Exagamglogene autotemcel for treating severe sickle cell disease

This is not a HST topic – this STA is being considered by the HST committee due to scheduling and capacity

For public – slides contain no confidential information

HST technology appraisal committee [14 February 2024], assessing ID4016 as a single technology appraisal

Chair: Paul Arundel

Lead team: Carole Pitkeathley, Angharad Shambler, Philip Mallender

External assessment group: Warwick Evidence

Technical team: Cara Gibbons, Alan Moore, Jasdeep Hayre

Company: Vertex

Committee meeting format

Part 1 – Meeting in public	Part 2a – Meeting in private with committee, EAG, NHSE, company, experts	Part 2b – Meeting in private with committee only
• Disease background • Expert perspectives • Equality considerations • Technology and treatment pathway • Decision problem • Key clinical evidence • Summary of economic model • Summary of key issues	• Key issues in further detail • Views from EAG and experts	• Committee preferences • Cost-effectiveness results • Committee recommendation

NICE National Institute for Health and Care Excellence

Background on sickle cell disease

Sickle cell disease (SCD) is a life-long disease characterised by unpredictable episodes of severe pain, chronic haemolytic anaemia, organ damage and shortened life expectancy

Causes

- Caused by mutation in a gene responsible for making haemoglobin
- Results in unusually shaped red blood cells (sickle-shaped) which do not live as long and can block blood vessels
- This results in a range of acute and chronic complications, such as an acute painful crisis, also known as vaso-occlusive crisis (VOC)

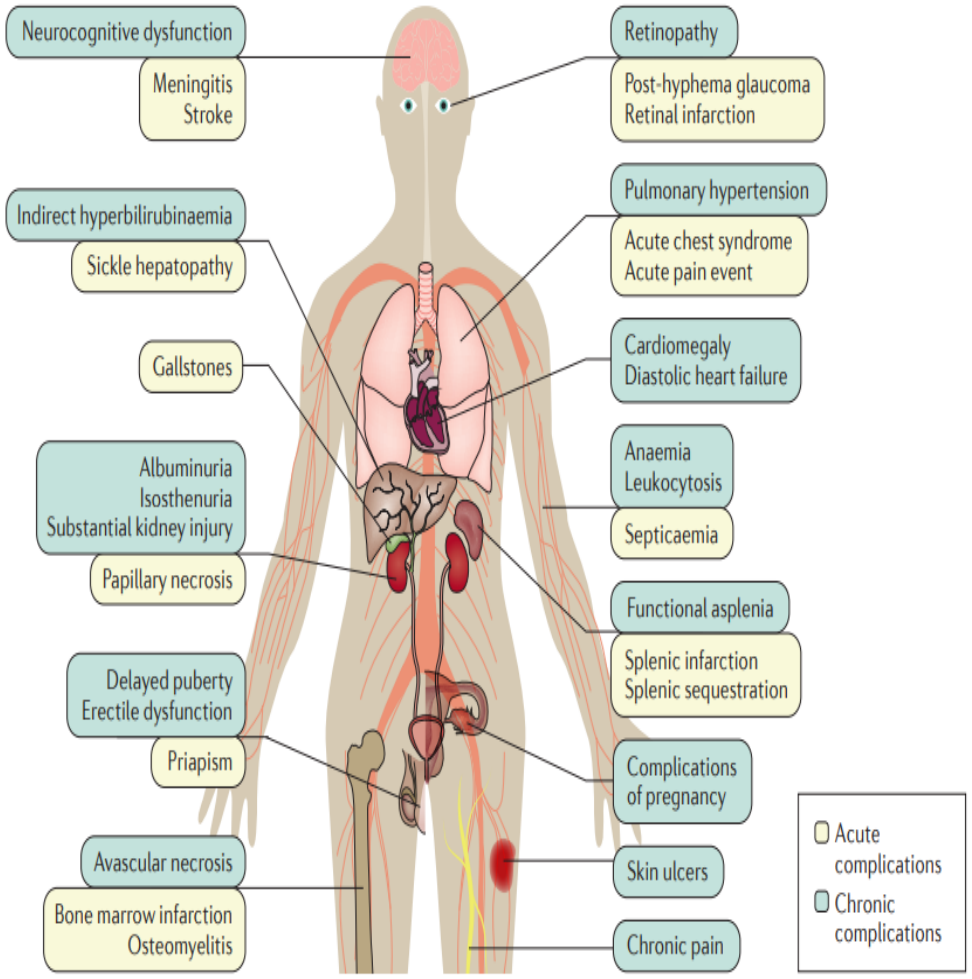
Symptoms and prognosis

- Life expectancy for people with SCD is substantially reduced
- People with SCD more likely to develop other severe illnesses e.g., stroke, heart conditions, kidney failure
- Allogeneic stem cell transplant only possible cure, but only ~15% of eligible people find a matching donor

Epidemiology

- Estimated 14,200 UK people with SCD, ~11,580 are age 12 years+
- Predominantly affects people of African, Caribbean, Middle Eastern or South Asian family background

Acute and chronic complications



NICE

Patient perspectives (1)

SCD is an invisible genetic condition that affects everyone differently

Submissions from Anthony Nolan and The Sickle Cell Society

- SCD burden is all-consuming and its emotional, social and QoL impact on patients and families is significant
- Most common symptoms: pain in multiple body parts (79%), chronic fatigue (73%) and intense localised pain at crisis site (70%)
  - ↳ Significant impact on mental health and daily activities which increases as symptoms become more severe

"…it feels like being stabbed everywhere repeatedly or having all your bones broken, but the words just don't do the pain justice"

30% of people with SCD say that existing treatments do not manage their disease very well.

- Unmet need for treatment – only 1 licensed drug to prevent VOCs (hydroxyurea), which does not work for everyone
- People want choice and empowerment in managing SCD and to resolve symptoms to where they have no significant impact on day-to-day lives, prospects and opportunities
- Serious health inequality issues affecting people with SCD. In UK, SCD overwhelmingly confined to black populations or people who have black heritage

"Being ill with sickle cell VOC can feel tantamount to being invisible for the amount you feel heard or respected"

Abbreviations: SCD, sickle cell disease; QoL, quality of life; VOC, vaso-occlusive crisis

Patient perspectives (2)

Submissions from 2 patient experts

"Trying to avoid crises often feels like walking a tightrope, it feels like there is very small margin for error"

- It takes longer than the pain episode to recover from the physical and mental effects of a crisis
- Pain severity often results in hospitalisation, but some avoid seeking hospital care, even when experiencing a severe crisis due to fear of poor treatment and discrimination
- There is a huge amount of variation in the care that can be offered from one hospital and region to another

"I feel like I have reached the ceiling of what current treatments can offer, yet continue to experience severe symptoms…this creates feelings of despair and hopelessness"

- Exa-cel would massively and drastically change lives – the difference would be night and day. Eradicating SCD burden would significantly increase QoL
- Concerns about the long-term effects of treatment e.g., 10, 20, 30 years after treatment? Risks of developing complications in immediate and long-term?
  - ↳ This need to be thoroughly explored to ensure patients can make an informed decision.

- Exa-cel would particularly benefit those who have exhausted current treatment options and those are more ill, more often, but there are also QoL improvements that should be made available to older people
  - ↳ May disadvantage those who do not have severe disease at present – should people to have to 'wait' until they deteriorate before being offered this treatment? Deciding who is more worthy is ethically tricky

"Since having an allogeneic SCT, I am healthier, fitter and stronger than at any point in my life before..I can feel the legacy of 33 years of SCD in my body and that means there are limits to what I can do"

Abbreviations: SCD, sickle cell disease; QoL, quality of life; SCT, stem cell transplant

Clinical perspectives

Current treatment is supportive for most patients; exa-cel is a potential SCD cure

Submissions from 2 clinical experts, Royal College of Pathologists, British Society for Haematology, United Kingdom Forum on Haemoglobin Disorders, National Haemoglobinopathy Panel, NHSE Haemoglobinopathy CRG

- Irregular and unpredictable crises can be life-threatening complications e.g., single or multi-organ failure
- Patients report poor experiences and are impacted by high deprivation levels
- Better supportive care has improved survival, but many continue to die in early adulthood from complications
- Very limited disease modifying therapies available (which often have intolerable side effects) and no real curative treatments except allogeneic SCT (only ~15% have suitable donors)
    - ↳ Exa-cel can avoid AEs of graft versus host disease that is seen with allogeneic SCTs
- Exa-cel could provide cure to wider population with severe SCD, and offer a chance at disease free survival, improved organ function, reduced symptoms (e.g., VOCs) and healthcare utilisation
- Ultimate outcome: safe cure that improves QoL → lack long-term data, but early results show improved PRO
- People with mild SCD and no VOCs are less likely to derive benefit → treatment risks may outweigh benefit
- Stem cell collection processes exist in NHS but may need training to ensure exa-cel follows ATMP principles
    - ↳ Treatment will be delivered only in JACIE (Joint Accreditation Committee International Society for Cell & Gene Therapy-Europe & European Society for Blood and Marrow Transplantation) accredited units

"SCD is a severe and distressing lifelong disease, from childhood in which individuals suffer enormously and have a severely impaired QoL and likelihood of early death. We currently have very limited treatment options"

Abbreviations: SCD, sickle cell disease; SCT, stem cell transplant; QoL, quality of life; PRO, patient reported outcomes; VOC, vaso-occlusive crisis; CRG, clinical reference group; AE, adverse events; ATMP, advanced therapy medicinal product

Equality considerations

Health inequalities are revisited in later slides as a key issue

Consultees raised several equality issues related to sickle cell disease:

- Decisions around SCD treatment availability primarily affect people from ethnic minorities, many of whom are economically disadvantaged and subject to health inequalities
    - Most UK SCD patients are of Black African and Caribbean heritage
    - People with SCD more likely to live in more deprived areas of UK, and majority aged 12-35 years with recurrent VOCs identified as being in 2 of most deprived quintiles (IMD)
    - SCD patients from most socioeconomically deprived areas are at highest risk of hospital re-admissions and in-hospital mortality → significant inequalities in healthcare access and outcomes
    - Careful consideration needs to be given to the ethnic, faith and cultural needs/aspects of individuals who are being offered this treatment.
- SCTAPPG 'No one's listening' report: highlighted issues of inequity, discrimination, racial bias, inequalities to access treatment, stigmatisation and a lack of understanding and prioritisation towards SCD patients
- Unmet need likely to remain for cohort of patients, especially those older than studied age group (12-35 years)
- Need pre-treatment or conditioning with busulfan before exa-cel, which may affect fertility

Committee considerations in other SCD appraisals:

- Unable to address issues related to poor healthcare and stigma around seeking pain relief - beyond TA remit
- Willing to take health inequality into account in its decision making by accepting a higher cost-effectiveness estimate than it otherwise would have done

Abbreviation: SCD, sickle cell disease; VOC, vaso-occlusive crisis; IMD, Index of Multiple Deprivation; SCTAPPG, All-Party Parliamentary Group on Sickle Cell and Thalassemia; TA, technology appraisals

Exagamglogene autotemcel (exa-cel) (Casgevy, Vertex)

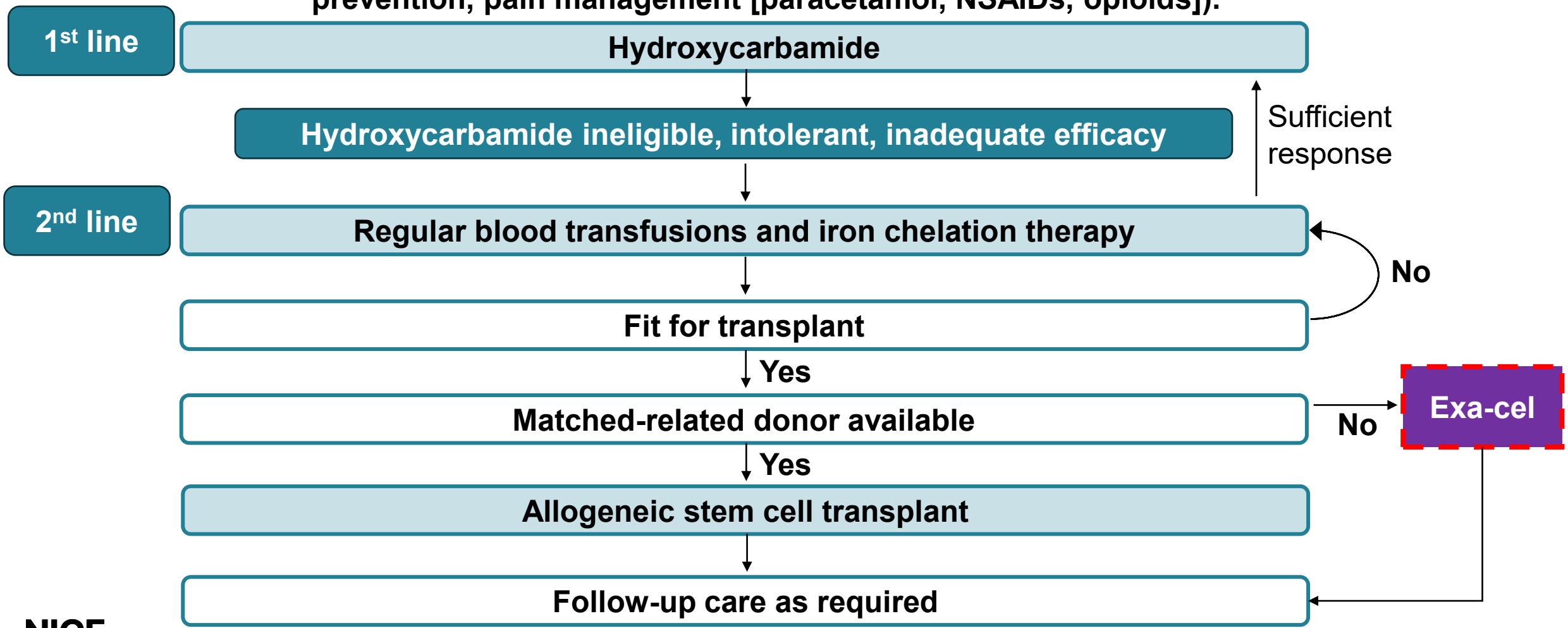
Marketing authorisation	**Indication (granted November 2023):** for the treatment of sickle cell disease in patients 12 years of age and older with recurrent vaso-occlusive crises who have the βS/βS, βS/β+ or βS/β0 genotype, for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available
Mechanism of action	Reactivates expression of gamma (γ)-globin mRNA, which increases foetal haemoglobin levels in circulating red blood cells, stopping effects of sickle haemoglobin in SCD and preventing the polymerisation of sickle haemoglobin which causes SCD
Administration	One-time, single dose intravenous infusion containing a dispersion of viable CD34+ cells in one or more vials. Exa-cel treatment process involves 4 key stages: • **Stage 1:** screening and pre-mobilisation • **Stage 2:** blood stem cells collected **(apheresis)**, sent to manufacturing facility → CD34+ cells isolated → CRISPR/Cas9 edited (gene editing technology)→ cells frozen and tested → cells returned for infusion • **Stage 3A+B:** preparative chemotherapy → **exa-cel infusion** • **Stage 4A+B:** post-infusion in-hospital follow-up during engraftment and discharge → post-engraftment follow-up for approx. 2 years Target dose: ≥15 x 10^6 $CD34^+$ cells/kg. Required back up collection: 2 x 10^6 $CD34^+$ cells/kg. Minimum cell dose: 3.0 x 10^6 $CD34^+$ cells/kg
Price	List price: [redacted] for a course of treatment

Abbreviations: SCD, sickle cell disease; mRNA, messenger ribonucleic acid

Treatment pathway

SCD in patients 12 years of age and older with recurrent VOCs who have βS/βS, βS/β0 or βS/β+, for whom a HLA-matched related HSC donor is not available

Supportive care: lifestyle advice (hydration, body temperature regulation, infection prevention, pain management [paracetamol, NSAIDs, opioids]).



NICE

Abbreviations: SCD, sickle cell disease; VOC, vaso-occlusive crisis; HLA, human leukocyte antigens; HSC, hematopoietic stem cell; NSAIDs, nonsteroidal anti-inflammatory drug

Decision problem

Company included non-reference case economic analysis - part of key issues

	NICE final scope	Company	EAG comments
Population	People with SCD	SCD ≥ 12 years for whom an HLA-matched related HSCT donor is not available	• Trial population is more specific (age 12-35 years with recurrent VOCs who have βS/βS, βS/β0 or βS/β+) • Severity and VOC definitions vary – many people may meet criteria
Intervention	Exa-cel	Exa-cel (cell preparation that is infused into patients)	Consider 'intervention' whole treatment pathway from screening to follow-up
Comparators	• Hydroxycarbamide • Blood transfusions • Best supportive care	Best supportive care: (including blood transfusions, chelating agents and hydroxycarbamide)	N/A
Outcomes	Aligns with scope. EAG: mortality and AE listed separately but outcome combined in submission		
Economic analysis	As per reference case	• Severity modifier Non-reference case: • 1.5% discount rate • DCEA	Should exclude non-reference case: • 1.5% discount rate • DCEA

Abbreviation: DCEA, distributional cost-effectiveness analysis; SCD, sickle cell disease; HSCT, haematopoietic stem cell transplant; AE, adverse events; VOC, vaso-occlusive crisis; HLA, human leukocyte antigens

Clinical effectiveness

NICE National Institute for Health and Care Excellence

CLIMB SCD-121

Follow-up after infusion: 2-years in CLIMB SCD 121 and ≥13 years in CLIMB-131

Design	Phase 1/2/3, single-arm, open-label, multicentre, single-dose study
Population	People aged 12 to 35 years with severe SCD (≥2 VOC per year, in 2 years prior) with βS/βS, βS/β0, or βS/β+ genotype. No willing and healthy 10/10 HLA-matched related donor
Data cuts	Modelled datacut (D120, April 2023): 46.2 month follow up (median 17.5 months) • 63 enrolled → 58 started mobilisation → 43 received exa-cel (FAS) → 29 followed for ≥16 months after exa-cel infusion and ≥14 months after RBC transfusions (PES) Latest datacut (June 2023): mean follow up 20.1 months. FAS = 44, PES = 30
Intervention	Exa-cel
Primary outcome	Proportion of people achieving absence of any severe VOC for ≥12 months after exa-cel*
Secondary outcomes	• Key: proportion of people free from hospitalisation for severe VOCs for ≥12 months* • Other endpoints: severe VOCs, HbF and Hb, allelic editing, haemolysis markers, RBC transfusions, patient reported outcomes
Locations	16 study centres. [redacted] people from UK at D120 ([redacted] in PES)
Used in model	Company: yes. EAG: primary outcome and some baseline outcomes used in model
Additional trials	All who had exa-cel who completed/discontinued trial asked to join CLIMB-131 study

* Evaluation starts 60 days after last RBC transfusion for post-transplant support or SCD management.

Abbreviation: PES, primary efficacy set; FAS, full analysis set; Hb, haemoglobin; HbF, foetal haemoglobin; RBC, red blood cell; VOC, vaso-occlusive crisis; HLA, human leukocyte antigen; SCD, sickle cell disease

Clinical trial results

Additional outcomes for D120 provided in supplementary slides

Comparison of key outcomes between the model datacut and latest datacut

Outcome	D120 (16-Apr-2023) – used in model	ASH 2023 (14-Jun-2023) – not used in model
Number in FAS (final analysis set)	43	44
Number in PES (primary efficacy set)	29	30
VOC-free for ≥12 months	96.6% (28/29)	96.7% (29/30)
VOC-free duration; mean (range)	20.7 months (13.6, 43.6 months)	22.4 months (14.8, 45.5 months)
VOC-free through follow-up (of those to achieve primary outcome)	96.4% (27/28)	96.6% (28/29)
Hospitalisation free for ≥12 months	100% (29/29)	100% (30/30)
VOC-free for duration of 1.3 - 43.6 months	86.0% (37/41)	N/A
Hospitalisation free for 1.3 - 43.6 months	97.6% (40/41)	N/A
Note: 41/43 people in D120 FAS had ≥60 days follow-up after last RBC transfusion		

Abbreviation: VOC, vaso-occlusive crisis; FAS, final analysis set; PES, primary efficacy set; N/A, not available; RBC, red blood cell

Indirect treatment comparison (ITC)

ITC not used in economic model. CLIMB SCD-121 data used to inform both exa-cel and SoC arms.

Company: exa-cel inclusion criteria = people on SoC with 2 VOCs/year for 2 consecutive years

- Baseline number of VOC includes SoC related efficacy, so SoC arm assumes baseline VOCs over time horizon

SLR: 5 studies → 3 had sufficient data: HOPE (voxelotor), SUSTAIN (crizanlizumab), NCT01179217 (L-glutamine)

Unanchored MAIC: CLIMB SCD-121 IPD matched to SoC data from the 3 studies

- Outcome: proportion of patients who remained VOC-free for 12 months. No other efficacy/safety outcomes
- Treatment effect modifiers (TEM): genotype, baseline annualised number of VOCs, age, gender, ethnicity
- Due to small sample (n=17), ≤ 3 TEM used for matching based on importance, HTA expert and data availability
  - ↳ ESS after matching : 12 (vs SUSTAIN), 13 (vs NCT01179217), 4 (vs HOPE)

EAG: ITC suggests a benefit of exa-cel relative to SoC but disagree efficacy is superior relative to all comparators

- Given limitations of ITC (e.g., sample size, varied VOC definition) and unanchored MAICs in general - level of evidence supporting exa-cel superiority relative to SoC is low

% VOC-free at 12m	SoC	Exa-cel unweighted	Exa-cel re-weighted	Rate ratio (95% CI), p value
SUSTAIN	(N = 65)	(N = 17)	(ESS = 12)	
Proportion (95% CI)	16.9% (-,-)	94.1% (71.3%, 99.9%)	92.7% (62.2%, 99.0%)	5.5 (3.1, 9.6), <0.0001
HOPE	(N = 91)	(N = 17)	(ESS = 4)	
Proportion (95% CI)	30.8% (-,-)	100% (80.5%, 100%)	100%	Not calculated, N/A (ESS <5)
No results presented for NCT01179217 ITC (Company: no proportion VOC-free data)				

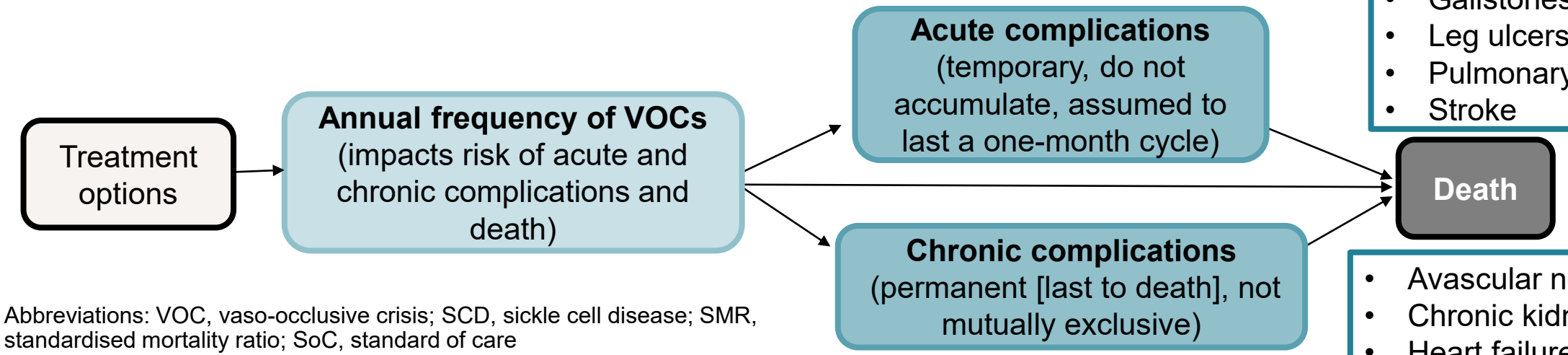
Abbreviations: SoC, standard of care; CI, confidence intervals; SLR, systematic literature review; IPD, individual patient data; VOCs, vaso-occlusive crisis; ESS, effective sample size; HTA, health technology assessment; MAIC, matching-adjusted indirect comparison

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

Company: developed a Markov cohort state-transition model



- Acute chest syndrome
- Acute infections
- Acute kidney injury
- Gallstones
- Leg ulcers
- Pulmonary embolism
- Stroke

- Avascular necrosis
- Chronic kidney disease
- Heart failure
- Neurocognitive impairment
- Post-stroke
- Pulmonary hypertension
- Sickle retinopathy

Abbreviations: VOC, vaso-occlusive crisis; SCD, sickle cell disease; SMR, standardised mortality ratio; SoC, standard of care

Input	Source / method
Time horizon, cycle length	Lifetime (model start age: 21.2), 1 month (half-cycle correction)
Discount rate	1.5% (3.5% scenario)
Treatment waning	No. If 12 months VOC-free, assumed "functionally cured" (96.6%)
Annual VOC frequency	CLIMB SCD-121 baseline VOCs: 4.2 a year/ 0.35 per cycle • Exa-cel: first 12 months baseline VOC frequency, 0 VOC after. • SoC: baseline VOC frequency maintained for time horizon
Acute and chronic complications	Literature-based rates and risk equations used to estimate rate of developing SCD complications based on VOC frequency.
Mortality	Exa-cel (cured): general population mortality + SMR SoC: SCD mortality rate + complication specific mortality rates

Can have multiple, concurrent and co-occuring complications and most independently contribute to mortality risk

Commentary on the model

EAG:

- Model structure is not organised as a Markov structure (i.e., mutually exclusive and exhaustive health states)
- Deaths calculated by applying mortality rates independently to non-mutually exclusive complications → leads to model predicting death rates of ~400% for SoC arm and over 500% for exa-cel arm
  - ↳ Model may overestimate incidence and mortality impact of SCD-related complications – these structural problems are likely to invalidate the cost-effectiveness results

Decision support unit:

- Model structure mostly affects SoC group - assumed to have continued VOCs and complications, which leads to negative impacts on survival, QALY losses and disease management costs
- Company's additive approach for estimating deaths is mathematically incorrect and reflects an error.
- Agree existing modelling approach may overestimate complication-related mortality risks because complications are independently associated with increased mortality risk, despite co-occurring in same people
  - ↳ Has implications for the credibility of modelled estimates of SoC complications, survival, QALYs and costs
- More straightforward and transparent approach: remove complication-related mortality risks, and model all-cause mortality in one step using conditional probabilities of death based on SMRs
- Resolving how mortality is modelled alone is not enough – important to ensure modelled complications are clinically plausible and consistent with external data, because these drive the SoC QALY losses and costs

Abbreviations: SoC, standard of care; QALY, quality-adjusted life years; VOC, vaso-occlusive crisis; SMR, standardised mortality ratio; SCD, sickle cell disease

Model update

Based on EAG and NICE DSU comments, the company provided an amended model; estimating mortality using a standardised mortality ratio (however company base case uses original model)

Company after technical engagement:
- Provided amended model which uses SMR– use rate from ICER report and Desai et al (2020)
- Original model survival estimates are more realistic so keep this in the base case

➡

EAG comments:
- Model structure cannot be justified based on results it generates
- Accept amended model structure but prefer different SMR
- Still limitations e.g. estimation of complications (large impact)

Company modelling summary

Parameter	Company original model (company base case)		Amended model
	Exa-cel	SoC	Comparison
Mortality	SMR: 1.25 (assumption)	SCD-specific mortality rate + mortality from complications	**Mortality:** Exa-cel: SMR = 1.25 (as original model) SOC: SMR by age = ICER report and Desai et al (2020)
Efficacy	96.6% VOC-free ('cured') at 12 months = no complications. Lifetime effect assumed. SoC complications (3.4%)	Baseline VOC rate assumed constant (4.2 yearly) VOCs predict complications (non-mutually exclusive) - big impact on QoL and costs.	
Quality of life (utilities):	Cured at 12 months: 0.92 Uncured at 12 months = SoC utility Disutility applied for transplant	0.81. Complication disutilities from literature: • -0.18 per VOC applied (based on TA743) • Acute complications (-0.05 to -0.57) • Chronic complications (-0.05 to -0.21)	
Costs	VOC-free at 12m: no complication costs. SoC complication costs otherwise	Complications increase costs. VOC = £1,567 Chronic complications range £24 to £314 monthly	

Abbreviations: SoC, standard of care; VOC, vaso-occlusive crisis; SMR, standardised mortality ratio; SCD, sickle cell disease; ICER, Institute for Clinical and Economic Review

Key issues that are not resolved

Largest ICER impact: non-reference case analysis, complications and model structure

Issues requiring committee decision	ICER impact	EAG view
Use of non-reference discount rate (1.5%) in the model	Large	Criteria for 1.5% discount not met
VOC rates used to predict complications	Large	Remove VOC as a predictor of events
Many complications included and based on assumptions	Large	Complications overestimated, use literature complication rates
Model: complications and mortality calculated unconditionally (non-mutually exclusive health states)	Moderate	Model overestimates complications and mortality, suggest alternative
Exa-cel treatment withdrawal in model was assumed to happen just after apheresis (blood stem cells collected)	Moderate	Include costs and outcomes of treatment withdrawals prior to infusion
Exa-cel utility value in the model is very high	Moderate	A lower value should be used
Model includes no adverse events (AE) for exa-cel	Small	Exa-cel-related AEs should be included
Exa-cel treatment effect	Unknown	Lack evidence to support lifetime ‘cure’
Limited clinical trial evidence	Unknown	Further data collection highly desirable
Issues for committee consideration		
Estimating impact on health inequalities	N/A	Defer to NICE
Managed access	N/A	Defer to NICE

Abbreviations: VOC, vaso-occlusive crisis; ICER, incremental cost-effectiveness ratio; AE, adverse events

The meeting will now move to Part 2a

Meeting in private with committee, EAG, company, experts

- Key issues in further detail
- Views from EAG and experts

NICE National Institute for Health and Care Excellence

NICE National Institute for Health and Care Excellence

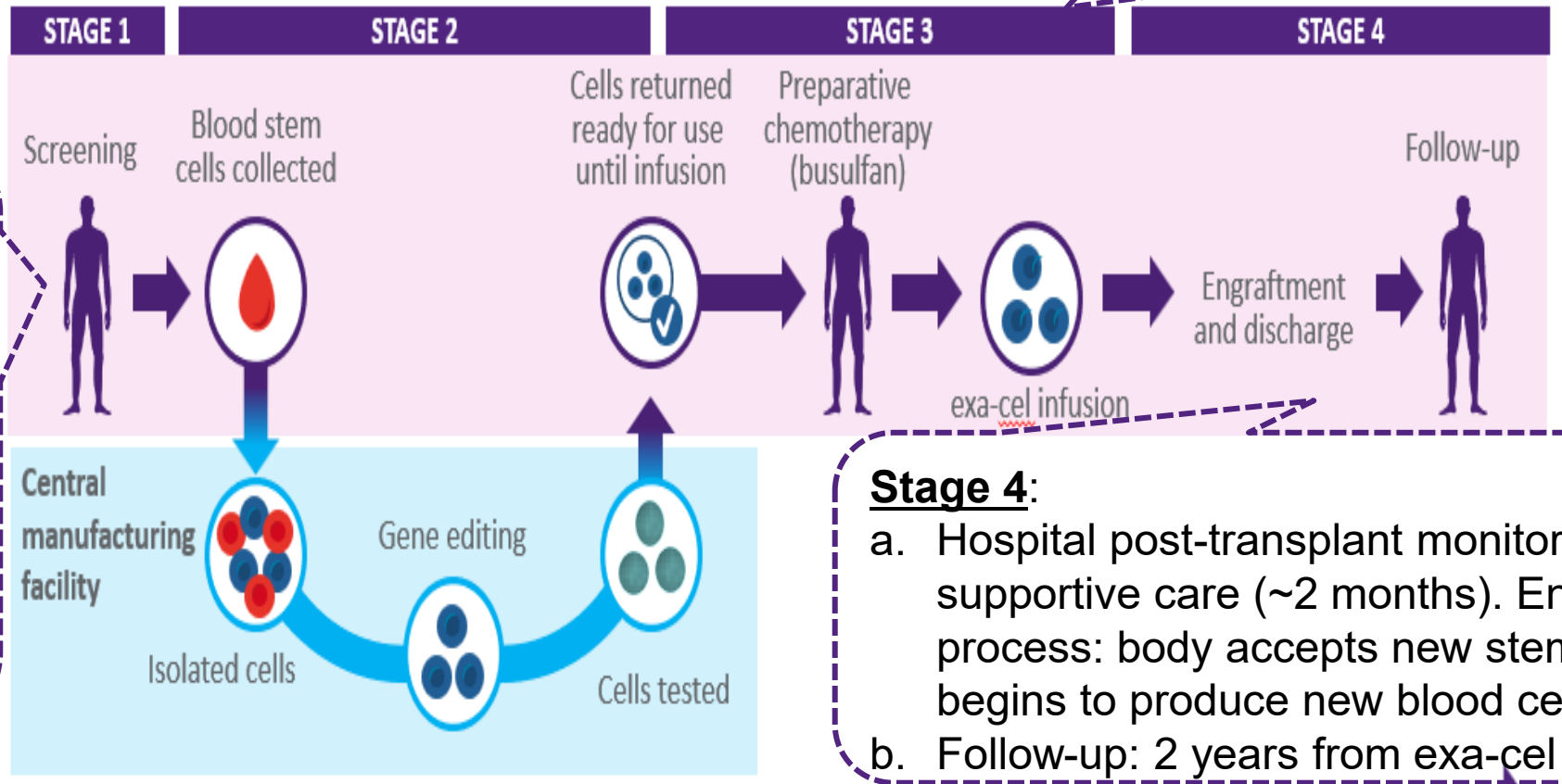
Thank you.

Supplementary slides

Exa-cel administration

Stage 2:
- Mobilisation: move stem cells from bone marrow into blood.
- Blood stem cells collected by apheresis (separates different blood cells), sent to manufacturing site and used to make exa-cel
- Exa-cel manufacturing/testing take >6 months from cell collection

Stage 3:
a. Myeloablative conditioning to clear cells from bone marrow, to be replaced with modified cells in exa-cel
b. Infusion of exa-cel: ≥1 exa-cel vials given intravenously



Stage 1:
- Informed consent
- Patient eligibility
- Red blood cell transfusions prior to mobilisation to achieve target sickle haemoglobin and total haemoglobin

Stage 4:
a. Hospital post-transplant monitoring and supportive care (~2 months). Engraftment process: body accepts new stem cells and begins to produce new blood cells.
b. Follow-up: 2 years from exa-cel infusion.

Additional clinical trial results

Additional outcomes from the D120 datacut

Efficacy endpoint	D120 (16-Apr-2023, FAS = 43*, PES = 29)*
Total Hb and HbF and concentration (mean [SD])	Hb: 12.0 (1.5) g/dL at 3 months; ≥ 12.0-13.5 g/dL up to month 24 HbF: 37.5% (9.05) g/dL; ≥ 39% g/dL thereafter
Proportion of patients with sustained HbF ≥20%	100% (29/29)
Proportion of alleles with intended genetic modification	CD34⁺ cells at 6 months: 86.1% (7.5%); ≥ 73.4% past month 12 Peripheral blood at month 3: 71.4% (10.1%); ≥ 69.9% past month 3
Changes in haemolysis biomarkers (month 24)	Reticulocytes (10^9/L) - mean (N): 106.75 (1/29) Indirect Bilirubin (µmol/L) - mean (N): 6.8 (1/29)
Reduction in transfusions	100% (29/29) reduction
F-cells over time	Mean (SD): 70.4% (14.0%) at month 3; ≥90% from 6 months
EQ-5D-5L (mapped to EQ-5D-3L)	Baseline: 0.81 (SD: 0.19); month 24: 0.88 (SD: [redacted])

*41/43 people in FAS had ≥60 days follow-up after last RBC transfusion
Outcomes for ASH datacut not presented – only one additional patients in analysis.

NICE

Abbreviation: VOC, vaso-occlusive crisis; FAS, final analysis set; PES, primary efficacy set; SD, standard deviation; Hb, haemoglobin; HbF, foetal haemoglobin; SD, standard deviation; RBC, red blood cell

Key issue: Adverse events

Overview of AEs before and after exa-cel infusion and overall

Visit	Enrolment to < exa-cel (n=58)	Exa-cel to month 24 (n = 43)
Patients with exa-cel infusion, n	-	43
Patients with busulfan dosing, n	35	43
Patients with any AEs, n (%)	56 (96.6)	43 (100.00)
AEs related / possibly related to exa-cel, n (%)	-	13 (30.2)
AEs related / possibly related to busulfan, n (%)	27 (77.1)	43 (100.0)
Grade 3 or 4 AEs	43 (74.1)	41 (95.3)
SAEs	38 (65.5)	16 (37.2)
SAEs related or possibly related to exa-cel	-	0
SAEs related or possibly related to busulfan	0	4 (9.3)
AEs leading to study discontinuation	0	0
AEs leading to death (*not related to exa-cel)	0	1 (2.3)*

Company

- SAS population (n=58, all who started mobilisation), median follow-up duration: 17.5 months [range: 1.2 - 46.2])
- Focus on AE from exa-cel infusion to month 24; >70% of SAE/grade 3+ AE occur in first 6 months after infusion.
- 0% of SAEs ≥6 months after exa-cel infusion were considered related/possibly related to busulfan or exa-cel.
- In long-term follow-up study CLIMB-131, no patients experienced AE/SAE related to exa-cel.
- All patients experienced AE, but most related to myeloablative conditioning with busulfan than exa-cel.

NICE

Abbreviations: AE, adverse events; SAE, serious adverse events; SAS, safety analysis set