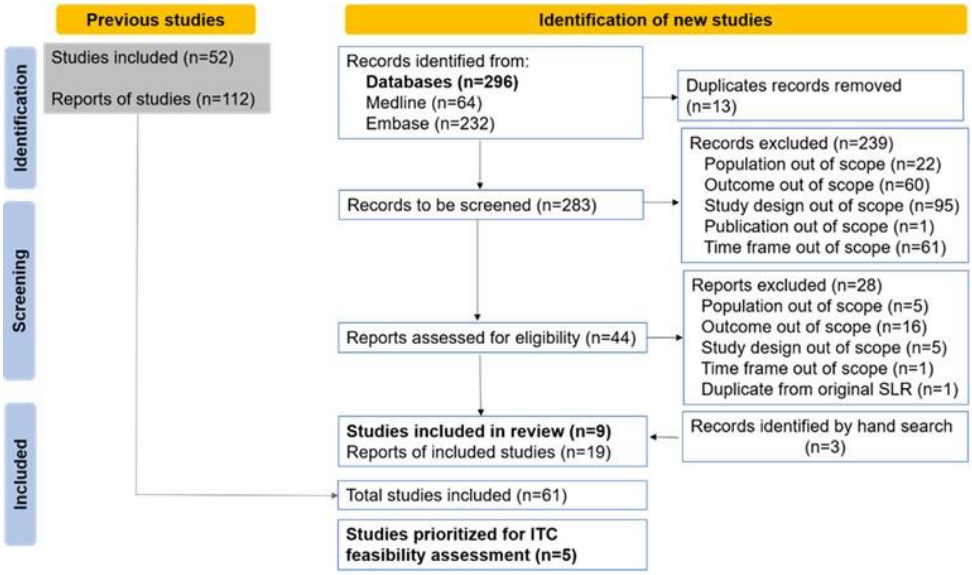
A total of 3,775 publications were identified through database searches. The searches were executed on 10 May 2022, and were re-run on 1 July 2023 for the clinical SLR update. After de-duplication, 2,840 titles/abstracts were screened for eligibility by two reviewers independently. During this first selection step, 2,581 records were excluded. Hence, 259 were assessed for inclusion for data extraction. Of these, 159 were excluded based on the pre-defined PICOS criteria and 100 records were included. In addition, the searching of conference proceedings resulted in the inclusion of 12 conference abstracts for data extraction. Therefore, 112 publications reporting 52 unique studies, were included for data extractions. Of the 52 included studies, five were prioritised for the ITC assessment. The PRISMA for the original clinical SLR (Figure 34), and SLR update (Figure 35), are presented below.

Figure 34. PRISMA flow for the original clinical SLR



Abbreviations: ITC: indirect treatment comparison; SLR: systematic literature review.

Figure 35. PRISMA flow for the updated clinical SLR



Abbreviations: ITC: indirect treatment comparison; SLR: systematic literature review.

H.1.4 Description of excluded studies

As described above, of the 52 studies identified in the SLR that were evaluated for inclusion in the MAIC, only five studies were prioritised for the ITC assessment based on initial comparability of study outcomes and patient characteristics with the target study, CLIMB SCD-121. Of the 9 studies identified in the updated SLR, no study was prioritised for the ITC assessment. The rationale behind the exclusion of the remaining studies is outlined below in Table 95: Summary of studies not prioritised for the ITC assessment for SCD

Table 95: Summary of studies not prioritised for the ITC assessment for SCD

Lead author, year	Study name (trial ID)	Intervention	Geography (sample size)	Age range (mean or median)	Exclusion reason
Original SLR					
Wang, 2011 Wang, W., Brugnara, C., Snyder, C., Wynn, L., Rogers, Z., Kalinyak, K., Brown, C., Qureshi, A., Bigelow, C., Neumayr, L., Smith-Whitley, K., Chui, D. H., Delahunty, M., Woolson, R., Steinberg, M., Telen, M. & Kesler, K. 2011. The effects of hydroxycarbamide and magnesium on haemoglobin SC disease: results of the multi-centre CHAMPS trial. *Br J Haematol,* 152**,** 771-6.	CHAMPS; NCT00532883	Hydroxyurea vs Magnesium	US (n=44)	5-53 years	No; lack of VOC-related outcome
Charache, 1995 Charache, S., Terrin, M. L., Moore, R. D., Dover, G. J., Barton, F. B., Eckert, S. V., Mcmahon, R. P. & Bonds, D. R. 1995. Effect of	Multicenter Study of Hydroxyurea (MSH); NCT00000586	Hydroxyurea vs Placebo	US and Canada (n=299)	18-59 years (Mean: 30.5)	No

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,* 332**,** 1317-22.					
Jain, 2012 Jain, D. L., Sarathi, V., Desai, S., Bhatnagar, M. & Lodha, A. 2012. Low fixed-dose hydroxyurea in severely affected Indian children with sickle cell disease. *Hemoglobin,* 36**,** 323-32.	NR	Hydroxyurea vs Placebo	India (n=60)	5-18 years	No; pediatric population
Voskaridou, 2009 Voskaridou, E., Christoulas, D., Bilalis, A., Plata, E., Varvagiannis, K., Stamatopoulos, G., Sinopoulou, K., Balassopoulou, A., Loukopoulos, D. & Terpos, E. 2010. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with	LaSHS	Hydroxyurea vs Conventional therapy	Greece (n=330)	20-76 years (Median: 42)	No

sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). *Blood,* 115**,** 2354-63.					
Nickel, 2021 Nickel, R.S., et al., Adding hydroxyurea to chronic transfusion for sickle cell anemia reduces transfusion burden: final results of the HAT prospective trial, Blood (2021) 138 (Supplement 1): 2036, https://ashpublications.org/blood/article/138/Supplement%201/2036/482555/Adding-Hydroxyurea-to-Chronic-Transfusion-for	HAT; NCT03644953	Hydroxyurea and transfusion (HAT)	US (n=14)	5.3-19 years (Median: 11.2)	No; pediatric population
George, 2019 George A, Dinu BR, Ware RE. Ndepth: novel dose escalation to predict treatment with hydroxyurea. *Blood* 2015;126(23):3419.	NDEPTH; NCT02042222	Hydroxyurea	US (n=68)	1-16 years	No; pediatric population
Yan, 2005	NR	Hydroxyurea	US (n=17)	23-69 years	No

Yan, J. H., Ataga, K., Kaul, S., Olson, J. S., Grasela, D. M., Gothelf, S., Kutlar, A. & Orringer, E. 2005. The influence of renal function on hydroxyurea pharmacokinetics in adults with sickle cell disease. *J Clin Pharmacol,* 45**,** 434-45.					
Kinney, 1999 Kinney, T. R., Helms, R. W., O'branski, E. E., Ohene-Frempong, K., Wang, W., Daeschner, C., Vichinsky, E., Redding-Lallinger, R., Gee, B., Platt, O. S. & Ware, R. E. 1999. Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. Pediatric Hydroxyurea Group. *Blood,* 94**,** 1550-4.	HUG-KIDS	Hydroxyurea	US (n=84)	5-15 years (Mean: 9.8)	No; pediatric population
Ballas, 1999 Ballas, S. K., Marcolina, M. J., Dover, G. J. & Barton, F. B. 1999.	NR	Hydroxyurea	US (n=17)	≥ 18 years	No

Erythropoietic activity in patients with sickle cell anaemia before and after treatment with hydroxyurea. *Br J Haematol,* 105**,** 491-6.					
Rogers, 1997 Rogers, Z. R. 1997. Hydroxyurea therapy for diverse pediatric populations with sickle cell disease. *Semin Hematol,* 34**,** 42-7.	NR	Hydroxyurea	US (n=16)	5.3-18.4 years (Median: 14.2)	No; pediatric population
Rankine-Mullings, 2021 Rankine-Mullings, A., Reid, M., Soares, D., Taylor-Bryan, C., Wisdom-Phipps, M., Aldred, K., Latham, T., Schultz, W. H., Knight-Madden, J., Badaloo, A., Lane, A., Adams, R. J. & Ware, R. E. 2021. Hydroxycarbamide treatment reduces transcranial Doppler velocity in the absence of transfusion support in	EXTEND; NCT02556099	Hydroxyurea	Jamaica (n=43)	2-17 years	No; pediatric population

children with sickle cell anaemia, elevated transcranial Doppler velocity, and cerebral vasculopathy: the EXTEND trial. *Br J Haematol,* 195**,** 612-620.					
Ambrose, 2020 Ambrose, E. E., Latham, T. S., Songoro, P., Charles, M., Lane, A. C., Stuber, S. E., Makubi, A. N., Ware, R. E. & Smart, L. R. 2023. Hydroxyurea with dose escalation for primary stroke risk reduction in children with sickle cell anaemia in Tanzania (SPHERE): an open-label, phase 2 trial. *Lancet Haematol,* 10**,** e261-e271	SPHERE; NCT03948867	Hydroxyurea	Tanzania (n=202)	2-16 years (Mean: 6.8)	No; pediatric population
McGregor, 2016 McGregor, N. et al., Hydroxyurea to treat pediatric sickle cell disease in Haiti – a preliminary report, Blood 2016 128, 1313, https://www.scie	NR	Hydroxyurea	Haiti (n=43)	2-15 years	No; pediatric population

ncedirect.com/science/article/pii/S00064971193131 4X					
Al-Jam'a, 2002 Al-Jam'a, A. H. & Al-Dabbous, I. A. 2002. Hydroxyurea in sickle cell disease patients from Eastern Saudi Arabia. *Saudi Med J,* 23**,** 277-81.	NR	Hydroxyurea	Saudi Arabia (n=36)	10-36 years	No; lack of VOC-related outcome
Loukopoulos, 2000 Loukopoulos, D., Voskaridou, E., Kalotychou, V., Schina, M., Loutradi, A. & Theodoropoulos, I. 2000. Reduction of the clinical severity of sickle cell/beta-thalassemia with hydroxyurea: the experience of a single center in Greece. *Blood Cells Mol Dis,* 26**,** 453-66.	NR	Hydroxyurea	Greece (n=69)	17-50 years	No
de Montalembert, 1997 De Montalembert, M., Belloy, M., Bernaudin, F.,	NR	Hydroxyurea	France (n=35)	3-20 years (Median: 11)	No; pediatric population

Gouraud, F., Capdeville, R., Mardini, R., Philippe, N., Jais, J. P., Bardakdjian, J., Ducrocq, R., Maier-Redelsperger, M., Elion, J., Labie, D. & Girot, R. 1997. Three-year follow-up of hydroxyurea treatment in severely ill children with sickle cell disease. The French Study Group on Sickle Cell Disease. *J Pediatr Hematol Oncol,* 19**,** 313-8.					
Ware, 2012 Ware, R. E., Helms, R. W. & Investigators, S. W. 2012. Stroke With Transfusions Changing to Hydroxyurea (SWiTCH). *Blood,* 119**,** 3925-32.	SWiTCH; NCT00122980	Blood transfusions and chelation vs Hydroxyurea and phlebotomy	US (n=134)	90.2% of patients ≤18 years (Mean: 13.1)	No; lack of VOC-related outcome
Styles, 2007 Styles, L. A., Abboud, M., Larkin, S., Lo, M. & Kuypers, F. A. 2007. Transfusion prevents acute chest syndrome predicted by elevated secretory	NR	Blood transfusions vs Standard of care	US (n=14)	NR (Mean: 15)	No; lack of VOC-related outcome

phospholipase A2. *Br J Haematol,* 136**,** 343-4.					
Vichinsky, 2001 Vichinsky, E. P., Luban, N. L., Wright, E., Olivieri, N., Driscoll, C., Pegelow, C. H., Adams, R. J. & Stroke Prevention Trail in Sickle Cell, A. 2001. Prospective RBC phenotype matching in a stroke-prevention trial in sickle cell anemia: a multicenter transfusion trial. *Transfusion,* 41**,** 1086-92.	STOP; NCT00000592	Blood transfusions vs Standard of care	US (n=130)	2-16 years	No; lack of VOC-related outcome
Kelly, 2020 Kelly, S., Rodeghier, M. & Debaun, M. R. 2020. Automated exchange compared to manual and simple blood transfusion attenuates rise in ferritin level after 1 year of regular blood transfusion therapy in chronically transfused children with	Silent Cerebral Infarct Multi-Center Clinical Trial	Blood transfusions	US (n=83)	7.5-13.1 years	No; lack of VOC-related outcome

sickle cell disease. *Transfusion,* 60**,** 2508-2516.					
Kwiatkowski, 2021 Kwiatkowski, J. L., Hamdy, M., El-Beshlawy, A., Ebeid, F. S. E., Badr, M., Alshehri, A., Kanter, J., Inusa, B., Adly, A. a. M., Williams, S., Kilinc, Y., Lee, D., Tricta, F. & Elalfy, M. S. 2022. Deferiprone vs deferoxamine for transfusional iron overload in SCD and other anemias: a randomized, open-label noninferiority study. *Blood Adv,* 6**,** 1243-1254.	FIRST; NCT02041299	Deferiprone vs Deferoxamine	Multi-national (n=228)	3-59 years	No; lack of VOC-related outcome
Calvaruso, 2014 Calvaruso, G., Vitrano, A., Di Maggio, R., Ballas, S., Steinberg, M. H., Rigano, P., Sacco, M., Telfer, P., Renda, D., Barone, R., Maggio, A. & Investigators of the Multicenter Randomized Clinical Trial of Deferiprone	NR	Deferiprone vs Deferoxamine	Italy (n=60)	≥13 years (Mean: 36)	No; lack of VOC-related outcome

Versus Deferoxamine In, S.-C.-D. 2014. Deferiprone versus deferoxamine in sickle cell disease: results from a 5-year long-term Italian multi-center randomized clinical trial. *Blood Cells Mol Dis,* 53**,** 265-71.					
Maggio, 2020 Maggio, A., Kattamis, A., Felisi, M., Reggiardo, G., El-Beshlawy, A., Bejaoui, M., Sherief, L., Christou, S., Cosmi, C., Della Pasqua, O., Del Vecchio, G. C., Filosa, A., Cuccia, L., Hassab, H., Kreka, M., Origa, R., Putti, M. C., Spino, M., Telfer, P., Tempesta, B., Vitrano, A., Tsang, Y. C., Zaka, A., Tricta, F., Bonifazi, D. & Ceci, A. 2020. Evaluation of the efficacy and safety of deferiprone compared with deferasirox in paediatric	DEEP-2; NCT01825512	Deferiprone vs Deferasirox	Multi-national (n=435)	1 month-18 years	No; lack of VOC-related outcome

patients with transfusion-dependent haemoglobinopathies (DEEP-2): a multicentre, randomised, open-label, non-inferiority, phase 3 trial. *Lancet Haematol,* 7**,** e469-e478.					
Vichinsky, 2013 Vichinsky, E., Torres, M., Minniti, C. P., Barrette, S., Habr, D., Zhang, Y., Files, B. & Study, C. a. I. 2013. Efficacy and safety of deferasirox compared with deferoxamine in sickle cell disease: two-year results including pharmacokinetics and concomitant hydroxyurea. *Am J Hematol,* 88**,** 1068-73.	NCT00110617	Deferasirox vs Deferoxamine	US and Canada (n=203)	2-57 years (Median: 13)	No; lack of VOC-related outcome
Cancado, 2012 Cancado, R., Olivato, M. C., Bruniera, P., Szarf, G., De Moraes Bastos, R., Rezende Melo, M. & Chiattone, C. 2012. Two-year analysis of	NR	Deferasirox	NR	9-49 years (Median: 25)	No; lack of VOC-related outcome

efficacy and safety of deferasirox treatment for transfusional iron overload in sickle cell anemia patients. *Acta Haematol,* 128**,** 113-8.					
Vichinsky, 2011 Vichinsky, E., Bernaudin, F., Forni, G. L., Gardner, R., Hassell, K., Heeney, M. M., Inusa, B., Kutlar, A., Lane, P., Mathias, L., Porter, J., Tebbi, C., Wilson, F., Griffel, L., Deng, W., Giannone, V. & Coates, T. 2011. Long-term safety and efficacy of deferasirox (Exjade) for up to 5 years in transfusional iron-overloaded patients with sickle cell disease. *Br J Haematol,* 154**,** 387-97.	NR	Deferasirox	US, UK, Canada, France, Italy	3-54 years (Mean: 19.2)	No; lack of VOC-related outcome
Soulieres, 2022 Soulieres, D., Mercier-Ross, J., Fradette, C., Rozova, A., Tsang, Y. C. & Tricta, F. 2022. The	NCT01835496	Deferiprone	Canada	18-45 years	No; lack of VOC-related outcome

pharmacokinetic and safety profile of single-dose deferiprone in subjects with sickle cell disease. *Ann Hematol,* 101**,** 533-539.					
Voskaridou, 2005 Voskaridou, E., Douskou, M., Terpos, E., Stamoulakatou, A., Meletis, J., Ourailidis, A., Papassotiriou, I. & Loukopoulos, D. 2005. Deferiprone as an oral iron chelator in sickle cell disease. *Ann Hematol,* 84**,** 434-40.	NR	Deferiprone	Greece	25-67 years	No; lack of VOC-related outcome
Heeney, 2022 Heeney, M. et al., S122: Safety and efficacy of crizanlizumab in adolescents with sickle cell disease (SCD): initial data from the phase II, multicenter, open-label Solace-Kids trial, Hemasphere 2022 6(Suppl):12, PMC8812070.	Solace-Kids; NCT03474965	Crizanlizumab with or without hydroxyurea	Multi-national (n=50)	6 months-17 years	No; pediatric population and dose was not FDA-approved
Liles, 2020	Solace-Adults; NCT03264989	Crizanlizumab	US (n=57)	16-70 years	No; study focused on pharmacokinetics

Liles, D., et al., 1715 Pharmacokinetics /pharmacodynamics, safety and efficacy of crizanlizumab in patients with sickle cell disease and a history of vaso-occlusive crises: results from the phase II, multicenter, open-label Solace-Adults study, https://ash.confex.com/ash/2020/webprogram/Paper137434.html					and pharmacodynamics
NR, 2009 https://clinicaltrials.gov/study/NCT00586209	NCT00586209	L-Glutamine vs Placebo	US (n=15)	18-65 years	No; lack of VOC-related outcome
Howard, 2019 Howard, J., Hemmaway, C. J., Telfer, P., Layton, D. M., Porter, J., Awogbade, M., Mant, T., Gretler, D. D., Dufu, K., Hutchaleelaha, A., Patel, M., Siu, V., Dixon, S., Landsman, N., Tonda, M. & Lehrer-Graiwer, J. 2019. A phase 1/2 ascending dose study and open-label extension	NCT02285088	Voxelotor vs Placebo	UK (n=40)	18-56 years	No; lack of VOC-related outcome

study of voxelotor in patients with sickle cell disease. *Blood,* 133**,** 1865-1875.					
Lehrer-Graiwer, 2016 Lehrer-Graiwer, J., et al., Accelerated approval of Oxbryta® (voxelotor): a case study on novel endpoint selection in sickle cell disease, Contemporary Clinical Trials 2020 98, 106161, https://www.sciencedirect.com/science/article/pii/S1551714420302391	NCT02285088	Voxelotor vs Placebo	NR (n=30)	18-60 years (Median: 32)	No; lack of VOC-related outcome
Brown, 2019 https://clinicaltrials.gov/study/NCT02850406	HOPE Kids; GBT440-007; NCT02850406	Voxelotor	US and Lebanon (n=15)	12-17 years	No; lack of VOC-related outcome
Bernaudin, 2019 Bernaudin, F., Verlhac, S., Peffault De Latour, R., Dalle, J. H., Brousse, V., Petras, E., Thuret, I., Paillard, C., Neven, B., Galambrun, C., Divialle-Doumdo, L., Pondarre, C.,	Drepagreffe; NCT01340404	Allogeneic (matched sibling donor) hematopoietic SCT vs Standard of care (transfusions)	France (n=67)	≤15 years (Median: 7.6)	No; lack of VOC-related outcome

Guitton, C., Missud, F., Runel, C., Jubert, C., Elana, G., Ducros-Miralles, E., Drain, E., Taieb, O., Arnaud, C., Kamdem, A., Malric, A., Elmaleh-Berges, M., Vasile, M., Leveille, E., Socie, G., Chevret, S. & Investigators, D. T. 2019. Association of Matched Sibling Donor Hematopoietic Stem Cell Transplantation With Transcranial Doppler Velocities in Children With Sickle Cell Anemia. *JAMA,* 321**,** 266-276.					
Parsons, 2022 Parsons, S. K., Rodday, A. M., Weidner, R. A., Morris, E., Braniecki, S., Shenoy, S., Talano, J. A., Moore, T. B., Panarella, A., Flower, A., Milner, J., Fabricatore, S., Mahanti, H., Van De Ven, C., Shi, Q. & Cairo, M. S. 2022. Significant	NCT01461837	Allogeneic (familial haploidentical) SCT	US (n=19)	3-20 years (Mean: 12.9)	No; lack of VOC-related outcome

improvement of child physical and emotional functioning after familial haploidentical stem cell transplant. *Bone Marrow Transplant,* 57**,** 586-592.					
Alzahrani, 2021 Alzahrani, M., Damlaj, M., Essa, M., Alahmari, B., Alaskar, A., Hejazi, A., Basher, E., Alsadi, H., Ahmed, M., Abujoub, R., Ghazi, S., Alshobaki, H., Abuelgasim, K., Salama, H., Gmati, G. & Alsultan, A. 2022. HLA-identical related hematopoietic stem cell transplantation in severe sickle cell disease: age is not a barrier to successful outcome. *Bone Marrow Transplant,* 57**,** 292-294.	NR	Allogeneic (matched related donor) hematopoietic, non-myeloablative SCT + Alemtuzumab/Low-Dose Irradiation	US and Saudi Arabia (n=122)	10-65 years (Median: 29)	No; lack of VOC-related outcome
Parikh, 2018 Parikh, S., Brochstein, J. A., Galamidi, E.,	NCT01590628	NiCord with unmanipulated unrelated cord blood	US (n=11)	2-45 years	No; lack of VOC-related outcome

Schwarzbach, A. & Kurtzberg, J. 2021. Allogeneic stem cell transplantation with omidubicel in sickle cell disease. *Blood Adv,* 5**,** 843-852.					
Bethge, 2017 Haen, S. P., Groh, C., Schumm, M., Backert, L., Loffler, M. W., Federmann, B., Faul, C., Dorfel, D., Vogel, W., Handgretinger, R., Kanz, L. & Bethge, W. A. 2017. Haploidentical hematopoietic cell transplantation using in vitro T cell depleted grafts as salvage therapy in patients with disease relapse after prior allogeneic transplantation. *Ann Hematol,* 96**,** 817-827.	NR	Haploidentical SCT	Germany and the Netherlands (n=30)	20-63 years (Median: 38.5)	No; lack of VOC-related outcome
Saraf, 2016 Saraf, S. L., Oh, A. L., Patel, P. R., Jalundhwala, Y., Sweiss, K., Koshy, M., Campbell-Lee, S., Gowhari, M., Hassan, J., Peace,	NCT01499888	Allogeneic (matched related donor) hematopoietic, non-myeloablative SCT + Alemtuzumab/Lo	US (n=13)	16-60 years	No; lack of VOC-related outcome

D., Quigley, J. G., Khan, I., Molokie, R. E., Hsu, L. L., Mahmud, N., Levinson, D. J., Pickard, A. S., Garcia, J. G., Gordeuk, V. R. & Rondelli, D. 2016. Nonmyeloablative Stem Cell Transplantation with Alemtuzumab/Low-Dose Irradiation to Cure and Improve the Quality of Life of Adults with Sickle Cell Disease. *Biol Blood Marrow Transplant,* 22**,** 441-8.		w-Dose Irradiation			
Shenoy, 2016 Shenoy, S., Eapen, M., Panepinto, J. A., Logan, B. R., Wu, J., Abraham, A., Brochstein, J., Chaudhury, S., Godder, K., Haight, A. E., Kasow, K. A., Leung, K., Andreansky, M., Bhatia, M., Dalal, J., Haines, H., Jaroscak, J., Lazarus, H. M., Levine, J. E., Krishnamurti, L., Margolis, D., Megason, G. C.,	SCURT, BMT CTN 0601; NCT00745420	Allogeneic (unrelated donor) marrow transplantation	US (n=29)	4-19 years	No; lack of VOC-related outcome

Yu, L. C., Pulsipher, M. A., Gersten, I., Difronzo, N., Horowitz, M. M., Walters, M. C. & Kamani, N. 2016. A trial of unrelated donor marrow transplantation for children with severe sickle cell disease. *Blood,* 128**,** 2561-2567.					
Krishnamurti, 2015 Krishnamurti, L. et al., Results of a multicenter pilot investigation of bone marrow transplantation in adults with sickle cell disease (STRIDE), https://ashpublications.org/blood/article/126/23/543/134396/Results-of-a-Multicenter-Pilot-Investigation-of	STRIDE	Hematopoietic (related or unrelated donor) SCT	US (n=22)	16-40 years	No; lack of VOC-related outcome
Hsieh, 2009 Hsieh, M. M., Kang, E. M., Fitzhugh, C. D., Link, M. B., Bolan, C. D., Kurlander, R., Childs, R. W., Rodgers, G. P., Powell, J. D. & Tisdale, J. F. 2009.	NCT00061568	Allogeneic (matched sibling donor) hematopoietic, non-myeloablative SCT	US (n=10)	16-45 years (Median: 26)	No; lack of VOC-related outcome

Allogeneic hematopoietic stem-cell transplantation for sickle cell disease. *N Engl J Med,* 361**,** 2309-17.					
Magrin, 2019 Magrin, E. et al., Results from the completed Hgb-205 trial of lentiglobin for β-thalassemia and lentiglobin for sickle cell disease gene therapy, https://ashpublications.org/blood/article/134/Supplement_1/3358/423811/Results-from-the-Completed-Hgb-205-Trial-of	HGB-205; NCT02151526	LentiGlobin (Zynteglo)	France (n=3)	5-35 years	No; study included only 3 patients
Locatelli, 2022 https://library.ehaweb.org/eha/2022/eha2022-congress/366210	CLIMB SCD-121	Exa-cel	Multi-national (31)	12-35	No; same patients as target trial
Grimley, 2022 Grimley, M. et al., P1453: Stable transduction of fetal hemoglobin in patients with sickle cell disease in the phase ½ momentum study of ARU-1801 gene	MOMENTUM; NCT02186418	ARU-1801 gene therapy	US and Jamaica (n=5)	19-35 years	No; not an approved treatment

therapy and reduced intensity conditioning, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9429142/					
Erica, 2019 Esrick, EB., et al., Validation of BCL11A as therapeutic target in sickle cell disease: results from the adult cohort of a pilot/feasibility gene therapy trial inducing sustained expression of fetal hemoglobin using post-transcriptional gene silencing, https://ashpublications.org/blood/article/134/Supplement_2/LBA-5/428838/Validation-of-BCL11A-As-Therapeutic-Target-in	NCT03282656	BCH-BB694 gene therapy	US (n=3)	21-26 years	No; not an approved treatment
Updated SLR					
Van Dijk, 2022 van Dijk MJ, Rab MA, van Oirschot BA, Bos J, Derichs C, Rijneveld AW, Cnossen MH, Nur E, Biemond BJ, Bartels M: Safety and efficacy of	EudraCT 2019–003438-18	Mitapivat	Netherlands, N=9	≥16 years	Comparator not relevant

mitapivat, an oral pyruvate kinase activator, in sickle cell disease: a phase 2, open-label study. *American journal of hematology* 2022, 97(7):E226-E229.					
Rai, 2023 Rai P, Okhomina VI, Kang G, Martinez HR, Hankins JS, Joshi V: Longitudinal effect of disease-modifying therapy on left ventricular diastolic function in children with sickle cell anemia. *American Journal of Hematology* 2023, 98(6):838-847.	NCT00842621 NCT02098863	Hydroxyurea and monthly erythrocyte transfusions	N=204	5 – 18 years	Outcome not relevant
Paul, 2022 Paul A SP, Mishra R, Singh SK, Patra PC, Bahirat H. : Efficacy of Thalidomide in Combination with Hydroxyurea in Patients with Sickle Cell Anemia: A Randomised Control Trial. In: *63rd Annual Conference of Indian Society of Hematology & Blood Transfusion (ISHBT) November 2022: 2022/11/01*. Indian Journal of Hematology and	NA	Thalidomide in combination with hydroxyurea	NA	NA	Comparator not relevant

Blood Transfusion 2022: S64-65.					
Brown, 2022 Brown C, Key C, Agodoa I, Olbertz J, Duchin K, Barth A, Lisbon E: S268: Safety, tolerability, and pharmacokinetic/ pharmacodynamic results from phase 1 studies of GBT021601, a next-generation HbS polymerization inhibitor for treatment of sickle cell disease. *HemaSphere* 2022, 6:169-170.	NA	GBT021601	N=18	≥ 4 years	Comparator not relevant
Silva-Pinto, 2022 Silva-Pinto AC, Colombatti R, Pasanisi A, Arcioni F, DeBonnett L, Soliman W, Sarkar R, Cançado RD: P1491: REAL-WORLD INCIDENCE OF VASO-OCCLUSIVE CRISES IN PATIENTS WITH SICKLE CELL DISEASE (SCD) AND A HIGH BASELINE DISEASE BURDEN TREATED WITH CRIZANLIZUMAB: RESULTS FROM A MANAGED ACCESS PROGRAM (MAP). *HemaSphere* 2022, 6(Suppl).	NA	Crizanlizumab	N=188	16 - 70	Comparator not relevant

Heeney, 2022 Heeney MM, Abboud MR, Githanga J, Inusa BP, Kanter J, Michelson AD, Nduba V, Musiime V, Apte M, Inati A: Ticagrelor vs placebo for the reduction of vaso-occlusive crises in pediatric sickle cell disease: the HESTIA3 study. *Blood, The Journal of the American Society of Hematology* 2022, 140(13):1470-1481	NCT03615924	Ticagrelor	N=193	2 - 17	Comparator not relevant
Xu, 2022 Xu JZ, Conrey A, Frey I, Gwaabe E, Menapace LA, Tumburu L, Lundt M, Lequang T, Li Q, Glass K: A phase 1 dose escalation study of the pyruvate kinase activator mitapivat (AG-348) in sickle cell disease. *Blood, The Journal of the American Society of Hematology* 2022, 140(19):2053-2062.	NCT04000165	Mitapivat	N=16	≥ 18	Comparator not relevant
Khaled, 2022 Khaled SAA, Ashry IEM: Drug therapy in patients with severe forms of	NCT05081349	l-carnitine in combination with hydroxycarbamide	N=91	≥18	Comparator not relevant

sickle cell anemia: A nonrandomized clinical trial of combining l-carnitine with hydroxycarbamide therapy. *Journal of Applied Hematology* 2022, 13(4):237					
Phan, 2023 Phan V, Hershenson J, Caldarera L, Larkin SK, Wheeler K, Cortez AL, Dulman R, Briere N, Lewis A, Kuypers FA: Effect of voxelotor on cardiopulmonary testing in youths with sickle cell anemia in a pilot study. *Pediatric Blood & Cancer* 2023:e30423	NCT04581356	Voxelotor	N=10	≥12	Outcome not relevant

Key: NA = not available

H.1.5 Characteristics of included studies

In the initial search, three publications retrieved reported on CLIMB SCD-121. The updated search 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 (X)(170). One poster and three oral presentations were retrieved from the CRISPR Therapeutics website which were not identified in the clinical SLR searches.

Table 96. Identified studies and associated publications for exa-cel in SCD

Lead author, year	Title
CLIMB SCD-121	
Frangoul, 2020 (62)	CRISPR-Cas9 Gene Editing for Sickle Cell Disease and beta-Thalassemia
Frangoul, 2020 (171)	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

Grupp, 2021 (172)	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
Soni, 2021 (173)	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)
Locatelli, 2022 (174)	Efficacy and Safety of a Single Dose of Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease
Frangoul, 2022 (175)	Efficacy and Safety of a Single Dose of Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease
de la Fuente, 2023 (125)	5612617 EFFICACY AND SAFETY OF A SINGLE DOSE OF EXAGAMGLOGENE AUTOTEMCEL FOR TRANSFUSION-DEPENDENT-THALASSEMIA AND SEVERE SICKLE CELL DISEASE
Locatelli, 2023 (176)	Transfusion Independence and Elimination of Vaso-Occlusive Crises After Exagamglogene Autotemcel in Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease

A complete reference list for excluded studies at data extraction in the original and updated clinical SLRs can be found below in Table 97.

Table 97. List of studies excluded at data extraction

Lead author, Year	Title	Reason for exclusion
Original SLR		
Talano, 2015	Familial haploidentical (FHI) t-cell depleted (TCD) with t-cell addback stem cell transplantation for patients with high-risk sickle cell disease (SCD) (IND 14359)	Population out of scope
Koren, 1999	Effect of hydroxyurea in sickle cell anemia: a clinical trial in children and teenagers with severe sickle cell anemia and sickle cell beta-thalassemia	Population out of scope
Voskaridou, 2011	Deferasirox effectively decreases iron burden in patients with double heterozygous HbS/beta-thalassemia	Population out of scope
DeBaun, 2014	Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia	Population out of scope
Galadanci, 2017	Feasibility trial for primary stroke prevention in children with sickle cell anemia in Nigeria (SPIN trial)	Population out of scope
Zimmerman, 2007	Hydroxyurea therapy lowers transcranial Doppler flow velocities in children with sickle cell anemia	Population out of scope

Aygun, 2013	Hydroxyurea treatment decreases glomerular hyperfiltration in children with sickle cell anemia	Population out of scope
Abdullahi, 2020	Low- Versus Moderate-Dose Hydroxyurea for Secondary Stroke Prevention in Children with Sickle Cell Disease in Sub-Saharan Africa: Final Results of a Randomized Controlled Trial, Sprint Trial	Population out of scope
Ndugwa. 2016	Novel Use Of Hydroxyurea in an African Region With Malaria	Population out of scope
Opoka, 2017	Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM): a trial for children with sickle cell anemia	Population out of scope
Ware, 2002	Predictors of fetal hemoglobin response in children with sickle cell anemia receiving hydroxyurea therapy	Population out of scope
Galadanci, 2019	Primary Prevention of Strokes in Nigerian Children with Sickle Cell Disease (SPIN Trial): Final Results	Population out of scope
Sanchez, 2018	Stroke avoidance for children in Republica Dominicana (sacred)	Population out of scope
Zahran, 2020	Effect of Hydroxyurea Treatment on the Inflammatory Markers Among Children With Sickle Cell Disease	Population out of scope
Wethers, 1994	Accelerated healing of chronic sickle-cell leg ulcers treated with RGD peptide matrix	Intervention out of scope
Karimi, 2006	Clinical response of patients with sickle cell anemia to cromolyn sodium nasal spray	Intervention out of scope
Gordeuk, 2018	Consistent compliance with hydroxyurea and hematology measures during L-glutamine therapy for sickle cell anemia	Intervention out of scope
Kharya, 2019	Myeloablative versus reduced intensity conditioning for matched related donor transplant for sickle cell disease	Intervention out of scope
Daigavane, 2013	Perinatal outcome in sickle cell anemia: a prospective study from India	Intervention out of scope
Brochstein, 2017	Successful engraftment of umbilical cord blood (UCB) Cells after co-transplantation of nicord (ex vivo expanded UCB progenitor cells with nicotinamide) and an unmanipulated UCB unit after myeloablative chemotherapy in severe sickle cell disease	Intervention out of scope

Kamani, 2012	Unrelated donor cord blood transplantation for children with severe sickle cell disease: Results of a phase II study from the blood and marrow transplant clinical trials network	Intervention out of scope
NCT00102791	A Phase III, Multicenter, 52-Week, Randomized, Double-Blind, Placebo-Controlled Study of the Clinical Efficacy and Safety of ICA-17043 with or without Hydroxyurea Therapy in Patients with Sickle Cell Disease who have had = 2 Acute Sickle-Related Painful Crises within the Preceding 12 Months. - A Stratified Sickle Event Randomised Trial - ASSERT	Intervention out of scope
Cabannes, 1983.	Acute painful sickle-cell crises in children. A double-blind, placebo-controlled evaluation of efficacy and safety of cetiedil	Intervention out of scope
Daak, 2018	Clinical effect of SC411 (Altemia TM) on children with sickle cell disease in the scot trial: A phase 2 randomized, double-blind, placebo-controlled, parallel-group, dose-finding multi-center study	Intervention out of scope
Biemond, 2019	Efficacy and safety of sevuparin, a novel non-anti-coagulant heparinoid, in patients with acute painful vaso-occlusive crisis; A global, multicenter double-blind, randomized, placebo-controlled phase 2 trial (TVOC01)	Intervention out of scope
Telen, 2015.	Randomized phase 2 study of GMI-1070 in SCD: Reduction in time to resolution of vaso-occlusive events and decreased opioid use	Intervention out of scope
van Dijk, 2022	Safety and Efficacy of Mitapivat (AG-348), an Oral Activator of Pyruvate Kinase R, in Subjects with Sickle Cell Disease: A Phase 2, Open-Label Study (ESTIMATE)	Intervention out of scope
Meneses, 2016	Autologous stem cell-based therapy for sickle cell leg ulcer: a pilot study	Outcome out of scope
King, 2008	Blood transfusion therapy is feasible in a clinical trial setting in children with sickle cell disease and silent cerebral infarcts	Outcome out of scope
Kanter, 2017	Crizanlizumab 5.0 mg/kg increased the time to first on-treatment sickle cell pain crisis: A subgroup analysis of the phase ii sustain study	Outcome out of scope
Kwiatkowski, 2006	Elevated blood flow velocity in the anterior cerebral artery and stroke risk in sickle cell disease: extended analysis from the STOP trial	Outcome out of scope

Hoffer, 2010	Liver biopsy in chronically transfused children with sickle cell anemia and stroke	Outcome out of scope
Wood, 2016	Organ iron accumulation in chronically transfused children with sickle cell anaemia: baseline results from the TWiTCH trial	Outcome out of scope
Styles, 2012	Refining the value of secretory phospholipase A2 as a predictor of acute chest syndrome in sickle cell disease: results of a feasibility study (PROACTIVE)	Outcome out of scope
NCT04218084	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Voxelotor (GBT440) in Pediatric Participants with Sickle Cell Disease (HOPE Kids 2)	Outcome out of scope
NCT00102791	A Stratified Sickle Event Randomized Trial (ASSERT)	Outcome out of scope
NCT02285088	A Study of the Safety, Blood Levels and Biological Effects of GBT440 in Healthy Subjects and Subjects With Sickle Cell Disease	Outcome out of scope
Wood, 2016	Agreement between R2 and R2* liver iron estimates is independent of the type of iron removal therapy: Results from the twitch trial	Outcome out of scope
Galaverna, 2019	Alpha/beta T-cell depleted Haploidentical HSCT followed by infusion of donor lymphocytes transduced with inducible caspase9 gene is safe and effective for patients with erythroid disorders	Outcome out of scope
McMahon, 1997	An extension of stochastic curtailment for incompletely reported and classified recurrent events: the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH)	Outcome out of scope
Voskaridou, 1995	Clinical and laboratory effects of long-term administration of hydroxyurea to patients with sickle-cell/beta-thalassaemia	Outcome out of scope
Niihara, 2018	Consistent benefit of L-glutamine observed across patients with low, medium, and high number of crises reported in the year prior to screening-analysis from the phase 3 study of L-glutamine in sickle cell anemia	Outcome out of scope
Peters, 2016	Contemporary conditioning regimen before allogeneic stem cell transplantation for children with non-malignant diseases	Outcome out of scope

Howard, 2019	Correlation of voxelotor exposure with hemoglobin response and measures of hemolysis in patients from the hope study	Outcome out of scope
Howard, 2020	Correlation of voxelotor exposure with hemoglobin response and measures of hemolysis in patients from the hope study	Outcome out of scope
Gay, 2016	Cost-effectiveness of blood transfusions versus observation for silent cerebral infarcts from the silent cerebral infarct trial	Outcome out of scope
Braga, 2016	Deferasirox associated to liver failure and death in a sickle cell anemia patient homozygous for the -1774delG polymorphism in the ABCC2 gene encoding multidrug resistance protein 2 (MRP2)	Outcome out of scope
NCT04058197	Deferoxamine for Sickle Cell Chronic Leg Ulcer Treatment	Outcome out of scope
Quinn, 2021	Early initiation of hydroxyurea (hydroxycarbamide) using individualised, pharmacokinetics-guided dosing can produce sustained and nearly pancellular expression of fetal haemoglobin in children with sickle cell anaemia	Outcome out of scope
Smith, 2009	Effect of geography and climate on pain frequency in patients enrolled in the Muticenter Study of Hydroxyurea in Sickle Cell Anemia	Outcome out of scope
Hackney, 1997	Effects of hydroxyurea administration on the body weight, body composition and exercise performance of patients with sickle-cell anaemia	Outcome out of scope
Lopez Domowicz, 2020	Effects of repleting organic phosphates in banked erythrocytes on plasma metabolites and vasoactive mediators after red cell exchange transfusion in sickle cell disease	Outcome out of scope
Daltro, 2015	Efficacy of autologous stem cell-based therapy for osteonecrosis of the femoral head in sickle cell disease: A five-year follow-up study	Outcome out of scope
Luban, 2010	Erythrocyte allo-and auto-antibody formation in sickle cell anemia during stroke prophylaxis	Outcome out of scope
Oliveira, 2019	Evaluation of hydroxyurea genotoxicity in patients with sickle cell disease	Outcome out of scope

Wood, 2013	Extrahepatic iron deposition in chronically transfused children with sickle cell anemia - Baseline findings from the twitch trial	Outcome out of scope
Galadanci, 2019	Feasibility trial for primary stroke prevention in children with sickle cell anemia in Nigeria (SPIN trial)	Outcome out of scope
Karkoska, 2021	Hydroyxurea improves cerebral oxygen saturation in children with sickle cell anemia	Outcome out of scope
Verlhac, 2021	Improved stenosis outcome in stroke-free sickle cell anemia children after transplantation compared to chronic transfusion	Outcome out of scope
Smith, 2020	Improvement in the Clinical Global Impression of Change with Voxelotor in Patients with Sickle Cell Disease in the Phase 3 HOPE Trial	Outcome out of scope
Inusa, 2022	Long-term efficacy and safety of deferiprone for patients with sickle cell disease or other anemias	Outcome out of scope
Abboud, 2004	Magnetic resonance angiography in children with sickle cell disease and abnormal transcranial Doppler ultrasonography findings enrolled in the STOP study	Outcome out of scope
Helton, 2014	Magnetic resonance imaging/angiography and transcranial Doppler velocities in sickle cell anemia: results from the SWiTCH trial	Outcome out of scope
Thibodeaux, 2016	More efficient exchange of sickle red blood cells can be achieved by exchanging the densest red blood cells	Outcome out of scope
Hsieh, 2014	Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle cell phenotype	Outcome out of scope
Ware, 2011	Pharmacokinetics, pharmacodynamics, and pharmacogenetics of hydroxyurea treatment for children with sickle cell anemia	Outcome out of scope
Silva Jr, 2014	Proteinuria in adults with sickle cell disease: The role of hydroxyurea as a protective agent	Outcome out of scope
Patwari, 2021	Recombinant ADAMTS13 for Patients with Sickle Cell Disease: Design of a Phase 1 Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study	Outcome out of scope

Bhatia, 2014	Reduced toxicity, myeloablative conditioning with BU, fludarabine, alemtuzumab and SCT from sibling donors in children with sickle cell disease	Outcome out of scope
NCT05561140	Resolution of Sickle Cell Leg Ulcers with Voxelotor (RESOLVE)	Outcome out of scope
Elalfy, 2021	Safety and efficacy of deferiprone vs deferoxamine for transfusion-dependent Anemias	Outcome out of scope
NCT03806452	SIKAMIC (SIklos on Kidney Function and AlbuMInuria Clinical Trial)	Outcome out of scope
Adams, 2004	Stroke and conversion to high risk in children screened with transcranial Doppler ultrasound during the STOP study	Outcome out of scope
Heeney, 2020	Study Design and Initial Baseline Characteristics in Solace-Kids: Crizanlizumab in Pediatric Patients with Sickle Cell Disease	Outcome out of scope
NCT04053764	Study exploring the effect of crizanlizumab on kidney function in patients with chronic kidney disease caused by sickle cell disease	Outcome out of scope
NCT03814746	Study of Two Doses of Crizanlizumab Versus Placebo in Adolescent and Adult Sickle Cell Disease Patients	Outcome out of scope
NCT03573882	Study to Assess the Effect of Long-term Treatment With GBT440 in Participants Who Have Completed Treatment in Study GBT440-031	Outcome out of scope
NCT04218084	Study to Evaluate the Effect of GBT440 on TCD in Pediatrics With Sickle Cell Disease	Outcome out of scope
Sheehan, 2014.	Whole exome sequencing identifies novel genes for fetal hemoglobin response to hydroxyurea in children with sickle cell anemia	Outcome out of scope
Lam, 2021	The Evaluation of Transfusion Data from the Phase 3 Clinical Study of L-Glutamine in Sickle Cell Disease	Outcome out of scope
Washington, 2018	The pharmacokinetics of voxelotor following single doses in pediatric patients with sickle cell disease	Outcome out of scope
Niihara, 2014.	A phase 3 study of L-glutamine therapy for sickle cell anemia and sickle s0-thalassemia	Outcome out of scope

Vichinsky, 2011.	A randomized phase II study evaluating the efficacy and safety of deferasirox versus deferoxamine in patients with sickle cell disease (SCD): 2-year results including pharmacokinetics (177) and safety of deferasirox with concomitant hydroxyurea therapy	Outcome out of scope
Ngwube, 2019	Abatacept is effective for Gvhd prophylaxis after unrelated donor stem cell transplantation (URD SCT) for severe sickle cell disease (SCD)	Outcome out of scope
Sanchez, 2018.	Building capacity to reduce stroke in children with sickle cell anemia in the Dominican Republic: the SACRED trial	Outcome out of scope
Walters, 1997	Collaborative multicenter investigation of marrow transplantation for sickle cell disease: current results and future directions	Outcome out of scope
Ware, 2019	Concomitant hydroxyurea and voxelotor: Results from the hope study	Outcome out of scope
Kutlar, 2017	Crizanlizumab, A P-selectin inhibitor, increases the likelihood of not experiencing a sickle cell-related pain crisis while on treatment: Results from the phase II sustain study	Outcome out of scope
Liles, 2018	Established prevention of vaso-occlusive crises with crizanlizumab is further improved in patients who follow the standard treatment regimen: Post-hoc analysis of the phase II sustain study	Outcome out of scope
Talano, 2017.	Familial haploidentical (FHI) T-cell depleted (TCD) with T-cell addback stem cell transplantation for patients with high-risk sickle cell disease (SCD) (IND 14359)	Outcome out of scope
Shah, 2020	Granulocyte Colony-Stimulating Factor Is Safe and Well Tolerated Following Allogeneic Transplantation in Patients with Sickle Cell Disease	Outcome out of scope
Vichinsky, 2020	Incidence of vaso-occlusive crisis does not increase with achieving higher hemoglobin levels on voxelotor treatment or after discontinuation: Analyses of the hope study	Outcome out of scope
Vichinsky, 2019	Incidence of vaso-occlusive crisis does not increase with achieving higher hemoglobin levels on voxelotor treatment or after discontinuation: Analyses of the hope study	Outcome out of scope

Nickel, 2021	Nonmyeloablative HLA-Identical Sibling Donor Transplantation for Children and Young Adults with Sickle Cell Disease: Interim Results of the SUN Multicenter Phase II Trial	Outcome out of scope
Verlhac, 2019	Stenosis outcome at 1 and 3 years after transplantation vs standard-care in children with sickle-cell anemia and abnormal transcranial doppler with stroke or no-stroke history	Outcome out of scope
Araujo, 1996	A novel delivery system for continuous desferrioxamine infusion in transfusional iron overload	Study design out of scope (SLR, MA/NMA, Case report)
Harmatz, 1999	Effects of red blood cell transfusion on resting energy expenditure in adolescents with sickle cell anemia	Study design out of scope (SLR, MA/NMA, Case report)
Horan, 2005	Hematopoietic stem cell transplantation for multiply transfused patients with sickle cell disease and thalassemia after low-dose total body irradiation, fludarabine, and rabbit anti-thymocyte globulin	Study design out of scope (SLR, MA/NMA, Case report)
Altura, 2002	Hydroxyurea therapy associated with declining serum levels of magnesium in children with sickle cell anemia	Study design out of scope (SLR, MA/NMA, Case report)
Adamkiewicz, 2004	Transplantation of unrelated placental blood cells in children with high-risk sickle cell disease	Study design out of scope (SLR, MA/NMA, Case report)
Kharbanda, 2014	Unrelated donor allogeneic hematopoietic stem cell transplantation for patients with hemoglobinopathies using a reduced-intensity conditioning regimen and third-party mesenchymal stromal cells	Study design out of scope (SLR, MA/NMA, Case report)
Porter, 2016	Utility of labile plasma iron and transferrin saturation in addition to serum ferritin as iron overload markers in different underlying anemias before and after deferasirox treatment	Study design out of scope (SLR, MA/NMA, Case report)
Power-Hays, 2021	Hydroxyurea Reduces the Transfusion Burden in Children with Sickle Cell Anemia: The Reach Experience	Study design out of scope (SLR, MA/NMA, Case report)

Cappellini, 2010	Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias	Study design out of scope (SLR, MA/NMA, Case report)
Lucarelli, 2012	Allogeneic cellular gene therapy in hemoglobinopathies--evaluation of hematopoietic SCT in sickle cell anemia	Study design out of scope (SLR, MA/NMA, Case report)
Kelly, 2018	Blood utilization and impact of chronic transfusion therapy (CTT) in a large cohort of brazilian sickle cell disease (SCD) patients	Study design out of scope (SLR, MA/NMA, Case report)
Steinberg, 2003	Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment	Study design out of scope (SLR, MA/NMA, Case report)
Hilliard, 1998	Erythrocytapheresis limits iron accumulation in chronically transfused sickle cell patients	Study design out of scope (SLR, MA/NMA, Case report)
Maier-Redelsperger, 1998	Fetal hemoglobin and F-cell responses to long-term hydroxyurea treatment in young sickle cell patients	Study design out of scope (SLR, MA/NMA, Case report)
Beverung, 2015	Health-related quality of life in children with sickle cell anemia: impact of blood transfusion therapy	Study design out of scope (SLR, MA/NMA, Case report)
Nickel, 2020	Human leukocyte antigen (HLA) class I antibodies and transfusion support in paediatric HLA-matched haematopoietic cell transplant for sickle cell disease	Study design out of scope (SLR, MA/NMA, Case report)
Abdel Raheem, 2019	Hydroxyurea and cardiac sequelae in children with sickle cell disease	Study design out of scope (SLR, MA/NMA, Case report)
Italia, 2009	Hydroxyurea in sickle cell disease--a study of clinico-pharmacological efficacy in the Indian haplotype	Study design out of scope (SLR, MA/NMA, Case report)

Saleh, 1997	Hydroxyurea therapy in sickle cell anemia patients in Curacao, The Netherlands Antilles	Study design out of scope (SLR, MA/NMA, Case report)
Mohanty, 2008	Iron deficiency anaemia in sickle cell disorders in India	Study design out of scope (SLR, MA/NMA, Case report)
Sayer, 2012	Long term outcome of patients enrolled into stop and stop II trials: A single center experience	Study design out of scope (SLR, MA/NMA, Case report)
de Azevedo, 2021	Long-Term Effects of Allogeneic Hematopoietic Stem Cell Transplantation on Systemic Inflammation in Sickle Cell Disease Patients	Study design out of scope (SLR, MA/NMA, Case report)
Detterich, 2013	Low-shear red blood cell oxygen transport effectiveness is adversely affected by transfusion and further worsened by deoxygenation in sickle cell disease patients on chronic transfusion therapy	Study design out of scope (SLR, MA/NMA, Case report)
el-Hazmi, 1995	On the use of hydroxyurea/erythropoietin combination therapy for sickle cell disease	Study design out of scope (SLR, MA/NMA, Case report)
Escobar, 2017	Partial Red Blood Cell Exchange in Children and Young Patients with Sickle Cell Disease: Manual Versus Automated Procedure	Study design out of scope (SLR, MA/NMA, Case report)
Cannizzo, 2017	Patients with sickle cell disease treated with red blood cells exchange: The experience of ragusa simt	Study design out of scope (SLR, MA/NMA, Case report)
Shah, 2019	Rate of sickle cell pain crises in patients who previously participated in the sustain trial in the United States: The successor study	Study design out of scope (SLR, MA/NMA, Case report)
Guilliams, 2018	Red cell exchange transfusions lower cerebral blood flow and oxygen extraction fraction in pediatric sickle cell anemia	Study design out of scope (SLR, MA/NMA, Case report)

Silva-Pinto, 2022	Reduced rate of vaso-occlusive crises (VOCs) in patients (pts) with sickle cell disease (SCD) treated with crizanlizumab for 12 months: Results from a real-world, managed access program (MAP)	Study design out of scope (SLR, MA/NMA, Case report)
Krishnamurti, 2008	Stable long-term donor engraftment following reduced-intensity hematopoietic cell transplantation for sickle cell disease	Study design out of scope (SLR, MA/NMA, Case report)
Walters, 2001	Stable mixed hematopoietic chimerism after bone marrow transplantation for sickle cell anemia	Study design out of scope (SLR, MA/NMA, Case report)
Zimmerman, 2004	Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease	Study design out of scope (SLR, MA/NMA, Case report)
Bennardello, 2013	The prevention of adverse reactions to transfusions in patients with haemoglobinopathies: a proposed algorithm	Study design out of scope (SLR, MA/NMA, Case report)
Steinberg, 2010	The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up	Study design out of scope (SLR, MA/NMA, Case report)
Ware, 2012	Stroke With Transfusions Changing to Hydroxyurea (SWiTCH): a phase III randomized clinical trial for treatment of children with sickle cell anemia, stroke, and iron overload	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Burnett, 2020	147 A Prospective Phase II, Open-Label, Single-arm, Multicenter Study to Assess the Efficacy and Safety of SEG101 (Crizanlizumab) in Sickle Cell Disease Patients With Priapism (SPARTAN)	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Foll, 2020	A phase ii stratified trial to assess haploidentical tdepleted stem cell transplantation in patients with sickle cell disease with no available sibling donor	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)

De Santis, 2020	Blood transfusion support for sickle cell patients during haematopoietic stem cell transplantation: a single-institution experience	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Telen, 1999.	Caring for patients with sickle cell disease in North Carolina	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Miniero, 1998	Cord blood transplantation (CBT) in hemoglobinopathies. Eurocord	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Anonymous, 2022	Crizanlizumab (adakveodegree) to prevent vaso-occlusive crises in sickle-cell disease	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Abboud, 2019	Crizanlizumab versus placebo, with or without hydroxyurea/hydroxycarbamide, in adolescent and adult patients with sickle cell disease and vaso-occlusive crises: A randomized, double-blind, phase iii study (178)	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Teixeira, 2003	Effect of hydroxyurea on G gamma chain fetal hemoglobin synthesis by sickle-cell disease patients	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Vasavda, 2012	Effects of co-existing alpha-thalassaemia in sickle cell disease on hydroxycarbamide therapy and circulating nucleic acids	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Bonner, 2010	Health related quality of life in sickle cell disease: Just scratching the surface	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Anonymous, 2009	Hydroxycarbamide in sickle cell syndrome: For severe cases only	Publication type out of scope (Narrative reviews, editorials,

		letters, notes, commentaries)
Al-Sakkaf, 2016	Hydroxyurea and sickle cell disease: Do we need to reach the maximally tolerated dose (MTD)?	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Svarch, 2006	Hydroxyurea treatment in children with sickle cell anemia in Central America and the Caribbean countries	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Choudhury, 2018	Intracranial vasculopathy and infarct recurrence in children with sickle cell anaemia, silent cerebral infarcts and normal transcranial Doppler velocities	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Alvarez, 2017.	Kidney function of transfused children with sickle cell anemia: Baseline data from the TWiTCH study with comparison to non-transfused cohorts	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Galadanci, 2020	Moderate fixed-dose hydroxyurea for primary prevention of strokes in Nigerian children with sickle cell disease: Final results of the SPIN trial	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Fabris, 2016	Modulation of hemolytic and hemoglobin/heme scavenging profiles in sickle cell anemia, hereditary spherocytosis and paroxysmal nocturnal hemoglobinuria	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Steinberg, 1993	New horizons in the management of sickle cell disease	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Amado, 2000	Nonmyeloablative approaches to the treatment of sickle hemoglobinopathies	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)

Tisdale, 2020.	Safety and feasibility of hematopoietic progenitor stem cell collection by mobilization with plerixafor followed by apheresis vs bone marrow harvest in patients with sickle cell disease in the multi-center HGB-206 trial	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Zarkowsky, 1974	Sickle cell anemia: therapeutic considerations	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Bartolucci, 2020	Steadfast: A phase ii study investigating the effect of crizanlizumab and standard of care (SOC) vs soc alone on renal function in patients with chronic kidney disease due to sickle cell nephropathy	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Ataga, 2019	The effect of crizanlizumab plus standard of care (Soc) versus soc alone on renal function in patients with sickle cell disease and chronic kidney disease: A randomized, multicenter, open-label, phase ii study (Steadfast)	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Bello-Manga, 2022	Translating research to usual care of children with sickle cell disease in Northern Nigeria: lessons learned from the SPRING Trial Team	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Kirkham, 2006	Trials in sickle cell disease	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Charache, 1995.	Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Charache, 1996	Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
Ballas, 2006	Hydroxyurea and sickle cell anemia: effect on quality of life	Publication type out of scope (Narrative reviews, editorials,

		letters, notes, commentaries)
NCT03036813	Study to Evaluate the Effect of Voxelotor Administered Orally to Patients With Sickle Cell Disease (GBTHOPE)	Publication type out of scope (Narrative reviews, editorials, letters, notes, commentaries)
SLR Update		
Barker, 2023	Audit of trust compliance with bsh guidelines for utilisation of hydroxycarbamide in patients with sickle cell disease	Irrelevant outcome
Levin, 2023	A phase -IIa-IIb, open label, single center trial to study safety, tolerability and efficacy of memantine as supportive long-term treatment of sickle cell patients: trial design and enrollment	Irrelevant outcome
Smart, 2023	Stroke Prevention with Hydroxyurea Enabled through Research and Education: A Phase 2 Primary Stroke Prevention Trial in Sub-Saharan Africa	Irrelevant population
Namazzi, 2023	Zinc for infection prevention in children with sickle cell anemia: a randomized double-blind placebo-controlled trial	Irrelevant population
Murphy, 2023	ABO Incompatibility Did Not Impact Outcomes after Haploidentical Bone Marrow Transplantation with Posttransplant Cyclophosphamide for Patients with Sickle Cell Disease: Single Center Experience	Irrelevant outcome
Dampier, 2023	A randomized clinical trial of the efficacy and safety of rivipansel for sickle cell vaso-occlusive crisis	Irrelevant outcome
Cronin, 2022	Creating an Automated Contemporaneous Cohort in Sickle Cell Anemia to Predict Survival After Disease-Modifying Therapy	Irrelevant study type
Phan, 2022	Ten-year longitudinal analysis of hydroxyurea implementation in a pediatric sickle cell program	Irrelevant outcome
Oliveira, 2022	Clinical predictors of vaso-occlusive pain hospitalization in patients with sickle cell disease (SCD)	Irrelevant study type
Kuo, 2022	A phase 2/3, randomized, double-blind, placebo-controlled study of mitapivat in patients with sickle cell disease	Irrelevant outcome

Prajapati, 2022	Effect of Counselling on Compliance of Hydroxyurea Therapy and Frequency of Hospital Admissions among Patients with Sickle Cell Disease- A Longitudinal Study	Irrelevant outcome
van Vuren, 2022	Proton pump inhibition for secondary hemochromatosis in hereditary anemia: a phase III placebo-controlled randomized cross-over clinical trial	Irrelevant population
Mahesri, 2022	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	Irrelevant study type
Strouse, 2022	Environmental modifiers of severity in children with sickle cell disease: a feasibility pilot study	Irrelevant study type
Van Vuren, 2022	Proton pump inhibition for secondary hemochromatosis in hereditary anaemia, a phase III placebo-controlled randomized cross-over clinical trial	Irrelevant outcome
Abdelhalim, 2022	Comparative effectiveness of adding Omega-3 or Vitamin D to standard therapy in preventing and treating episodes of painful crisis in pediatric sickle cell patients	Irrelevant outcome
Carson, 2022	How I treat anemia with red blood cell transfusion and iron	Irrelevant outcome
Fraser, 2023	Feasibility study of busulfan, fludarabine, and thiotepa conditioning regimen for allogeneic hematopoietic stem cell transplantation for children and young adults with non malignant disorders	Irrelevant outcome
Lin, 2023	Multicenter Long-Term Follow-Up of Allogeneic Hematopoietic Cell Transplantation with Omidubicel: A Pooled Analysis of Five Prospective Clinical Trials	Irrelevant population
Abdullahi, 2023	Hydroxyurea for secondary stroke prevention in children with sickle cell anemia in Nigeria: a randomized controlled trial	Irrelevant population
Gajjar, 2022	Cerebral hemo-dynamics in children with sickle cell disease in India: An observational cohort study	Irrelevant study type
Sisler, 2022	Satisfaction and access to care for adults and adolescents with sickle cell disease: ASCQ-Me quality of care and the SHIP-HU study	Irrelevant outcome
Salvi, 2022	Preoperative Transfusion and Surgical Outcomes for Children with Sickle Cell Disease	Irrelevant outcome

Walter, 2022	The effects of glutamine supplementation on markers of apoptosis and autophagy in sickle cell disease peripheral blood mononuclear cells	Irrelevant outcome
Creary, 2022	Impact of hydroxyurea dose and adherence on hematologic outcomes for children with sickle cell anemia	Irrelevant outcome
Smith, 2022	A randomised controlled provider-blinded trial of community health workers in sickle cell anaemia: effects on haematologic variables and hydroxyurea adherence	Copy duplicate from original SLR
Shah, 2022	Granulocyte Colony-Stimulating Factor Is Safe and Well Tolerated following Allogeneic Transplantation in Patients with Sickle Cell Disease	Irrelevant outcome
Kanter, 2022	Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease	Irrelevant timeframe

Of the 52 studies identified in the SLR for SCD, five studies were prioritised by Vertex for data extraction and the ITC feasibility assessment (). In addition, the standard of care/ control group of the crizanlizumab, voxelotor and L-glutamine RCTs were included in the ITC assessment (Table 98).

Table 98. Summary of studies prioritized for the ITC assessment for SCD (n=5)

Author, Year (publication type)	Aim	Study design	Patient population	Intervention and comparator (sample size, n)	Primary outcome and follow-up period	Secondary outcome and follow-up period
Vichinsky, 2010 (conference abstract)	Number of VOCs in patients with blood transfusions	US based	Patients 21-55 years	Blood transfusions vs Standard of care (RCT) (n=36)	Total number of VOCs	Not mentioned
Ataga, 2017 (journal article) (SUSTAIN; NCT01895361)	The safety and efficacy of crizanlizumab	Double-blind, randomized, placebo-controlled, phase 2 trial in the US, Brazil, and Jamaica	Patients 16-65 years with sickle cell disease who were receiving concomitant hydroxyurea as well as those not receiving hydroxyurea	High-dose vs low-dose crizanlizumab vs Placebo + Standard of care (n=198)	Annual rate of sickle cell-related pain crises with high-dose crizanlizumab versus placebo. Follow-up: 52 weeks	Annual rate of days hospitalized, the times to first and second crises, annual rates of uncomplicated crises (defined as crises other than the acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism) and the acute chest syndrome, patient-reported outcomes
Niihara, 2018 (journal article) (NCT01179217)	If oral therapy with pharmaceutical -grade l-glutamine (USAN, glutamine) increases the proportion of the reduced form of	US based randomized, placebo-controlled, double-blind, phase 3 trial	Patients 5-58 years with sickle cell anaemia or sickle β0-thalassemia and a history of two or more pain crises during the previous year	L-Glutamine vs Placebo + Standard of care (n=230)	The efficacy of pharmaceutical-grade l-glutamine (0.3 g per kilogram of body weight per dose) administered twice daily by mouth, as compared with placebo, in reducing the incidence of pain crises	Adverse events

	nicotinamide adenine dinucleotides in sickle cell erythrocytes					
Howard, 2021 (journal article) (HOPE; NCT03036813)	Long-term efficacy and safety of voxelotor	Multi-national randomised, double-blind, placebo-controlled, phase 3 trial	Patients 12-65 years with confirmed sickle cell disease, a haemoglobin concentration of 5·5-10·5 g/dL at enrolment, and who had between one and ten vaso-occlusive crisis events in the previous 12 months	Voxelotor 1500 mg vs Voxelotor 900 mg vs Placebo + Standard of care (n=274)	The primary endpoint (already reported) was the proportion of patients who achieved a haemoglobin response at week 24.	Changes in haemoglobin concentrations from baseline to week 72, changes in the concentration of haemolysis markers (absolute and percentage reticulocytes, indirect bilirubin concentrations, and lactate dehydrogenase concentrations) from baseline to week 72, the annualised incidence of vaso-occlusive crises, and patient functioning, as assessed with the Clinical Global Impression of Change (CGI-C) scale. Safety was assessed in patients who received at least one dose of treatment (modified intention-to-treat population)
Kanter, 2022 (66) (NCT02140554)	Evaluation of the efficacy	Nonrandomized, open-label, single-dose clinical trial, at 11 sites	12-50 years (n=43)	LentiGlobin (Zynteglo) (non-RCT)	Complete resolution of severe vaso-occlusive events, which was measured	All vaso-occlusive events and severe vaso-occlusive events that were assessed in

	and safety of LentiGlobin	across the United States, phase 1-2 trial		between 6 months and 18 months after the LentiGlobin infusion.	accordance with the protocol in the TPVOE group from the time of infusion through the last visit

Abbreviations: ACS: acute chest syndrome; RCT: randomized controlled trial; VOC: vaso-occlusive crisis
NOTE: the standard of care/control group in the three (3) highlighted studies were included in the ITC assessment.

H.1.6 Quality assessment

Based on the evidence review of HTA guidelines by NICE, HAS, and G-BA, the NICE quality appraisal checklist was selected as an appropriate risk of bias tool to assess the quality of RCTs included in the SLR (179).

Of the studies prioritized for data extraction for the ITC three were RCTs and were assessed using the NICE checklist. All RCTs were assessed as 'no' for at least two domains, suggesting that the evidence was low to moderate overall (Table 99).

Table 99. NICE quality assessment of RCTs (n=4)

Author, Year	Interventions	Assessment domains*						
		1	2	3	4	5	6	7
Ataga, 2017	High-dose vs low-dose crizanlizumab vs Placebo + Standard of care	Yes	Yes	Yes	Yes	No	No	Yes
Niihara, 2018	L-Glutamine vs Placebo + Standard of care	No	No	Yes	No	No	No	Yes
Howard, 2021	Voxelotor 1500 mg vs Voxelotor 900 mg vs Placebo + Standard of care	Yes	Yes	Yes	No	No	No	Yes

*Assessment domains:
Was randomization carried out appropriately?
Was the concealment of treatment allocation adequate?
Were the groups similar at the outset of the study in terms of prognostic factors?
Were the care providers, participants and outcome assessors blind to treatment allocation?
Were there any unexpected imbalances in drop-outs between groups?
Is there any evidence to suggest that the authors measured more outcomes than they reported?
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

H.1.7 Unpublished data

The clinical and health economic publication plan is presented in the table below.

Table 100: Publication plan (non-exhaustive list)

	Study #	Short title	Description/rationale	Data availability	2024-1H 2025 planned publications*
Clin Dev	CLIMB 111	Exa-cel in TDT, 12-35 years	Continue to demonstrate exa-cel as a transformative and functional cure in SCD & TDT	Nov 2023 May 2024 Oct 2024	Q1: Blood Advances PRO manuscripts (2) Q2: Blood manuscripts (2)
	CLIMB 121	Exa-cel in SCD, 12-35 years			
HEOR	HEOR-21-001-008	PRO Survey Study	Highlight QoL impact and health equity issues faced by persons with SCD with an updated analysis of the PRO survey (update from ASH 2022) to support timely and equitable access to exa-cel	Mar 2023	Q2 2024 manuscript
	HEOR-21-001-009	UK exa-cel CEA Clinical Projections	Economic model to project that lifetime economic burden with SCD and TDT in the tier 1 countries is substantially higher than previously published and projected long-term clinical outcomes of exa-cel, supporting access and reimbursement.	Sep 2023	ISPOR EU 2024

Abbreviations: HEOR = health economics outcomes research; SCD = sickle cell disease; TDT = transfusion-dependent thalassemia (TDT), A form of β--thalassemia in which patients require lifelong regular blood transfusions to survive; UK = United Kingdom; CEA = cost-effectiveness analysis

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

HRQoL studies were identified from the SLR as detailed in Appendix H. The same search strategy detailed in Appendix H was thus applied but with alternative inclusion/exclusion criteria for HRQoL studies. The purpose of this SLR was to identify and examine studies reporting the HRQoL data of all relevant treatments for SCD.

Table 101. Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Medline® Daily, Medline and Versions® Cochrane Central Register of Controlled Trials	OvidSP®	No limit	June 6, 2023
EMBASE®	Elsevier	No limit	June 6, 2023

No other sources (except for conference material) were included in the literature search

Table 102. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search completion
Not applicable			

Conference abstracts were hand searched for the last three years (January 2020 onwards) to retrieve evidence from the latest clinical studies, which have not yet been published in journals as full text articles or supplement results of previously published studies. The relevant conferences for abstract screening included the ones in the table below.

Table 103. Conference material included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
American Society of Haematology (ASH)	https://www.hematology.org/	Jan 2020 onwards	June 6, 2023
European Society for Blood and Marrow Transplantation (EBMT)	https://www.ebmt.org/	Jan 2020 onwards	June 6, 2023
European Haematology Association (EHA)	https://ehaweb.org/		

The SLR followed standard methods outlined for PRISMA, Cochrane guidelines, and NICE guidelines. The PICOS elements that were used to guide the identification and selection of relevant studies for evidence synthesis are reported in Table 104 below.

Table 104. PICO eligibility criteria for HRQoL SLR

Criterion	Inclusion Criteria	Exclusion Criteria
Population	Patients with Sickle Cell Disease (SCD) and aged ≥12 years	Patients without Sickle Cell Disease Paediatric SCD patients (aged <12 years)
Intervention	Any	Not applicable
Comparators	Any	Not applicable
Outcomes	Preference-based multi-attribute utility values (e.g., EQ-5D, HUI-3, SF-6D) Direct utility elicitation tools (TTO, standard gamble, rating scale) Generic health-related quality of life questionnaires (e.g., SF-36, SF-12)	Any other outcomes not listed in the inclusion criteria
Study design	Studies reporting original HRQoL data	Commentaries and letters Systematic and non-systematic reviews Study protocols with no results
Time frame	Any	Not applicable

Language	Studies with abstracts in English language	None

I.1.1 Search strategies

Identifying search results

Table 105. Search strategy for Medline and Cochrance using Ovid

Search No.	Search term	Hits
1	(exp hemoglobin S/ or exp Sickle Cell Disease/ or anemia, sickle cell/ or hemoglobin, sickle/ or Sickle cell disease.mp. or (sickle cell* adj3 (disease* or anemia* or anaemia*)):ab,ti or (hemoglobinopath* or haemoglobinopath*):ab,ti or ((hemoglobin* or haemoglobin*) adj1 SC*):ab,ti or (sickle cell or sickle hemoglobin or drepanocyt* or drepanotic or drepanocytemia or hemoglobin-s or Hb-S or sickle anemia or meniscocytosis).mp.)	2,000
2	((health adj1 utilit*) or (economic adj1 utilit*) or (utilit* adj1 (value* or function*)) or "standard gamble" or "time trade-off" or "time trade off" or "tto").ab,ti.	7,758
3	("quality of life*" or "life quality" or hrqol or "eq 5d*" or "eq-5d*" or eq5d* or eqol* or euroqol* or euroquol* or aqol or "quality of wellbeing" or "quality of well being" or "quality of well-being" or qwb* or 15d or "15-dimensional" or "15 dimensional" or "fifteen-dimensional" or "fifteen dimensional" or ("quality of life*" or "life quality" or hrqol or "eq 5d*" or "eq-5d*" or eq5d* or eqol* or euroqol* or euroquol* or aqol or "quality of wellbeing" or "quality of well being" or "quality of well-being" or qwb* or 15d or "15-dimensional" or "15 dimensional" or "fifteen-dimensional" or "fifteen dimensional")).ab,ti.	378,857
4	((ferrans adj2 powers) or "ferrans-powers" or "international classification of functioning disability and health" or (icf adj1 (classification* or code* or core)) or qli).ab,ti. or "short from 36".mp. or "short form 36".ab,ti. or sf36.ab,ti. or "sf 36".ab,ti. or "sf-36".ab,ti. or "36 item short form health survey".ab,ti. or "short form 12".ab,ti. or sf12.ab,ti. or "sf 12".ab,ti. or "sf-12".ab,ti. or "12 item short form health survey".ab,ti. or "short form 8".ab,ti. or sf8.ab,ti. or "sf 8".ab,ti. or "sf-8".ab,ti. or "8 item short form health survey".ab,ti. or "sf-6*".ab,ti. or sf6*.ab,ti. or "sf 6*".ab,ti. or "short form 6*".ab,ti. or "shortform 6*".ab,ti. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	0
5	("adjusted life year*" or "adjusted life-year*" or "quality-adjusted life-year*" or qaly* or qualy* or "healthy years equivalent*" or "disability adjusted life	3,2165

	year*" or "disability adjusted life-year*" or "disability-adjusted life-year*" or daly* or "years lived with disabilit*" or "willingness to pay" or (utilit* adj1 score*) or (utilit* adj1 weight*) or "whoqol-100" or "who-qol 100" or "world health organi?ation qol" or "who qol").ab,ti.	
6	"health utility index".mp. or exp utility value/ or utility value.mp. or exp Standard Gamble/ or standard gamble.mp. or exp time trade-off method/ or time trade-off method.mp. or exp "quality of life"/ or exp "European Quality of Life 5 Dimensions questionnaire"/ or european quality of life 5 dimensions questionnaire.mp. or exp "European Quality of Life 5 Dimensions 3 Level questionnaire"/ or european quality of life 5 dimensions 3 level questionnaire.mp. or exp "European Quality of Life 5 Dimensions 5 Level questionnaire"/ or european quality of life 5 dimensions 5 level questionnaire.mp. or exp "European Quality of Life 5 Dimensions Visual Analogue Scale"/ or european quality of life 5 dimensions visual analogue scale.mp. or assessment of quality of life.mp. or quality of well being scale.mp. or (ferrans and powers quality of life index).mp. or (international classification of functioning, disability and health).mp. or exp WHOQOL-100/ or whoqol-100.mp. or exp "Quality of Life Index"/ or quality of life index.mp. or exp Short Form 12/ or short form 12.mp. or short form 8.mp. or short form 6.mp. or short form 6d.mp. or exp quality adjusted life year/ or exp Quality-Adjusted Life Years/ or exp disability-adjusted life year/ or exp Disability-Adjusted Life Years/ or exp Willingness To Pay/ or willingness to pay.mp.	292,043
7	2 or 3 or 4 or 5 or 6	465,895
8	1 and 7	29
9	limit 8 to human	24
10	(comment or letter or case report or editorial or case study or case report or case series or note or short survey or in vitro).pt.	2,163,541
11	9 not 10	24

Table 106. Search strategy Embase using Elsevier

S. No.	Search Term	Hits
1	exp hemoglobin S/ or exp Sickle Cell Disease/ or anemia, sickle cell/ or hemoglobin, sickle/ or Sickle cell disease.mp. or (sickle cell* adj3 (disease* or anemia* or anaemia*)):ti,ab or (hemoglobinopath* or haemoglobinopath*):ti,ab or ((hemoglobin* or haemoglobin*) adj1 SC*): ti,ab or (sickle cell or sickle hemoglobin or drepanocyt* or drepanotic or drepanocytemia or hemoglobin-s or Hb-S or sickle anemia or meniscocytosis).mp.	65,936
2	'health utility index'/exp OR ((health NEAR/1 utilit*):ab,ti) OR 'utility value'/exp OR ((economic NEAR/1 utilit*):ab,ti) OR ((utilit* NEAR/1 (value* OR function*)):ab,ti) OR 'standard gamble'/exp OR 'standard gamble':ab,ti OR 'time trade-off method'/exp OR 'time trade-off':ab,ti OR 'time trade off':ab,ti OR 'tto':ab,ti OR 'quality of life'/exp OR 'quality of life*':ab,ti OR 'life quality':ab,ti OR hrqol:ab,ti OR 'european quality of life 5 dimensions questionnaire'/exp OR 'eq 5d*':ab,ti OR 'eq-5d*':ab,ti OR eq5d*:ab,ti OR eqol*:ab,ti OR euroqol*:ab,ti OR euroquol*:ab,ti OR 'european quality of life 5 dimensions 3 level questionnaire'/exp OR 'european quality of life 5 dimensions 5 level questionnaire'/exp OR 'european quality of life 5 dimensions visual analogue scale'/exp OR 'assessment of quality of life'/exp OR aqol:ab,ti OR 'quality of well being scale'/exp OR 'quality of wellbeing':ab,ti OR 'quality of well being':ab,ti OR 'quality of well-being':ab,ti OR qwb*:ab,ti OR 15d:ab,ti OR '15-dimensional':ab,ti OR '15 dimensional':ab,ti OR 'fifteen-dimensional':ab,ti OR 'fifteen dimensional':ab,ti OR 'ferrans and powers quality of life index'/exp OR ((ferrans NEAR/2 powers):ab,ti) OR 'ferrans-powers':ab,ti OR 'international classification of functioning, disability and health'/exp OR 'international classification of functioning disability and health':ab,ti OR ((icf NEAR/1 (classification* OR code* OR core)):ab,ti) OR 'quality of life index'/exp OR qli:ab,ti OR 'short from 36' OR 'short form 36':ab,ti OR sf36:ab,ti OR 'sf 36':ab,ti OR	825,099

	'sf-36':ab,ti OR '36 item short form health survey':ab,ti OR 'short form 12'/exp OR 'short form 12':ab,ti OR sf12:ab,ti OR 'sf 12':ab,ti OR 'sf-12':ab,ti OR '12 item short form health survey':ab,ti OR 'short form 8'/exp OR 'short form 8':ab,ti OR sf8:ab,ti OR 'sf 8':ab,ti OR 'sf-8':ab,ti OR '8 item short form health survey':ab,ti OR 'short form 6'/exp OR 'short form 6d'/exp OR 'sf-6*':ab,ti OR sf6*:ab,ti OR 'sf 6*':ab,ti OR 'short form 6*':ab,ti OR 'shortform 6*':ab,ti OR 'quality adjusted life year'/exp OR 'adjusted life year*':ab,ti OR 'adjusted life-year*':ab,ti OR 'quality-adjusted life-year*':ab,ti OR qaly*:ab,ti OR qualy*:ab,ti OR 'healthy years equivalent*':ab,ti OR 'disability-adjusted life year'/exp OR 'disability adjusted life year*':ab,ti OR 'disability adjusted life-year*':ab,ti OR 'disability-adjusted life-year*':ab,ti OR daly*:ab,ti OR 'years lived with disabilit*':ab,ti OR 'willingness to pay'/exp OR 'willingness to pay':ab,ti OR ((utilit* NEAR/1 score*):ab,ti) OR ((utilit* NEAR/1 weight*):ab,ti) OR 'whoqol-100'/exp OR 'whoqol-100':ab,ti OR 'who-qol 100':ab,ti OR 'world health organisation qol':ab,ti OR 'who qol':ab,ti	
3	#1 AND #2	2,354
4	'animal'/exp NOT 'human'/exp	596,6062
5	comment*:ti OR 'letter':it OR 'editorial':it OR 'case report'/exp OR 'case stud*':ti OR 'case report*':ti OR 'case series':ti OR 'note':it OR 'short survey':it OR 'in vitro':ti	6,512,968
6	#3 NOT (#4 OR #5)	2,024

Table 107. Search strategies for hand-searching of relevant congresses

Conference database	Search	Hits
ASH	'Sickle cell'	922
	'Exa-cel'	2
	'Beti-cel'	5
	'Gene therapy'	61
	'CTX001'	2

	'CLIMB SCD-121'	2
	'NCT03745287'	2
EBMT	'Sickle cell'	65
	'Exa-cel'	0
	'Beti-cel'	20
	'Gene therapy'	79
	'CTX001'	0
	'CLIMB SCD-121'	0
	'NCT03745287'	0
EHA	'Sickle cell'	635
	'Exa-cel'	0
	'Beti-cel'	31
	'Gene therapy'	245
	'CTX001'	49
	'CLIMB SCD-121'	2
	'NCT03745287'	2

Abbreviations: ASH = American Society of Hematology; EBMT: European Society for Blood and Marrow Transplantation; EHA: European Haematology Association.

I.1.1.1 Study selection

I.1.1.2 Data collection

The data collection was performed using inclusion/exclusion criteria guided by the PICOS approach and relevant studies were selected using a two-step process: (a) title/abstract screening and (b) full-text screening.

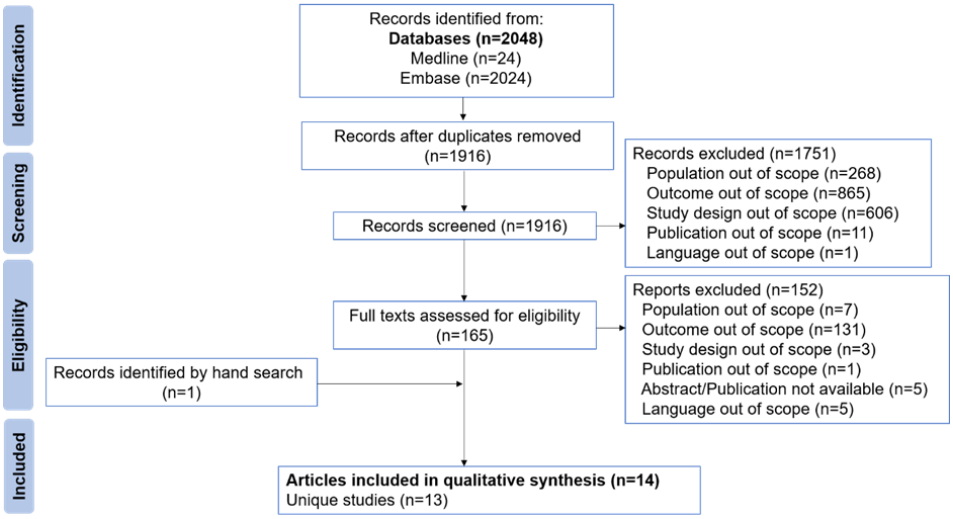
Two investigators working independently screened all citations identified in the literature search. The same two investigators independently reviewed the full texts. If any discrepancies occurred between the studies selected by the two investigators, a third investigator provided the arbitration.

I.1.1.3 Data extraction

Two investigators working independently extracted data on study characteristics, interventions, patient characteristics, and outcomes for the study population of interest for the final list of selected eligible studies. Any discrepancies observed between the data extracted by the two data extractors were resolved by discussion and coming to a consensus.

Checking for duplicates resulted in the exclusion of 108 potential articles and the remaining 1,916 articles were screened. After preliminary screening of titles/abstracts, 1,751 records were excluded, and 165 were included for full-text screening. After a secondary screening of full-text articles, 152 studies were excluded. Additionally, one studies were included from bibliography searching. Ultimately, this resulted in the inclusion of 14 publications in the SLR. Figure 36 presents the PRISMA flow diagram of studies identified in this SLR.

Figure 36. PRISMA flow diagram for HRQoL SLR



Details of the included studies are provided in and Table 108.

Table 108. Overview of HRQoL and utility studies

Author, year	Population (characteristics), sample size	Intervention/ Comparator	Response rates	Description of health states	Adverse reactions
Lubeck 2019 (180)	Adults and adolescents with sickle cell disease Overall sample size: 1950	NR	NR	HSUVs were derived from the mEQ-5D and EQ-5D VAS for adults (pain by diary days) and adolescent (pain in past month) SCD patients based on pain severity and age	NR
Ojelabi 2019 (110)Ojelabi 2019 (110)	Adults with sickle cell disease Overall sample size: 200	NR	All 200 SCD patients responded	HSUVs were estimated using SF-6D (Derived from SF-36) provided across domains of health that ranged from "0: dead to 1: perfect health" for SCD patients with age 18 years or older at baseline	NR
Spackman 2014 (181)	Patients aged >12 years with sickle cell disease Overall sample size: 67	Intervention: Pre-operative transfusion; Comparator: No-operative transfusion	NR	HSUVs were estimated using EQ-5D at baseline and 30 days post-surgery follow-up for patients aged more than 12 years	NR
Tsironi 2014 (182)	Adults with sickle cell disease Overall sample size: 102	NR	NR	HSUVs were derived using EQ VAS scale for SCD patients from urban, semi-urban and rural regions	NR
Lanzkron 2021 (183)	Adults with sickle cell disease Overall sample size: 32	NR	NR	HSUVs were derived using EQ-5D-3L and EQ-5D VAS scale for SCD patients aged > 18 years at baseline	NR
Arnold 2014 (184)	Children with sickle cell disease: Surviving allogenic stem cell transplantation recipients (Group A): 16 Patients with SCD referred for alloSCT and/or	Intervention: Allogenic stem-cell transplantation, hydroxyurea and chronic transfusions	NR	HSUVs were determined using EQ-5D VAS and mean utility scores based on responses in children with SCD	NR

	HLA typed, SCD controls (Group B): 19				
Anie 2012 (146)	Adults with sickle cell disease Overall sample size: 510	NR	All 510 SCD patients responded	HSUVs were estimated using EQ-5D for SCD patients undergoing hospital admissions at three time-points: T1-on admission to hospital, T2-before discharge from hospital, and T3-7 days post discharge from hospital (telephone)	NR
Nietert 2000 (185)	Adults with sickle cell disease Overall sample size: 117	Intervention: Bone marrow transplantation (BMT) Comparator: Periodic blood transfusion (PBT)	NR	HSUVs were estimated using a series of 1-way sensitivity analysis with quality-of-life values ranging from 0 (death) to 1 (perfect health) at baseline; Scale unclear	NR
Drahos 2022 (186)	Adults with sickle cell disease Overall sample size: 142	NR	137 out of 142 patients responded	HSUVs were estimated with EQ-5D-5L VAS score in adult patients with SCD (aged ≥18 years) at baseline	NR
Bailey 2020 (187)	Adults with sickle cell disease Overall sample size: 181	NR	181 out of 498 SCD patients responded	HSUVs were estimated using EQ-5D (mapped from SF-36 scores) for adult SCD patients (>18 years) with <1VOC/year and >3 VOCs/year	NR
Thom 2019 (35)	Adults with sickle cell disease Overall sample size: 299	NR	299 out of 326 individuals screened were included in the final analytic sample	HSUVS were estimated using EQ-5D for adult SCD patients during a VOC and not during a VOC	NR
Shafrin 2021 (188)	Adults with sickle cell disease	NR	All 301 SCD patients responded	HSUVs were estimated using EQ-5D scale for patients aged > 18 years when not	NR

	Overall sample size: 301			experiencing a VOC to that of experiencing a VOC	
O'Brien 2009 (118)	Children with severe sickle cell disease	Intervention: Hydroxyurea, chronic transfusion, stem cell transplant	NR	HSUVs were estimated using utility values, utilities range from 0 (death) to 1 (perfect health) over a five-year period	NR
Jiao 2022 (189)	Children and adolescents with sickle cell disease Overall sample size: 533	NR	533 out of 859 patients is the final sample for analysis, both patient and proxy responded	HSUVs were estimated with mapped PedsQL GCS scores at baseline	NR

Abbreviations: 3L, 3 level; 5L, 5 level; BMT, Bone marrow transplantation; EQ-5D, Euro qol-5 dimension; HSUV, Health state utility value; mEQ-5D, Mapped Euro qol-5 dimension; NR, Not reported; PBT, Periodic blood transfusion; SF-6D, Short form-6 dimension; SCD, Sickle cell disease; SF-36, Short Form Health Survey (36); VAS, Visual analogue scale; VOC, Vaso occlusive crises.

Table 109. Outcomes of studies reporting HRQoL and utilities

Author, year	Method of elicitation	Method of valuation	Mapping	Summary of HRQoL/utilities outcomes	Uncertainty around values	Consistency with reference case
Lubeck 2019 (180)	NR	HSUVs derived from the mEQ-5D from 3 SCD studies that reported on pain using VAS, Valuation unclear	Mapping of VAS to EQ-5D was based on Anie KA et al (2012)	Summary utility data VAS for adult SCD patients, severe pain: 5.9; SD: 0.1 VAS for adult SCD patients, moderate pain: 5; SD: 0.1 VAS for adult SCD patients, mild pain: 3.9; SD: 0.1 VAS for children/adolescent SCD patients, severe pain: 8.1; SD: 0.6 VAS for children/adolescent SCD patients, moderate pain: 5.3; SD: 1 VAS for children/adolescent SCD patients, mild pain: 1.8; SD: 1.1 mEQ-5D for adult SCD patients, severe pain: 0.437 mEQ-5D for adult SCD patients, moderate pain: 0.492 mEQ-5D for adult SCD patients, mild pain: 0.557 mEQ-5D for adult SCD patients, no pain: 0.887 mEQ-5D for adult SCD patients, overall: 0.695 mEQ-5D for children/adolescent SCD patients, severe pain: 0.27	Data expressed as utility (mEQ-5D and EQ-5D VAS) for adults (pain by diary days) and adolescent (pain in past month) SCD patients based on pain severity and age	HSUVs estimated through EQ-5D, UK general population not included, not consistent with NICE reference case

				mEQ-5D for children/adolescent SCD patients, moderate pain: 0.474 mEQ-5D for children/adolescent SCD patients, mild pain: 0.703 mEQ-5D for children/adolescent SCD patients, no pain: 0.887 mEQ-5D for children/adolescent SCD patients, overall: 0.692		
Ojelabi 2019 (110) Ojelabi 2019 (110)	SF-6D was derived from SF-36 scores using standard gamble	HSUVs estimated using SF-6D (derived from SF-36) for SCD adult patients, valued using UK weights	NR	Summary utility data SF-6D (Derived from SF-36) utility score, Overall: 0.65; SD: 0.12; 95% CI (Lower limit; Upper limit): 0.63-0.67 SF-6D (Derived from SF-36) score, Gender, Male (n=83): 0.66; SD: 0.11; 95% CI (Lower limit; Upper limit): 0.64-0.69 SF-6D (Derived from SF-36) score, Gender, Female (n=117): 0.64; SD: 0.12; 95% CI (Lower limit; Upper limit): 0.62-0.66 SF-6D (Derived from SF-36) score, Living situation, Alone (n=18): 0.62; SD: 0.08; 95% CI (Lower limit; Upper limit): 0.58-0.65 SF-6D (Derived from SF-36) score, Living situation, With others (n=182): 0.65; SD: 0.12;	Data expressed as utility, SF-6D (Derived from SF-36) provided across domains of health that ranged from "0: dead to 1: perfect health" for SCD patients with age 18 years or older at baseline	HSUVs estimated through SF-6D (Derived from SF-36), standard gamble utilised for elicitation, UK general population included, not consistent with NICE reference case

95% CI (Lower limit; Upper limit): 0.64–0.67

SF-6D (Derived from SF-36) score, Confidants, Yes (n=171): 0.651; SD: 0.11; 95% CI (Lower limit; Upper limit): 0.60–0.70

SF-6D (Derived from SF-36) score, Confidants, No (n=29): 0.647; SD: 0.13; 95% CI (Lower limit; Upper limit): 0.63–0.67

SF-6D (Derived from SF-36) score, Genotype, HbSS (n=170): 0.651; SD: 0.12; 95% CI (Lower limit; Upper limit): 0.63–0.67

SF-6D (Derived from SF-36) score, Genotype, HbSC (n=30): 0.648; SD: 0.12; 95% CI (Lower limit; Upper limit): 0.61–0.69

SF-6D (Derived from SF-36) score, Co-morbidity, No (n=135): 0.67; SD: 0.12; 95% CI (Lower limit; Upper limit): 0.65–0.69

SF-6D (Derived from SF-36) score, Co-morbidity, Yes (n=65): 0.6; SD: 0.1; 95% CI (Lower limit; Upper limit): 0.58–0.63

SF-6D (Derived from SF-36) score, Marital status, Never

married (n=151): 0.66; SD: 0.12; 95% CI (Lower limit; Upper limit): 0.64–0.68

SF-6D (Derived from SF-36) score, Marital status, Married (n=41): 0.63; SD: 0.09; 95% CI (Lower limit; Upper limit): 0.61–0.66

SF-6D (Derived from SF-36) score, Marital status, Others (divorced, separated, widowed) (n=8): 0.61; SD: 0.12; 95% CI (Lower limit; Upper limit): 0.53–0.69

SF-6D (Derived from SF-36) score, Education, < Primary (n=19): 0.6; SD: 0.12; 95% CI (Lower limit; Upper limit): 0.55–0.65

SF-6D (Derived from SF-36) score, Education, Secondary (n=97): 0.65; SD: 0.11; 95% CI (Lower limit; Upper limit): 0.63–0.67

SF-6D (Derived from SF-36) score, Education, Post secondary (n=84): 0.66; SD: 0.12; 95% CI (Lower limit; Upper limit): 0.64–0.67

SF-6D (Derived from SF-36) score, Employment, Full-time (n=43): 0.66; SD: 0.11; 95% CI (Lower

				limit; Upper limit): 0.63–0.67 SF-6D (Derived from SF-36) score, Employment, Part-time (n=30): 0.64; SD: 0.1; 95% CI (Lower limit; Upper limit): 0.60–0.68 SF-6D (Derived from SF-36) score, Employment, Not-employed (n=127): 0.65; SD: 0.12; 95% CI (Lower limit; Upper limit): 0.63–0.70		
Spackman 2014 (181)	NR	HSUVs estimated using EQ-5D for patients aged > 12 years, valuation unclear	NR	Summary utility data Mean baseline EQ-5D, no preoperative transfusion (n=17): 0.793; SD: 0.298; Min: 0.055; Max: 1 Mean baseline EQ-5D, pre-operative transfusion (n=18): 0.76; SD: 0.236; Min: -0.016; Max: 1 Mean follow-up EQ-5D, no pre-operative transfusion (n=15): 0.864; SD: 0.19; Min: 0.516; Max: 1 Mean follow-up EQ-5D, pre-operative transfusion (n=14): 0.854; SD: 0.166; Min: 0.516; Max: 1	Data expressed as utility (EQ-5D) at baseline and 30 days post-surgery follow-up for patients aged more than 12 years	HSUVs estimated through EQ-5D, UK general population utility values reported, consistent with NICE reference case
Tsironi 2014 (182)	NR	HSUVs estimated using EQ VAS for SCD patients,	NR	Summary utility data Mean EQ VAS score: 64.33	Data expressed as utility (EQ VAS scale) for SCD	HSUVs estimated through EQ-VAS, UK general

		valuation unclear			patients from urban, semi-urban and rural regions	population not included, not consistent with NICE reference case
Lanzkron 2021 (183)	NR	HSUVs estimated using EQ-5D-3L and EQ-5D VAS for SCD patients, valuation unclear	NR	Summary utility data Mean EQ-5D VAS score, Overall: 63.4 Mean EQ-5D VAS score, US (35-44 age group population norm): 81.8 Mean EQ-5D-3L score: 0.79 Mean EQ-5D-3L score, US (35-44 age group population norm): 0.85	Data expressed as utility (EQ-5D-3L and EQ-5D VAS scale) for SCD patients aged > 18 years at baseline	HSUVs estimated through EQ-5D-3L and EQ-5D VAS, UK general population not included, not consistent with NICE reference case
Arnold 2014 (184)	NR	HSUVs estimated using EQ-5D VAS and mean utility scores for children with SCD, Valuation unclear	NR	Summary utility data EQ-5D VAS score for Group A: 92 EQ-5D VAS score for Group B: 87 EQ-5D utility score for Group A: 0.87 EQ-5D utility score for Group B: 0.91	Data expressed as utility (EQ-5D VAS and mean utility scores based on responses) in children with SCD	HSUVs estimated through EQ-5D and EQ-5D VAS, UK general population not included, not consistent with NICE reference case
Anie 2012 (146)	NR	HSUVs estimated based on EQ-5D utility and VAS scores at three time-points, UK weights (Kind et al. 1999)	NR	HRQoL domains measured Domain score Mean (SD) VAS score for pain from admission T1: 5.1 (2.5) VAS score for pain to discharge T2: 3 (2.4) VAS score for pain from discharge T2 to 1-week follow-up T3: 2 (2.2)	Data expressed as utility (EQ-5D) for SCD patients undergoing hospital admissions at three time-points	HSUVs estimated through EQ-5D and VAS scores, valued using UK weights, UK general population included, consistent with NICE

				VAS score for mood from admission T1: 5 (2.2) VAS score for mood to discharge T2: 5.7 (2.3) VAS score for mood from discharge T2 to 1-week follow-up T3: 6.8 (2.2) VAS score for general health status from admission T1: 47.7 (22.3) VAS score for general health status to discharge T2: 59.4 (21.7) VAS score for general health status from discharge T2 to 1-week follow-up T3: 71 (20) Summary utility data EQ-5D utility score for patients from admission T1: 0.39; SD: 0.40 EQ-5D utility score for patients to discharge T2: 0.65; SD: 0.29 EQ-5D utility score for patients from discharge T2 to 1-week follow-up T3: 0.75; SD: 0.26		reference case
Nietert 2000 (185)	NR	HSUV scale and valuation unclear	NR	Summary utility data Utility for BMT success: 0.95; Range: 0.0 to 1.0 Utility for BMT chronic GVHD: 0.85; Range: 0.0 to 1.0	Data expressed as utility using a series of 1-way sensitivity analysis with quality-of-	HSUVs utilised to determine QALYs using sensitivity analysis, utility scale unclear,

				Utility for BMT rejection: 0.7; Range: 0.0 to 1.0 Utility for PBT success: 0.85; Range: 0.0 to 1.0 Utility for PBT alloimmunized: 0.8; Range: 0.0 to 1.0 Utility for PBT noncompliant with transfusion regimen: 0.85; Range: 0.0 to 1.0 Utility for PBT noncompliant with iron chelation: 0.75; Range: 0.0 to 1.0 Utility for Refusal of BMT and PBT: 0.8; Range: 0.0 to 1.0 Utility for Hemorrhagic stroke: 0.45; Range: 0.0 to 1.0 Utility for Ischaemic stroke: 0.45; Range: 0.0 to 1.0 Utility for major stroke (Age range: 18-57 years): 0.45	life values ranging from 0 (death) to 1 (perfect health) at baseline; Scale unclear	UK general population not included, not consistent with NICE reference case
Drahos 2022 (186)	NR	HSUVs estimated with EQ-5D-5L VAS score in adult patients with SCD (aged ≥18 years), Valuation unclear	NR	Summary utility data EQ-5D-5L VAS score: 58.7; SD: 19.4	Data expressed as utility (EQ-5D-5L VAS score) in adult patients with SCD (aged ≥18 years) at baseline	HSUVs estimated through EQ-5D VAS scale, UK general population not included, not consistent with NICE reference
Bailey 2020 (187)	NR	HSUVs estimated using mapped EQ-5D for adult SCD patients	NR	HRQoL (Overall) Scale: SF-36 HRQoL Domains measured Domain score Mean	Data expressed as utility, EQ-5D (mapped from SF-36 scores) for	HSUVs estimated through mapped EQ-5D, UK general populatio

		(>18 years), Valuation unclear		SF-36 Physical Component Score for patients with <1 VOCs/year: 51.164 SF-36 Physical Component Score for patients with >3 VOCs/year: 48.684 (2.480 lower; p:0.025) Summary utility data mEQ-5D score for patients with <1 VOCs/year: 0.691 mEQ-5D score for patients with >3 VOCs/year: 0.6213	adult SCD patients (>18 years) with <1VOC/year and >3 VOCs/year	n not included, not consistent with NICE reference case
Thom 2019 (35)	NR	HSUVs estimated using EQ-5D during a VOC and not during a VOC, United States EuroQoL value set	NR	Summary utility data EQ-5D utility value during a VOC: 0.311 EQ-5D utility value not during a VOC for Severity Class III: 0.733 EQ-5D utility value not during a VOC for Severity Class II: 0.775	Data expressed as utility (EQ-5D) for adult SCD patients during a VOC and not during a VOC	HSUVs estimated through EQ-5D, UK general population not included, not consistent with NICE reference case
Shafrin 2021 (188)	NR	HSUVs estimated using EQ-5D score when not experiencing a VOC to that of experiencing a VOC, valuation unclear	NR	Summary utility data SCD-related health states, All, All SCD respondents, not during VOC, n=299: 0.738; 95% CI (Lower limit; Upper limit): 0.72-0.756 SCD-related health states, Asymptomatic, No symptoms, not during VOC, n=3: 0.835; 95% CI (Lower limit;	Data expressed as utility (EQ-5D) for patients aged > 18 years when not experiencing a VOC to that of experiencing a VOC	HSUVs estimated through EQ-5D, UK general population not included, not consistent with NICE reference case

	Upper limit): 0.781-0.889
	SCD-related health states, Class I, Symptomatic, but without a SCD-related emergency department visit or hospital admission in prior year, not during VOC, n=22: 0.721; 95% CI (Lower limit; Upper limit): 0.635-0.808
	SCD-related health states, Class II, > 1 emergency department visit or hospital admission for a VOC or an SCD-related acute complication in the past year, without any organ damage, not during VOC, n=36: 0.775; 95% CI (Lower limit; Upper limit): 0.725-0.826
	SCD-related health states, Class III, Long-term organ damage, not during VOC, n=238: 0.733; 95% CI (Lower limit; Upper limit): 0.713-0.753
	SCD-related health states, All, All SCD respondents, during VOC, n=292: 0.311; 95% CI (Lower limit; Upper limit): 0.286-0.337

SCD-related health states, Asymptomatic, No symptoms, during VOC, n=3: 0.511; 95% CI (Lower limit; Upper limit): 0.355-0.667

SCD-related health states, Class I, Symptomatic, but without a SCD-related emergency department visit or hospital admission in prior year, during VOC, n=22: 0.394; 95% CI (Lower limit; Upper limit): 0.27-0.517

SCD-related health states, Class II, > 1 emergency department visit or hospital admission for a VOC or an SCD-related acute complication in the past year, without any organ damage, during VOC, n=30: 0.436; 95% CI (Lower limit; Upper limit): 0.36-0.513

SCD-related health states, Class III, Long-term organ damage, during VOC, n=237: 0.286; 95% CI (Lower limit; Upper limit): 0.259-0.313

Utility during VOC, n=292: 0.311; 95% CI (Lower limit; Upper limit): -0.864

				Utility not during VOC, n=299: 0.738; 95% CI (Lower limit; Upper limit): 0.339-1		
O'Brien 2009 (118)	NR	HSUVs estimated using mean utility values for SCD children over a five-year period, Valuation unclear	NR	Summary utility data Utility value of child with severe SCD, no treatment: 0.68 Utility value of child with severe SCD, no treatment, live with severe SCD: 0.7 Utility value of child with severe SCD, hydroxyurea: 0.79 Utility value of child with severe SCD, hydroxyurea, live: 0.79 Utility value of child with severe SCD, hydroxyurea, live with severe SCD: 0.65 Utility value of child with severe SCD, hydroxyurea, live with non-severe SCD: 0.85 Utility value of child with severe SCD, stem cell transplant: 0.85 Utility value of child with severe SCD, chronic transfusion: 0.72 Utility value of child with severe SCD, chronic transfusion, live: 0.73 Utility value of child with severe SCD, chronic	Data expressed utility; utilities range from 0 (death) to 1 (perfect health) over a five-year period	HSUVs were estimated for treatment strategies utilised to estimate QALYs for decision analysis, utility scale unclear, UK general population not included, not consistent with NICE reference case

transfusion, iron overload: 0.72

Utility value of child with severe SCD, chronic transfusion, no iron overload: 0.77

Utility value of child with severe SCD, chronic transfusion, iron overload, severe SCD: 0.55

Utility value of child with severe SCD, chronic transfusion, iron overload, non-severe SCD: 0.75

Utility value of child with severe SCD, chronic transfusion, no iron overload, severe SCD: 0.6

Utility value of child with severe SCD, chronic transfusion, non-severe SCD: 0.8

Utility value of child with severe SCD, stem cell transplant, live: 0.9

Utility value of child with severe SCD, stem cell transplant, live, no graft failure: 0.94

Utility value of child with severe SCD, stem cell transplant, live, graft failure: 0.55

Utility value of child with severe SCD, stem cell transplant, live, no graft failure, extensive chronic GVHD: 0.65

Utility value of child with severe SCD, stem cell

				transplant, no graft failure, no extensive chronic GVHD: 0.95 Average utility for no treatment: 0.68 Average utility for hydroxyurea: 0.8 Average utility for chronic transfusion: 0.71 Average utility for stem cell transplant: 0.85		
Jiao 2022 (189)	EQ-5D-Y-3L and CHU-9D which was used for mapping studies (Khan et al. 2014, Lambe et al. 2018, Mpundu-Kaambwa et al. 2017, Sweeney et al. 2017) in general population of children, was used for elicitation in this study for SCD children	HSUVs were estimated with mPedsQL GCS at baseline, Valuation unclear	PedsQL GCS was mapped with EQ-5D-3L-Y, CHU-9D to obtain HSUVs (Khan et al. 2014, Lambe et al. 2018, Mpundu-Kaambwa et al. 2017, Sweeney et al. 2017)	Summary utility data Mapped utility for overall population: 0.792; 95% CI (Lower limit; Upper limit): 0.782-0.801 Mapped utility for age group 13-17 years: 0.734; 95% CI (Lower limit; Upper limit): 0.710–0.757 Mapped utility for female: 0.781; 95% CI (Lower limit; Upper limit): 0.768–0.794 Mapped utility for male: 0.802; 95% CI (Lower limit; Upper limit): 0.791–0.814 Mapped utility for black race: 0.791; 95% CI (Lower limit; Upper limit): 0.782–0.801 Mapped utility for SCD genotype, Sickle Cell Anemia (HbSS or HbSβ0-thalassemia): 0.788; 95% CI (Lower limit;	Data expressed as utility (mapped PedsQL GCS scores) at baseline	HSUVs estimated by mPedsQL GCS score, EQ-5D-3L-Y and CHU-9D used for elicitation, UK general population not included, not consistent with NICE reference case

	Upper limit): 0.776–0.799 Mapped utility for SCD genotype, Sickle Hemoglobin-C Disease (HbSC): 0.797; 95% CI (Lower limit; Upper limit): 0.780–0.815 Mapped utility for SCD genotype, Sickle Beta-Plus Thalassemia (HbSβ+-thalassemia): 0.799; 95% CI (Lower limit; Upper limit): 0.774–0.824 Mapped utility for SCD genotype, Sickle Hemoglobin-O Disease (HbSO): 0.796; 95% CI (Lower limit; Upper limit): 0.749–0.842

Abbreviations: 3L, 3 level; 5L, 5 level; BMT, Bone marrow transplantation; CHU-9D, Child health utility 9 dimension; CI, Confidence interval; EQ-5D, Euro qol-5 dimension; EQ-5D-Y, Euro qol-5 dimension youth; GVHD, Graft-versus-host disease; HRQoL, Health related quality of life; HSUV, Health state utility value; Max, Maximum; mEQ-5D, Mapped Euro qol-5 dimension; Min, Minimum; NR, Not reported; PBT, Periodic blood transfusion; QALY, Quality adjusted life years; SF-6D, Short form-6 dimension; SCD, Sickle cell disease; SD, Standard deviation; SF-36, Short Form Health Survey (36); UK, United Kingdom; US, United States; VAS, Visual analogue scale; VOC, Vaso occlusive crises.

I.1.2 Quality assessment and generalizability of estimates

There are no agreed reporting standards for HSUV studies. Therefore, the quality of included studies was evaluated through a set of generic criteria as described by Papaioannou et al., (2013) (190).

I.1.3 Unpublished data

Not applicable.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

A single SLR was conducted to identify published cost-effectiveness studies as well as cost and HCRU studies (Appendix I).

A systematic search of MEDLINE and the Cochrane library were searched using the Ovid platform, while searches in Embase were conducted using the Elsevier platform. A combination of Emtree subject headings (Embase), MeSH (medical subject headings) and free text terms was used to retrieve all the relevant publications. The search period was from the inception of the databases to 10 July 2023, with the exception of conference proceedings, which were hand searched from January 2020 onwards.

J.1.1 Systematic search for economic evaluations and cost burden evidence related to the treatment of SCD

The purpose of the SLR was to identify and summarise the economic evaluations and cost burden evidence related to the treatment of 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 haematopoietic stem cell (HSC) donor is not available.

Searches were carried out in databases in Embase, MEDLINE, Cochrane, conferences proceedings, and previous HTA submissions.

Table 110. Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
EMBASE®	Elsevier	No limit	July 10, 2023
MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Medline® Daily, Medline and Versions®	OvidSP®	No limit	July 10, 2023
Cochrane Central Register of Controlled Trials	OvidSP®	No limit	July 10, 2023

The purpose of the targeted literature search was to identify and summarise the economic evaluations and cost burden evidence related to the treatment of 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 haematopoietic stem cell (HSC) donor is not available.

Table 111. Sources included in the targeted literature search

Search engine	Platform/source	Relevant period for the search	Date of search completion
International Network Association of Health Technology Assessment (INAHTA) Cost-Effectiveness Analysis (CEA) Registry Institute for Clinical and Economic Review (ICER) Canadian Agency for Drugs and Technologies in Health (191) National Institute of Health and Care Excellence (192) Scottish Medicines Consortium (193)	HTA databases	Jan 2020 onwards	July 10, 2023

Table 112. Conference material included in the literature search

Search engine	Platform/source	Relevant period for the search	Date of search completion
Conference proceedings	American Society of Haematology (ASH) European Society for Blood and Marrow Transplantation (EBMT) European Haematology Association (EHA)	Jan 2020 onwards	July 10, 2023

The inclusion/exclusion criteria for studies in the economic SLR are reported in Table 113 below.

Table 113. Inclusion and exclusion criteria for the cost-effectiveness studies

	Inclusion criteria	Exclusion criteria
Population	Patients with SCD	Patients without SCD
Interventions	exa-cel or LentiGlobin	Other interventions not mentioned in inclusion criteria
Outcomes	Cost outcomes related to SCD; Health outcomes, e.g., utilities, life expectancy, LYs, QALYs, incremental QALYs; ICER	Outcomes of interest not reported
Study Type	Economic modelling studies: Cost-effectiveness analysis (CEA); Cost-utility analysis (CUA); Cost-benefit analysis; Cost-minimization analysis; Cost-of-illness (COI) analysis; Cost-consequence analysis	Trials; Real-world studies; Case reports; Editorials, letters, comments, case reports of individual patients, erratum, and notes; Systematic literature reviews, meta-analyses, or review articles
Other	English only	Non-English

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; SCD, sickle cell disease.

Table 114. Search strategy for MEDLINE® and Cochrane using Ovid

#	Query	Results
1	(exp hemoglobin S/ or exp Sickle Cell Disease/ or anemia, sickle cell/ or hemoglobin, sickle/ or Sickle cell disease.mp. or (sickle cell* adj3 (disease* or anemia* or anaemia*)):ab,ti or (hemoglobinopath* or haemoglobinopath*):ab,ti or ((hemoglobin* or haemoglobin*) adj1 SC*):ab,ti or (sickle cell or sickle hemoglobin or drepanocyt* or drepanotic or drepanocytemia or hemoglobin-s or Hb-S or sickle anemia or meniscocytosis).mp.)	2,746
2	exp "cost of illness"/ or "economic aspects of illness".tw. or exp "health care costs"/ or (health* and (economics or sector*)).tw. or exp "drug costs"/ or ((drug* or treatment* or therap* or medication* or medical or prescription* or hospital* or nursing or pharmac*) and (expense* or charg* or payment* or rate*)).tw. or "health care financing".mp. or ((health* or hospital*) and financ*).tw. or exp "hospital costs"/ or "hospital finance".mp. or exp "purchasing, hospital"/ or (hospital* and suppl*).tw. or (purchas* and (group* or hospital* or joint or shared)).tw. or "hospitalization cost".mp. or "nursing cost".mp. or fee.mp. or fee*.tw. or ("rate setting" and review).tw. or exp "capitation fee"/ or "dental fee".mp. or "dispensing fee".mp. or "hospital billing".mp. or (hospital and bill*).tw. or exp "hospital charges"/ or exp "fees, medical"/ or (physician and payment).tw. or "nursing fee".mp. or "pharmacy fee".mp. or exp pharmacoeconomics/ or pharmacoeconomic*.tw. or "pharmaco economic*".tw. or "pharmaceutical economics".tw. or pharmaco-economic*.tw. or exp "drug approval"/ or (drug* and approval).tw. or "resource utilization*".tw. or exp "resource allocation"/ or (resource* and allocation).tw. or "resource utilization".tw. or exp budget/ or budget*.tw. or "expenditure* health care utilization".mp. or (utilization and (health or healthcare)).tw. or (equipment and "supplies utilization").tw. or (facilities and "services utilization").tw. or (procedures and "techniques	5,352,650

	utilization").tw. or "productivity cost".mp. or "productivity loss".mp. or "societal cost".mp. or "opportunity cost".mp. or "prospective cost".mp. or "retrospective cost".mp. or "economic benefit".mp. or "economic burden".mp. or (economic and (burden or benefit*)).tw. or exp employment/ or "employment status".mp. or "neet status".mp. or neet*.tw. or "parental employment status".mp. or "maternal employment status".mp. or exp unemployment/ or unemploy*.tw. or un-employ*.tw. or non-employ*.tw. or exp work/ or work*.tw. or job*.tw. or exp absenteeism/ or absenteeism.tw. or (absence* and (disabilit* or sickness)).tw. or exp presenteeism/ or presenteeism.tw. or presenteism.tw. or (presence* and (disabilit* or sickness)).tw. or "job performance".mp. or exp "job satisfaction"/ or "job security".mp. or exp productivity/ or productivity.tw. or "quality of working life".mp. or exp "return to work"/ or "work capacity".mp. or "working time".mp. or exp cost/ or cost*.tw. or economic*.tw. or exp pricing/ or pricing.tw.	
3	((((((((((((((((((((((((((((((((exp cost/ or cost*.tw. or exp "cost benefit analysis"/ or "health economics".mp. or "economic* health*".tw. or clinical.tw. or dental.tw. or hospital*.tw. or medical.tw. or nursing.tw. or exp pharmacoeconomics/ or pharmac*.tw.) and economic*.tw.) or pharmacoeconomic*.tw. or exp "drug approval"/ or drug*.tw.) and approval*.tw.) or "biologic license application".mp. or "license application*".tw.) and biologic*.tw.) or "drug registration".mp. or drug*.tw.) and registration.tw.) or emergency.tw.) and authorization*.tw.) or "marketing authorization".mp. or market*.tw.) and authorization*.tw.) or "new drug application".mp. or "new drug application*".tw. or "drug cost".mp. or drug*.mp.) and expense*.tw.) or expenditure*.tw. or "drug formulary".mp. or drag.tw.) and formular*.tw.) or formal*.tw.) and drug*.tw.) or medication*.tw. or medicine*.tw. or prescription*.tw. or exp "drug utilization"/ or drug*.tw.) and utiliation.tw.) or exp "utilization review"/ or utiliation.tw.) and review*.tw.) or concurrent.tw.) and review*.tw.) or "device economics".mp. or device*.tw.) and economics.tw.) or "economic evaluation".mp. or economic.tw.) and evaluation*.tw.) or exp "cost control"/ or exp "cost effectiveness analysis"/ or "cost minimization".mp. or exp "cost of illness"/ or "cost utility analysis".mp. or exp "models, economic"/ or exp "models, econometric"/ or econom*.tw.) and model*.tw.) or econometric*.tw. or exp "models, statistical"/ or model*.tw.) and statistic*.tw.) or linear.tw. or logistic.tw. or "budget impact analysis".tw. or "budget impact model".tw. or "budget impact".tw. or "markov chain".mp. or markov.tw. or "continuous time markov chain".mp. or ctmc.tw. or "discrete time markov chain".mp. or dtmc.tw. or "hidden markov model".mp. or hmc.tw. or exp "markov decision process"/ or mdp.tw. or exp "markov random field"/ or mrf.tw. or "markov state model".mp. or "decision analysis".tw. or "discrete event simulation".mp. or discrete.tw.) and model*.tw.) or simulation*.tw.	1,061,729
4	2 or 3	6,126,904
5	4 and 1	371
6	(comment or letter or case report or editorial or case study or case report or case series or note or short survey or in vitro).pt.	2,171,541
7	5 NOT 6	371
8	limit 7 to human	328

Table 115. Search strategy Embase® using Elsevier

#	Query	Results
1	exp hemoglobin S/ or exp Sickle Cell Disease/ or anemia, sickle cell/ or hemoglobin, sickle/ or Sickle cell disease.mp. or (sickle cell* adj3 (disease* or anemia* or anaemia*)):ti,ab or (hemoglobinopath* or haemoglobinopath*):ti,ab or ((hemoglobin* or haemoglobin*) adj1 SC*): ti,ab or (sickle cell or sickle hemoglobin or drepanocyt* or drepanotic or drepanocytemia or hemoglobin-s or Hb-S or sickle anemia or meniscocytosis).mp.	60,344
2	'cost of illness'/exp OR 'economic aspects of illness':ti,ab OR 'health care costs'/exp OR (health*:ti,ab AND (economics:ti,ab OR sector*:ti,ab)) OR 'drug costs'/exp OR ((drug*:ti,ab OR treatment*:ti,ab OR therap*:ti,ab OR medication*:ti,ab OR medical:ti,ab OR prescription*:ti,ab OR hospital*:ti,ab OR nursing:ti,ab OR pharmac*:ti,ab) AND (expense*:ti,ab OR charg*:ti,ab OR payment*:ti,ab OR rate*:ti,ab)) OR 'health care financing' OR ((health*:ti,ab OR hospital*:ti,ab) AND financ*:ti,ab) OR 'hospital costs'/exp OR 'hospital finance' OR 'purchasing, hospital'/exp OR (hospital*:ti,ab AND suppl*:ti,ab) OR (purchas*:ti,ab AND (group*:ti,ab OR hospital*:ti,ab OR joint:ti,ab OR shared:ti,ab)) OR 'hospitalization cost' OR 'nursing cost' OR fee OR fee*:ti,ab OR ('rate setting':ti,ab AND review:ti,ab) OR 'capitation fee'/exp OR 'dental fee' OR 'dispensing fee' OR 'hospital billing' OR (hospital:ti,ab AND bill*:ti,ab) OR 'hospital charges'/exp OR 'fees, medical'/exp OR (physician:ti,ab AND payment:ti,ab) OR 'nursing fee' OR 'pharmacy fee' OR 'pharmacoeconomics'/exp OR pharmacoeconomic*:ti,ab OR 'pharmaceutical economics':ti,ab OR 'pharmaco economic*':ti,ab OR 'drug approval'/exp OR (drug*:ti,ab AND approval:ti,ab) OR 'resource utilization*':ti,ab OR 'resource allocation'/exp OR (resource*:ti,ab AND allocation:ti,ab) OR 'resource utilization':ti,ab OR 'budget'/exp OR budget*:ti,ab OR 'expenditure* health care utilization' OR (utilization:ti,ab AND (health:ti,ab OR healthcare:ti,ab)) OR (equipment:ti,ab AND 'supplies utilization':ti,ab) OR (facilities:ti,ab AND 'services utilization':ti,ab) OR (procedures:ti,ab AND 'techniques utilization':ti,ab) OR 'productivity cost' OR 'productivity loss' OR 'societal cost' OR 'opportunity cost' OR 'prospective cost' OR 'retrospective cost' OR 'economic benefit' OR 'economic burden' OR (economic:ti,ab AND (burden:ti,ab OR benefit*:ti,ab)) OR 'employment'/exp OR 'employment status' OR 'neet status' OR neet*:ti,ab OR 'parental employment status' OR 'maternal employment status' OR 'unemployment'/exp OR unemploy*:ti,ab OR 'un employ*':ti,ab OR 'non employ*':ti,ab OR 'work'/exp OR work*:ti,ab OR job*:ti,ab OR 'absenteeism'/exp OR absenteeism:ti,ab OR (absence*:ti,ab AND (disabilit*:ti,ab OR sickness:ti,ab)) OR 'presenteeism'/exp OR presenteeism:ti,ab OR presenteism:ti,ab OR (presence*:ti,ab AND (disabilit*:ti,ab OR sickness:ti,ab)) OR 'job performance' OR 'job satisfaction'/exp OR 'job security' OR 'productivity'/exp OR productivity:ti,ab OR 'quality of working life' OR 'return to work'/exp OR 'work capacity' OR 'working time' OR 'cost'/exp OR cost*:ti,ab OR economic*:ti,ab OR 'pricing'/exp OR pricing:ti,ab	7,456,046
3	((((((((((((((((('cost'/exp OR cost OR cost*:ti,ab OR 'cost benefit analysis'/exp OR 'cost benefit analysis' OR 'health economics'/exp OR 'health economics' OR 'economic* health*':ti,ab OR clinical:ti,ab OR dental:ti,ab OR hospital*:ti,ab OR medical:ti,ab OR nursing:ti,ab OR 'pharmacoeconomics'/exp OR pharmacoeconomics OR pharmac*:ti,ab) AND economic*:ti,ab OR pharmacoeconomic*:ti,ab OR 'drug approval'/exp OR 'drug approval' OR drug*:ti,ab) AND approval*:ti,ab OR 'biologic license application'/exp OR 'biologic license application' OR 'license application*':ti,ab) AND biologic*:ti,ab OR 'drug registration'/exp OR 'drug registration' OR drug*:ti,ab) AND registration:ti,ab OR emergency:ti,ab) AND authorization*:ti,ab OR 'marketing authorization'/exp OR 'marketing authorization' OR market*:ti,ab) AND	1,313,841

	authorization*:ti,ab OR 'new drug application'/exp OR 'new drug application' OR 'new drug application*':ti,ab OR 'drug cost'/exp OR 'drug cost' OR drug*) AND expense*:ti,ab OR expenditure*:ti,ab OR 'drug formulary'/exp OR 'drug formulary' OR drag:ti,ab) AND formular*:ti,ab OR formal*:ti,ab) AND drug*:ti,ab OR medication*:ti,ab OR medicine*:ti,ab OR prescription*:ti,ab OR 'drug utilization'/exp OR 'drug utilization' OR drug*:ti,ab) OR 'utilization review'/exp OR 'utilization review') AND review*:ti,ab OR concurrent:ti,ab) AND review*:ti,ab OR 'device economics'/exp OR 'device economics' OR device*:ti,ab) AND economics:ti,ab OR 'economic evaluation'/exp OR 'economic evaluation' OR economic:ti,ab) AND evaluation*:ti,ab OR 'cost control'/exp OR 'cost control' OR 'cost effectiveness analysis'/exp OR 'cost effectiveness analysis' OR 'cost minimization'/exp OR 'cost minimization' OR 'cost of illness'/exp OR 'cost of illness' OR 'cost utility analysis'/exp OR 'cost utility analysis' OR 'models, economic'/exp OR 'models, economic' OR 'models, econometric'/exp OR 'models, econometric' OR econom*:ti,ab) AND model*:ti,ab OR econometric*:ti,ab OR 'models, statistical'/exp OR 'models, statistical' OR model*:ti,ab) AND statistic*:ti,ab OR linear:ti,ab OR logistic:ti,ab OR 'budget impact analysis':ti,ab OR 'budget impact model':ti,ab OR 'budget impact':ti,ab OR 'markov chain'/exp OR 'markov chain' OR markov:ti,ab OR 'continuous time markov chain'/exp OR 'continuous time markov chain' OR ctmc:ti,ab OR 'discrete time markov chain'/exp OR 'discrete time markov chain' OR dtmc:ti,ab OR 'hidden markov model'/exp OR 'hidden markov model' OR hmc:ti,ab OR 'markov decision process'/exp OR 'markov decision process' OR mdp:ti,ab OR 'markov random field'/exp OR 'markov random field' OR mrf:ti,ab OR 'markov state model'/exp OR 'markov state model' OR 'decision analysis':ti,ab OR 'discrete event simulation'/exp OR 'discrete event simulation' OR discrete:ti,ab) AND model*:ti,ab OR simulation*:ti,ab	
4	#2 OR #3	8,370,912
5	#1 AND #4	13,036
6	'letter'/exp OR 'editorial'/exp OR 'case report'/exp OR commentary*:ti OR 'case stud*':ti OR 'case report*':ti OR 'case series':ti OR 'note'/exp OR 'short survey':ti OR 'in vitro':ti	6,025,990
7	#5 NOT #6 AND ([article]/lim OR [article in press]/lim OR [review]/lim)	5,943
8	#5 NOT #6 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2020-2023]/py	1,547
9	#7 OR #8	7,490
10	(#7 OR #8) AND [english]/lim AND [humans]/lim	6,800

Table 116. Search strategies for hand-searching of relevant congresses

Conference proceedings	Search	Hits
ASH	'Sickle cell'	922
	'Exa-cel'	2
	'Beti-cel'	5
	'Gene therapy'	61
	'CTX001'	2
	'CLIMB SCD-121	2
	'NCT03745287'	2
EBMT	'Sickle cell'	65
	'Exa-cel'	0
	'Beti-cel'	20
	'Gene therapy'	79
	'CTX001'	0
	'CLIMB SCD-121'	0
	'NCT03745287'	0
EHA	'Sickle cell'	887
	'Exa-cel'	8
	'Beti-cel'	31
	'Gene therapy'	375
	'CTX001'	49
	'CLIMB SCD-121'	2
	'NCT03745287'	2

Abbreviations: ASH: American Society of Hematology; EBMT: European Society for Blood and Marrow Transplantation; EHA: European Haematology Association.

Table 117. Search strategies for HTA databases

Database	Search	Hits
INAHTA	'Sickle cell'	30
CEA	'Sickle cell'	3
ICER	'Sickle cell'	2
CADTH	'Sickle cell'	19
NICE	'Sickle cell'	19
SMC	'Sickle cell'	4

Abbreviations: CADTH: Canadian Agency for Drugs and Technologies in Health; CEA: Cost-Effectiveness Analysis Registry; ICER: Institute for Clinical and Economic Review; INAHTA: International Network Association of Health Technology Assessment; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium.

The data collection was performed using inclusion/exclusion criteria guided by the PICOS approach and relevant studies were selected using a two-step process: (a) title/abstract screening and (b) full-text screening.

Two investigators working independently screened all citations identified in the literature search. The same two investigators independently reviewed the full texts. If any discrepancies occurred between the studies selected by the two investigators, a third investigator provided the arbitration.

Two investigators working independently extracted data on study characteristics, interventions, patient characteristics, and outcomes for the study population of interest for the final list of selected eligible studies. Any discrepancies observed between the data extracted by the two data extractors were resolved by discussion and coming to a consensus.

The critical appraisal of economic evaluations was carried out using the adapted Drummond's checklist as recommended in the NICE single technology appraisal (STA) manufacturer's template (194).

An overview of included studies reporting cost-effectiveness and cost and healthcare resource utilisation can be found in Table 118 and Table 119 respectively.

A systematic database search performed until 10 July 2023, identified 7,205 hits, which included 77 hits from manual search. Checking for the duplicates resulted in the exclusion of 311 hits, and the remaining 6,894 hits were screened. After preliminary screening of title/abstracts, 6,804 records were excluded, and 90 records were included for full publication screening. After a secondary screening of full-text articles, 81 studies were excluded. Additionally, a single study was included from the bibliography searching. Ultimately, this resulted in the inclusion of 10 publications in the SLR. Figure 37 presents the PRISMA flow diagram of studies identified in this review.

Figure 37. PRISMA flow diagram for the economic SLR

Table 118: Overview of included studies reporting cost-effectiveness

Study, Year	Country	Study type	Title	Objective	Type of data
Cost-effectiveness studies					
[redacted]					
[redacted]					
[redacted]					

Table 119: Overview of included studies reporting cost and healthcare resource use

Study, Year	Country	Study type	Title	Objective	Type of data
Cost and HCRU studies					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

The critical appraisal of economic evaluations was carried out using the adapted Drummond's checklist as recommended in the NICE single technology appraisal (STA) manufacturer's template.

J.1.2 Targeted literature search for [estimate]

No targeted literature search was performed.

J.2 Transition probabilities

J.2.1 Transition probabilities for acute complications

[redacted]

[redacted]Table 120.

Table 120. Monthly incidence rate of acute complications, used to calculate transition probabilities to acute complication health states

Variable	Value	Reference
Stroke		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]
Acute chest syndrome		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]

Cured from SCD	[redacted]	[redacted]
Acute infections		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]
Acute kidney injury/infarction		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]
Gallstones		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]
Pulmonary embolism		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]
Leg ulcers		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]

Abbreviations: HR, hazard ratio; OR, odds ratio; VOC, vaso-occlusive crisis

J.2.2 Transition probabilities for chronic complications

[redacted]

The model inputs for chronic complications are summarized in Table 121.

Table 121. Monthly risk of chronic complications, used to calculate transition probabilities in the model

Variable	Value	Reference
Chronic kidney disease		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]
Pulmonary hypertension		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]
Avascular necrosis		
Severe SCD	[redacted]	[redacted]

Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]
Heart failure		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]
Neurocognitive impairment		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]
Post-stroke		
[redacted]	[redacted]	[redacted]
Sickle retinopathy		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]
Liver complications		
Severe SCD	[redacted]	[redacted]
Improved SCD	[redacted]	[redacted]
Cured from SCD	[redacted]	[redacted]

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

J.2.3 Other transition probabilities

[redacted]

J.2.4 Transition probabilities for mortality

[redacted]

Table 122. Mortality inputs

Variable	Value	Reference
Health state specific mortality		
SMR for SCD cured cohort	[redacted]	[redacted]
SMRs for severe SCD cohort (calculated based on CLIMB SCD-121)		
Ages 13-18	[redacted]	[redacted]
Ages 19-35	[redacted]	
Ages 35+	[redacted]	
SMRs for improved SCD cohort		
Ages 13-18	[redacted]	[redacted]

Ages 19-35	[redacted]	[redacted]
Ages 35+	[redacted]	
Transplant-related mortality		
Instant risk (rate) of death due to procedure (%)		
Exa-cel	[redacted]	[redacted]
Infertility mortality, SMR		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]

Abbreviations: HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; SCD, sickle cell disease; SMR, standardized mortality ratio; VOC, vaso-occlusive crisis

Appendix K. Mapping of health state utility values to Danish tariff

In the study by Jensen et al., composite time trade off (cTTO) and discrete choice (DC) tasks were conducted between October 2018 and November 2019 by study participants selected from the Danish adult population, to derive utility index values for 86 EQ-5D-5L health states. In the cTTO task, which combines TTO and lead-time TTO tasks, participants were asked to state their preference between 10 years in full health and 10 years in EQ-5D-5L health states. The time in full health state (x) was then reduced until the interviewee considered the two choices the same. The ratio of the reduced years to 10 years (x/10) gave the value of the health state. In case participants considered the health state worse than death, they were given the choice between '10 years in full health' and '10 years in full health plus 10 more years with the health state' and were asked to trade off '10 years in full health' (x) until the two options were deemed the same. In this case the value of the health state was considered to be (x-10)/10 (i.e., between -1 and 0). In the cTTO task, each participant evaluated one of the blocks of 10 EQ-5D-5L states, randomly selected from the 86 health states. Each block of 10 states included one mild state with four '1' scores and a single '2' score, eight moderate states, and the worst state (55555). In DC tasks, pairs of health states were shown to participants, and they stated their preference between each pair of health states. There was no time component in the DCE. Each participant was randomly assigned to one of 28 blocks of 7-pairs of health states (196 pairs of EQ-5D-5L states were used in the DC task).

The final sample included utility index values elicited from cTTO and DC tasks from 1041 participants, who were largely representative of the Danish adult population (based on Statistics Denmark 2018 data) in terms of gender, age (with an underrepresentation of 18- to 24-year-olds and over representation of 65- to 74-year-olds), marital status, and geographical region. The proportion with higher education in the sample was higher than

the general population. Based on the utility index values for the EQ-5D-5L states elicited through cTTO and DC tasks, a conditional logit model for the DC data and a random-effects Tobit model for the cTTO data were combined in a 'heteroskedastic censored Tobit hybrid' model. The resulting model enables assigning utility index values, directly from EQ-5D-5L results (no mapping to 3L required), for each one of the 3,125 possible EQ-5D-5L results.

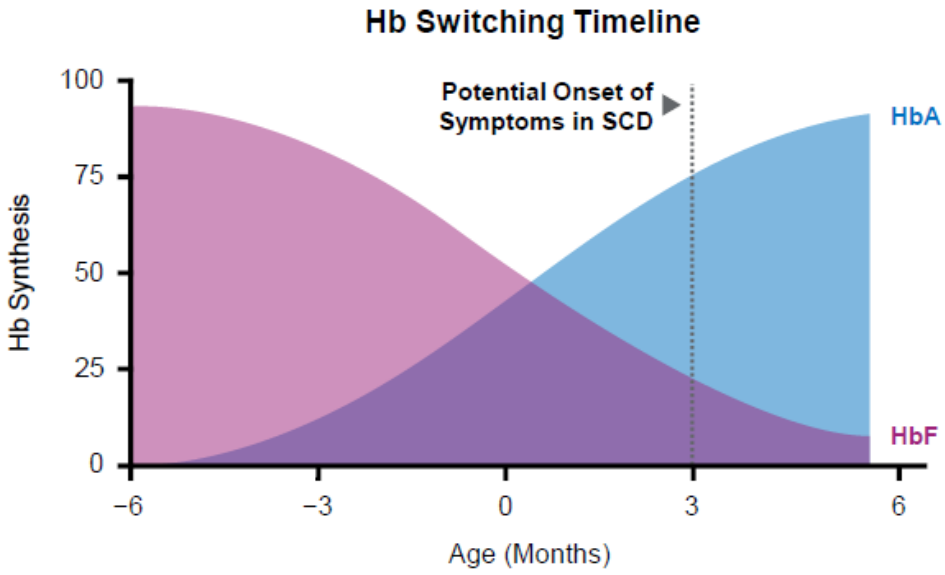
The coefficients presented in the Jensen article (Table 2 in the article) were used to assign a utility index to the EQ-5D-5L results observed in the trial. As a hypothetical example, if a patient's EQ-5D-5L assessment result was 23415, the utility index value for this assessment was calculated as: 1 - 0.041 - 0.05 - 0.139 - 0 - 0.618 = 0.152. This value was then used in the estimation of health state utility values.

Appendix L. Additional background information

L.1 The protective role of HbF in SCD

Different forms of haemoglobin are produced during different stages of human development. Fetal haemoglobin (HbF) is the predominant haemoglobin type prior to birth and during the newborn period. HbF is a tetrameric globin protein containing two γ-globin and two α-globin chains (α2γ2). Around 12 weeks of gestation, a gradual switch in production from γ-globin to β-globin begins which completes by 6 months of age (Figure 38). After the newborn period, the main form of haemoglobin is HbA (a heterotetramer comprised of two α-globin and two β-globin chains, α2β2). In adults, HbA normally accounts for >95% of the total haemoglobin with only traces of HbF typically present (210, 211).

Figure 38. Haemoglobin switching timeline

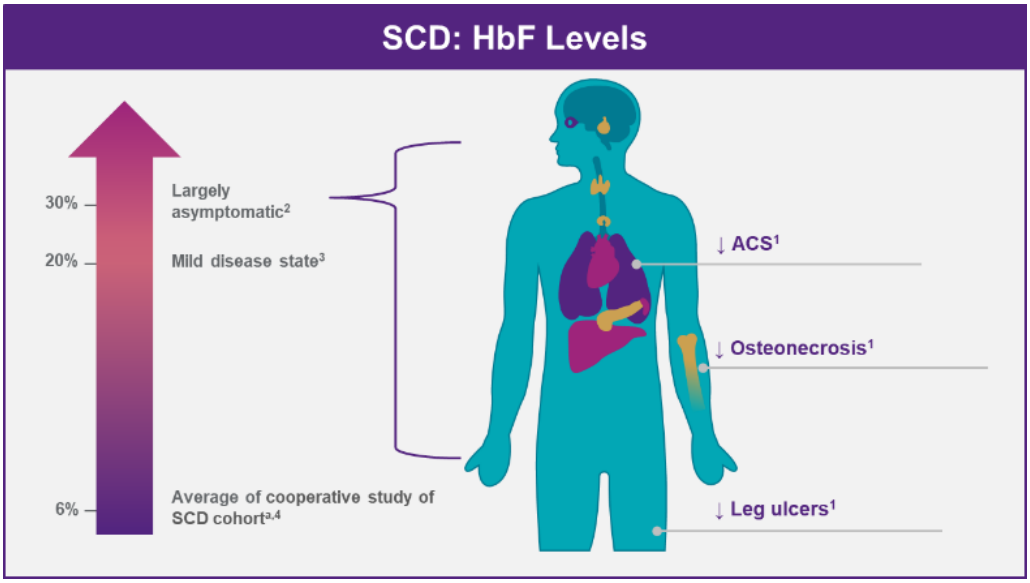


Abbreviations: HbA = haemoglobin A; HbF = haemoglobin F; SCD = sickle cell disease
Source: Adapted from (210).

Children with SCD are generally asymptomatic during their infancy, when HbF is still present and the onset of symptoms typically occurs several months after birth when HbA becomes the predominant type of haemoglobin, the production of which is affected by the disease-causing mutation in the β-globin gene (210, 212). Mutations leading to hereditary persistence of fetal hemoglobin (HPFH) can ameliorate the clinical phenotype of SCD and may decrease mortality (210). HPFH is a condition in which HbF production does not stop in early childhood and instead continues in later life (213). Patients with SCD and HPFH who have high HbF levels (approximately 30%) experience no symptoms of SCD (69). Indeed, HbF is a known modifier of clinical and hematologic signs and symptoms of SCD (214). In patients with SCD, higher levels of HbF are associated with reduced rates of

acute pain crises, less frequent acute chest syndrome (ACS) episodes, fewer leg ulcers, less osteonecrosis and reduced disease severity overall. This mutation leads to a decrease in the symptoms associated with SCD, which has led to the understanding that increased HbF production is a potential mechanism to treat patients with SCD (Figure 39) (210).

Figure 39: Impact of HbF levels on the severity of SCD symptoms

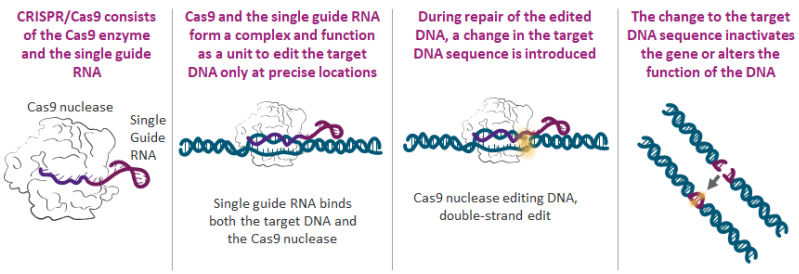


Abbreviations: ACS = acute chest syndrome; HbF = fetal hemoglobin; SCD = sickle cell disease
Sources: (215); (216); (68); (217)

L.2 Exa-cel mechanism of action

Exa-cel acts by reactivating the expression of γ-globin messenger RNA (mRNA) in erythroid precursors, which in turn leads to an increase in HbF protein levels in erythroid precursors and circulating RBCs, thereby potentially ameliorating the effects of HbS in SCD, including painful and debilitating VOCs (refer to 3.1.2 'the protective role if HbF') (218). Thus, exa-cel provides a potential functional cure for SCD by addressing the underlying cause of the disease (219). The manufacturing of exa-cel relies on non-viral, *ex-vivo* CRISPR/Cas9 gene editing (62). CRISPR/Cas9 systems are naturally occurring bacterial immune systems that enable modification of DNA at a precise location and have been repurposed for gene editing (Figure 40) (220, 221, 222).

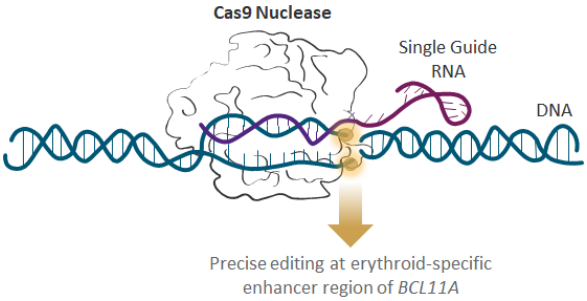
Figure 40. CRISPR/Cas9 gene editing
DNA = desoxyribonucleic acid; RNA = ribonucleic acid



Sources: (220, 223, 224)

In exa-cel, CRISPR/Cas9 mediated gene editing only occurs at the erythroid lineage-specific enhancer region of the *BCL11A* gene using a specific single-guide RNA and Cas9 nuclease (Figure 41), thereby conferring lineage specificity and avoiding pleiotropic effects (62). The goal of this genetic modification is to reactivate the expression of γ-globin mRNA in erythroid precursors, which results in an increase in HbF protein levels in adult erythroid cells.

Figure 41. Exa-cel mechanism of action



Abbreviations: DNA = desoxyribonucleic acid; RNA = ribonucleic acid
Sources: (223)

L.2.1 Advantages of CRISPR/Cas9 vs earlier gene therapies

Earlier gene therapies rely on insertion of a functional gene, usually using a viral vector. In comparison, exa-cel is unique in that it is a non-viral system that uses CRISPR/Cas9 gene editing to disrupt *BCL11A* and restore the production of HbF. Furthermore, traditional gene insertion strategies are based on overexpressing a transgene, which may result in an unbalanced α/β chain ratio in patients with hemoglobinopathies. Exa-cel, in contrast, reactivates HbF expression while preserving the α/β chain balance. Importantly, as exa-cel is a non-viral gene editing system, it does not carry the risk of insertional mutagenesis. The nonclinical safety assessment of exa-cel demonstrated no evidence of off-target editing or chromosomal translocations (1). Moreover, the CRISPR/Cas9 technology overcomes the limited durability associated with some other gene therapies, for example, adeno-associated virus (AAV) vector-based gene therapies. As gene therapies delivered by the AAV platform are non-replicating episomes, transduced vector genomes are gradually lost in dividing cells and leads to waning treatment effects (225). [redacted]

L.3 Exa-cel manufacturing process

The exa-cel manufacturing process includes collecting the patient's own haematopoietic stem and progenitor cells (HSPCs) via apheresis, followed by gene editing using the CRISPR/Cas9 system which is delivered inside the cell using electroporation. Collected cells are edited *ex-vivo* in a manufacturing facility, cryopreserved, and shipped back to the hospital to be transplanted into the patient (Figure 42).

Figure 42: Stages that the patient goes through when receiving exa-cel treatment

As shown in, in the clinic, patients receiving exa-cel go through a four-step process; pre-mobilisation preparation with transfusion therapy (Stage 1), stem cell mobilisation, collection, and exa-cel manufacturing (Stage 2), conditioning and single-dose exa-cel infusion (Stage 3), and post-infusion follow-up (Stage 4) (218):

- Stage 1: It is recommended that patients be transfused at least 8 weeks prior to the initiation of myeloablative conditioning with a goal of maintaining HbS levels <30% of total Hb while keeping total Hb concentration ≤11 g/dL. SCD-specific symptomatic therapies (e.g. hydroxyurea, crizanlizumab, voxelotor) should be discontinued at initiation of red blood cell exchange or simple transfusions (1). Iron chelation should be stopped at least 7 days prior to myeloablative conditioning. Depending on the myeloablative conditioning regimen administered, prophylaxis for seizures should also be considered (226).
- Stage 2: Cell collection should be maximized to obtain as many CD34+ cells as possible during each mobilization and apheresis cycle. If clinically tolerated, patients should undergo up to 3 consecutive days of cell collection per cycle. Each mobilization and apheresis cycle must be separated by a minimum of 14 days. If the minimum dose of exa-cel is not met after initial medicinal product manufacturing, the patient needs to undergo additional cycles of mobilization and apheresis to obtain more cells for additional product manufacture. A back-up collection of ≥2 × 10^6 CD34+ cells/kg is required. These unmodified cells must be collected from the patient and cryopreserved prior to myeloablative conditioning and infusion with exa-cel, and may be needed for rescue treatment under any one of the following conditions: compromise of exa-cel after initiation of myeloablative conditioning and before exa-cel infusion; neutrophil engraftment failure; or loss of engraftment after infusion with exa-cel (226).
- Stage 3: Full myeloablative conditioning must be administered before infusion of exa-cel. In the CLIMB SCD-121 trial, all patients received myeloablative conditioning with busulfan administered for 4 consecutive days intravenously 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. After completion of myeloablative conditioning, exa-cel infusion must be administered between 48 hours and 7 days of the last dose of the conditioning agent used. Premedication for exa-cel infusion should include an antipyretic (e.g., acetaminophen or paracetamol) and an antihistamine (e.g., diphenhydramine hydrochloride) (226).

- Stage 4:
  - Short-term monitoring: Standard procedures for patient management after HSCT should be followed after exa-cel infusion. Any blood products required within 3 months from exa-cel infusion should be irradiated. While restarting iron chelation after exa-cel infusion may be necessary, the use of non-myelosuppressive iron chelators should be avoided for at least 3 months and use of myelosuppressive iron chelators for at least 6 months after exa-cel infusion. Phlebotomy can be used in lieu of iron chelation, when appropriate. The EMA label additionally stipulates that patient's vital signs should be monitored every 30 minutes from when the first vial of exa-cel is infused until 2 hours after the last vial of exa-cel is infused (226). Patients undergoing HSCT may experience adverse events (AEs) unrelated to the administration of exa-cel (227). [redacted]
  - Follow-up: As indicated in, in the CLIMB SCD-121 study, patients were followed for 2 years post-infusion for efficacy and safety, with physical examinations, laboratory and imaging assessments, and evaluation of AEs (82). Patients who complete the study will be able to enroll in the long-term follow-up study CTX001-131, in which they will be monitored for a total of 15 years following exa-cel infusion.Advantages of CRISPR/Cas9 vs traditional gene therapies

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Vedr. langtidseffekt af exa-cel

Ved Rådets møde nr. 100 drøftedes forskellige aspekter af behandlingen med Exagamglogene autotemcel (exa-cel) til TDT og SCD.
Som et forstærkende argument imod prissætningen anførte et rådsmedlem, at der kunne være en risiko for svigtende funktion af de transplanterede stamcellers funktion på et tidspunkt senere end den observationstid der er meddelt i de to CLIMB-studier (gennemsnit 36 mdr. maksimal 67 mdr.), hvor der ikke synes at være tegn herpå. Med ordstyrerens tilladelse anførte jeg, at al erfaring med transplantation af autologe stamceller – en rutineprocedure i hæmatologiske afdelinger i Danmark i 35 år – viser at sent svigt af transplanterede stamceller ikke er et kendt fænomen. Et rådsmedlem bemærkede derefter, at det kunne skyldes, at patienterne fik recidiv af deres maligne sygdom, inden problemet indtraf.
Som bekendt tillod tiden ikke yderligere diskussion.
Som fagudvalgsforperson finder jeg det uheldigt og beklageligt, at det anførte udsagn står uimodsagt.

Jeg tillader mig derfor at fremsende supplerende materiale vedrørende durabiliteten af transplanterede stamcellers funktion in vivo.

Silverberg et al. Bone Marrow Transplantation (2024) 59:1601–1610; https://doi.org/10.1038/s41409-024-02397-x: En populationsbaseret opgørelse fra det svenske MS-register (Multipel sclerose) og EBMT (Den europæiske organisation for stamcelletransplantationer) med 174 sclerose-patienter behandlet med højdosis kemoterapi (4-stof konditionering) og stamcellestøtte med autologe stamceller, mobiliseret med cyklofosfamid og G-CSF. Dermed altså en mere traumatiserende mobilisering end i CLIMB studierne, hvor der kun anvendes vækstfaktorer (plerixafor og G-CSF). Procedurerne er foretaget mellem 2004 og 26/11 2019. Den mediane observationstid er ikke anført. Af tabel 2 fremgår at over halvdelen har mere end 5 års observation. Langtids hæmatologisk effekt indgik hverken i primære eller sekundære endepunkter, men der er en omhyggelig tabel 3 med anførelse af alle SAE, og heri er der ikke anført stamcellesvigt, idet febril neutropeni er snævert procedurerelaterede.

Pasvolsky et al. Br J Haematol. 2023 August ; 202(4): 866–873. doi:10.1111/bjh.18944 er et materiale fra en førende institution inden for stamcelletransplantation, MD Anderson Cancer Center. Man har her samlet data vedrørende autolog stamcelletransplantation efter højdosis kemoterapi for myelomatose i en speciel kohorte, nemlig patienter under 40 år (aldersgruppen er relevant for den aktuelle problematik). Materialet er indsamlet fra 1989 til 2021. Her er naturligvis mange recidiver. Median progressionsfri overlevelse er dog 43 måneder og median overall overlevelse svimlende 146 måneder. Dette betyder at disse mange patienter med recidiv har haft en så stabil knoglemarvsfunktion, at de har tålt omfattende recidivbehandling. Svigtende funktion af stamcellerne ville i sig selv medføre stor dødelighed og desuden utilgængelighed for yderligere behandling. Desuden finder jeg det relevant at anføre funktionen af allogene stamceller, selvom der her er principielle forskelle fra de autologe – i førstnævntes disfavør.

Aydin et al. © 2021 The American Society for Transplantation and Cellular Therapy. https://doi.org/10.1016/j.jtct.2021.09.009 er en metaanalyse af opgørelser over allogene transplantationresultater med vægt på haploidentiske donorer ved SCD. Haploidentisk donor er én af mulighederne for at øge donortilbudet i forhold til den eksklusive brug af matchede vævstypeidentiske søskende, som er dansk standard. Som det fremgår af tabel 1 er ”graft failure” (svigt af stamcellerne) et hyppigt problem (15%) med samtidig stor procedure relateret mortalitet (6 %). I ganske få studier (fig. 2) kunne man sammenligne haplo- med søskende, og her ses graft failure fortrinsvis ved haplo-. Resultaterne har generelt meget store udsving. Man kan mene om metaanalysen, hvad man vil, men den vedrører præcis den samme

patientgruppe som den i CLIMB-SCD 121, og efterlader ikke undertegnede i tvivl om hvilken retning kurativ behandling af SCD vil tage af disse to.

Som baggrundslæsning kan jeg anbefale en lidt ældre gennemgang af knoglemarvens biologi med vægt på kliniske relevante forhold:
Van Zant et Liang Stem cells translational medicin http://dx.doi.org/10.5966/sctm.2012-0033

Endelig kunne man hypotetisere, om procederingen af stamcellerne kunne tilføre nye og ukendte defekter. Håndtering af stamceller er velkendt i mange sammenhænge, og et sådant fænomen er ikke beskrevet. Selve CRISPR værktøjet er targetteret og rører ikke ved gener der menes at have betydning for stemness og proliferation. Jeg vil betegne mistanken som nærmere usund fremfor sund skepsis.

Med venlig hilsen

Jesper Stentoft
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Blodsygdomme
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Anvendelse af alvorlighedsprincippet

Medicinrådets anbefalinger vedrørende nye lægemidler og indikationsudvidelser hviler som udgangspunkt på en vurdering af lægemidlets effekt, sikkerhed og omkostningseffektivitet og Folketingets syv overordnede principper for prioritering af sygehuslægemidler. Ved etableringen af Medicinrådet den 15. december 2016 fik Medicinrådet desuden mandat af Danske Regioners bestyrelse til i særlige tilfælde at inddrage alvorlighed i sit beslutningsgrundlag[1].

Alvorlighedsprincippet baserer sig på et veletableret og anerkendt fagligt grundlag. Et fælles træk ved forskellige teorier om retfærdighed[2] [3] [4] og ved befolkningens tanker om retfærdighed[5] er således en særlig bekymring for de dårligst stillede samfundsborgere. Denne bekymring implicerer, at goder anses for at have større vægt, jo værre modtagerne har det. Alvorlighedsprincippet afspejler således et hensyn til alvorlighed udover behandlingseffekt og omkostninger[6]. En sådan bekymring for de, der er dårligst stillede, adskiller sig dermed fra den utilitaristiske tankegang om, at ressourcer bør fordeles udelukkende ud fra et ønske om at maksimere den samlede sundhed[7] [8].

Medicinrådets alvorlighedsprincip

For at sikre en retfærdig prioritering af samfundets ressourcer har Medicinrådet fået mandat til at inddrage alvorlighed i sit beslutningsgrundlag[9]. Herved kan Medicinrådet acceptere en større betalingsvillighed ved en meget dyr behandling, jo større afstand en patientgruppes helbred er fra perfekt sundhed ud fra en betragtning om, at dette har højere moralsk værdi. Derudover kan alvorlighed også afspejle sig i et samfundsmæssigt perspektiv, hvis behandling eller mangel på samme har alvorlige konsekvenser for samfundet og ikke bare for den enkelte. Rådets anbefalinger baserer sig dog altid på en helhedsvurdering, hvorfor alvorlighedsprincippet ikke trumfer andre nødvendige og relevante hensyn.

Når det intuitive alvorlighedsprincip tages med i Rådets beslutningsgrundlag, åbner Rådet op for:

1) At acceptere udgifter ved ibrugtagning af et nyt lægemiddel, som er højere end, hvad Rådet almindeligvis accepterer.
2) At anbefale et nyt lægemiddel, hvis evidensgrundlag ikke er tilstrækkeligt til, at Rådet almindeligvis anbefaler det.

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[1] Danske Regioner (2016): https://medicinraadet.dk/media/3giddjva/ad-pkt-4-medicinraadet-etablering_final-a.pdf
[2] Daniels (1993). Rationing fairly: Programmatic considerations. Bioethics, 7, 224-233.
[3] Rawls (1971). A theory of justice. Cambridge: Harvard University Press.
[4] Holtug, N. (2007). 'Prioritarianism', in N. Holtug and K. Lippert-Rasmussen (eds.) Egalitarianism: New Essays on the Nature and Value of Equality. Oxford: Clarendon, 125-56.
[5] Nord (1999). Cost-value analysis in health care. Making sense out of QALYs. New York: Cambridge University Press.
[6] Nord (1993). The trade-off between severity of illness and treatment effect in cost-value analysis of health care. Health Policy, 24, 227-238.
[7] Nord (2005). Concerns for the worse off: fair innings versus severity. Social Science & Medicine, 60, 257-263.
[8] Eksempel: Kan man således forbedre person A's helbred på en skala over individuel nytteværdi fra 0,4 til 0,6, og person B's helbred fra 0,6 til 0,8 på den samme skala, vil samfundet værdsætte behandling af person A højere end behandling af person B, ifald alt andet er lige.
[9] Danske Regioner (2016): http://www.medicinraadet.dk/media/4377/ad-pkt-4-medicinraadet-etablering.pdf

Eksempler på mulig ibrugtagning af alvorlighedsprincippet

Der er særlige tilfælde, hvor Medicinrådet kan vælge at inddrage alvorlighed i sit beslutningsgrundlag. Det kunne være i situationer, hvor det nye lægemiddel:

- Er rettet mod børn og unge personer (0-25 år).
- Vedrører sygdom med ualmindeligt tidlig død.
- Kurerer, forebygger eller modificerer kronisk invaliditet eller andre symptomer, der er *grundlæggende* livsbegrænsende[10].
- Er rettet mod alvorlige og særligt smitsomme sygdomme.
- Er eneste reelle sygdomsmodificerende eller kurative behandling[12].

Rådet kan ligeledes inddrage alvorlighed i andre end ovenstående tilfælde, ifald det vurderes, at andre særlige problematikker gør sig gældende ved sygdommen, patientgruppen, samfundet, lægemidlet eller lignende.

/Revideret den 18. december 2020

[10] Disse eksempler relaterer sig til Folketingets syvende princip for prioritering af sygehuslægemidler (*adgang til behandling*): Sundheds- og Ældreministeriet (2016) Princippapir om prioritering for sygehuslægemidler: http://www.sum.dk/Aktuelt/Nyheder/Medicin/2016/April/~/media/Filer%20-%20Publikationer_i_pdf/2016/Princippapir-om-prioritering-for-sygehuslaegemidler/Princippapir-om-prioritering-for-sygehuslaegemidler.ashx