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 8 May 2024, assessing ID4016 as a single technology appraisal

Chair: Paul Arundel

External assessment group: Warwick Evidence

Technical team: Cara Gibbons, Alan Moore, Jasdeep Hayre

Company: Vertex

RECAP

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

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

Background on sickle cell disease

RECAP

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)

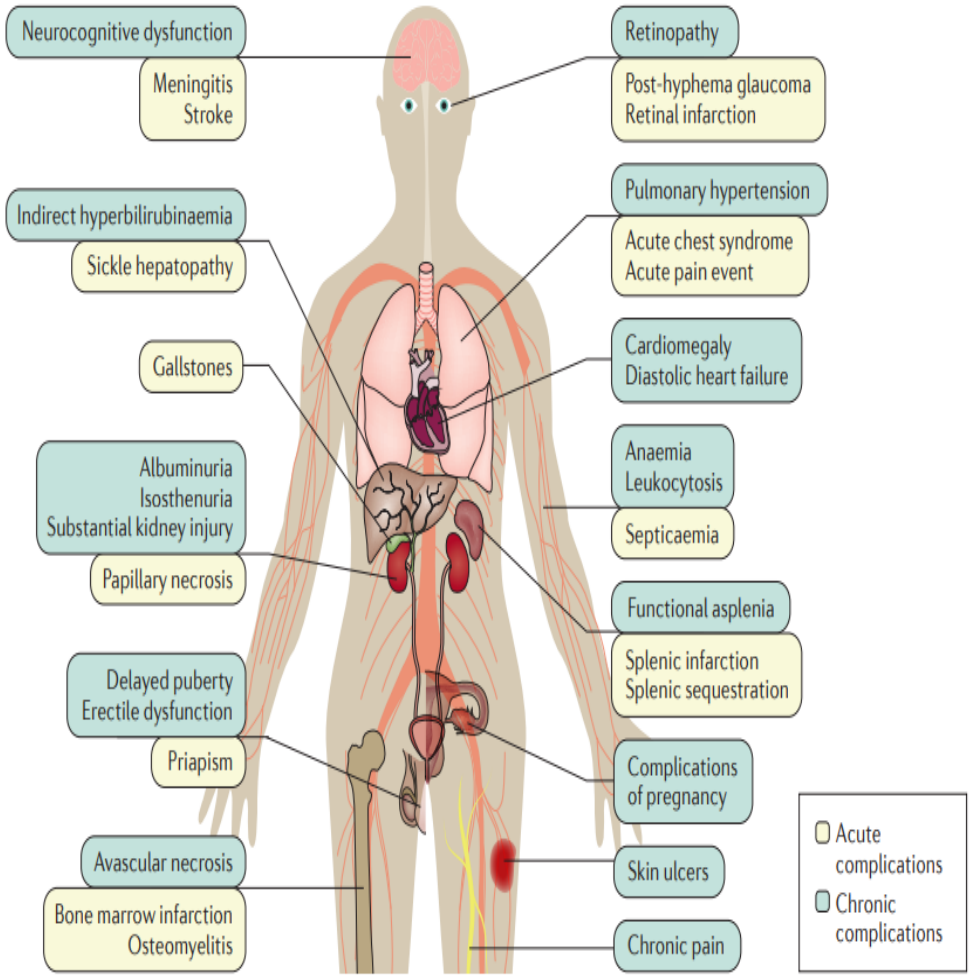
Symptoms and prognosis

- 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

Preliminary recommendation and conclusion

Exagamglogene autotemcel (exa-cel) is not recommended, within its marketing authorisation, for treating sickle cell disease (SCD) in people 12 years and over with recurrent vaso-occlusive crises (VOCs) who have a βS/βS, βS/β+ or βS/β0 genotype, when a haematopoietic stem cell transplant (HSCT) is suitable and a human leukocyte antigen-matched related haematopoietic stem cell donor is not available.

Rationale:

- NICE requires more information to address the uncertainties in the clinical and economic evidence.
- The acceptable cost-effectiveness estimate for exa-cel is higher than what NICE normally considers to be a cost-effective use of NHS resources. This is a reasonable adjustment to account for health inequalities and the innovative nature of the technology.
    - ↳ Even when taking this into account, the cost-effectiveness estimate for exa-cel is still above this. So, it is not recommended for routine use.
- Uncertainty in the cost-effectiveness evidence could be addressed through managed access, but the company has not proposed to collect data to fully address this.

Key issues

Unresolved issues for discussion	ACM1 conclusion	Draft guidance section
VOC definition	Hospitalisation VOC	3.10
Complications: estimation, source and ACS	Brousse et al (2023) severe population	3.11
Health utility (both exa-cel and SoC)	0.81 (SoC), 0.88 (exa-cel)	3.12
Exa-cel treatment withdrawals	Include costs and outcomes	3.14
Discount rate	1.5% criteria not met	3.15
Severity modifier	Not met	3.16
Committee considerations		
Uncaptured benefits	-	-
Health inequalities and innovation	Will adjust its acceptable ICER	3.17, 3.18, 3.19 3.20, 3.22
Managed access	Update managed access proposal	3.24
Resolved issues		
Limited clinical trial evidence	Requires additional data collection	3.5
Model structure	Alternative model	3.6, 3.7
SoC mortality	SMR - Desai et al (2020)	3.8
Exa-cel treatment effect	Requires additional data collection	3.9
VOCs used to predict complications	VOC should not predict complications	3.10
Exa-cel adverse events	Excluded	3.13

Abbreviations: VOC, vaso-occlusive crisis; ACS, acute chest syndrome; ICER, incremental cost-effectiveness ratio; SMR, standardised mortality ratio; SoC, standard of care

Key questions for committee

Issues	Key questions	ICER impact
VOC definition	Does the committee change its preferred VOC rate definition from hospitalisation VOCs to all-event VOCs?	Moderate
Complications: estimation, source and ACS	• Has the committee's preferred complication source changed from Brousse et al (2023) severe population ('literature') to Udeze et al (2023)? • If Udeze, which population should be used – severe SCD population, or 12-35 years SCD population? • If Udeze, should the data be matched to the CLIMB SCD-121 population? • Are complications estimated appropriately? Should ACS cost and outcomes be excluded?	Moderate
Health utility (exa-cel and SoC)	What utility values should be modelled for the SoC and exa-cel "functionally cured" population?	Moderate
Exa-cel treatment withdrawals	Does committee change its position of including costs and outcomes for people who withdraw from exa-cel?	Large
Discount rate	Should a 3.5% (reference case) or 1.5% (non-reference case) discount rate be applied?	Large
Severity modifier	Has the severity modifier been met? If so, which QALY weight should be applied?	Large

Abbreviations: VOC, vaso-occlusive crisis; SCD, sickle cell disease; SoC, standard of care; QALY, quality-adjusted life year; ACS, acute chest syndrome

Draft guidance consultation comments

Comments received from:

- **Web comments (including patients, carers, clinicians and public) (n=96)**
- **Patient expert and group comments from:**
  - Anthony Nolan and the Sickle Cell Society
  - 2 patient experts
- **Clinical expert & Professional group comments from:**
  - 2 clinical experts
  - British Society for Haematology
  - UK Forum on haemoglobin disorders
  - Royal College of Pathologists
  - Cell and Gene Therapy Catapult
- **Consultee comments, Vertex:**
  - Draft guidance response, updated managed access proposal
  - Revised base case

Web comments

Patients, carers, family, clinicians and public comments (1)

Impact of SCD	Current treatments
• Everyday life significant disrupted • Life-limiting, debilitating, unpredictable, and progressive condition • Significantly reduced life expectancy • Severity of SCD worsens overtime • Considerable QoL impact on patients and family • Symptoms e.g., fatigue, chronic pain, organ damage, other life-threatening health complications • Significant negative social, emotional, psychological and physical impact • Affects education, employment, finances • Severity and long-term organ damage has not been fully appreciated	• High unmet need for an effective, well-tolerated treatment • Frequent inpatient treatment interferes with daily life • Current treatments offer temporary relief and do not address underlying cause • Pain relief often fails, exacerbated by delays in following pain relief commissioning requirements, poor care, conflict and confrontation • Other treatment options have been withdrawn • Few African and Caribbean blood donors – need other treatment forms • Care and access to treatment options are extremely limited compared to other inherited conditions

Abbreviation: SCD, sickle cell disease; QoL, quality of life

Web comments

Patients, carers, family, clinicians and public comments (2)

Exa-cel	Wider considerations

• Exa-cel should be made available - innovative, one-time and safe treatment
• Long-term benefits:
  ○ reduces hospitalisations, costs and treatment
  ○ improves life expectancy and QoL
  ○ removes clinical, social, and economic burdens
  ○ halts bodily deterioration, enables repairs
• Dramatically change lives of patients and families
• QoL and survival benefits not fully addressed
• More research and data collection needed
• Treatment R&D will stop if always rejected, funding exa-cel will encourage new treatments
• Should be for available for those <12 and >35 years
• No biological mechanism for edited cells to revert
• Want the benefits for future generations
	• Mainly affects African and Caribbean communities – more likely to experience poverty, discrimination, barriers to accessing healthcare
	• Draft recommendation seen as discriminatory and people feel stuck, abandoned and forgotten
	• "Burden of proof" seems higher for SCD community to be taken seriously
	• Should consider factors broader than direct healthcare costs e.g., loss of earnings
	• Little trust in NHS and clinical professionals – lack of understanding and pain often not believed
	• Recognise exa-cel is an expensive treatment
	• Lack of equity and funding for SCD
	• QoL not captured e.g., cultural reasons, nature of SCD and patient adaptations
	• Cure would help to redress some inequalities

Abbreviation: R&D, research and development, SCD, sickle cell disease, QoL, quality of life

Anthony Nolan and the Sickle Cell Society

250+ responses from patients, parents, family members, clinicians and others

"My veins are a graveyard, a reminder of the many battles I have fought"

"Traumatic for all involved. Day to day life is a challenge."

"He says [son] it's as if more than one thousand ants are biting his bones from inside at the same time"

"It's a horrific condition, every day is a battle to prevent pain and as some of the triggers are things we have little control over, it's very difficult."

"I wake up every day in pain, and I go to sleep in pain, I have never known a pain-free" life

"It's not just the pain; it's the feeling of being trapped in your own body, unable to escape the torment"

"Living with sickle cell means living with constant fear." "Constant fear – fear of the next crisis, the next hospitalisation, the next brush with death"

"The spectre of a shortened life expectancy looms over me, a grim reminder of the fragility of my existence".

"I am stuck in a corner stagnant with nothing, but a heart full of sadness, and wishing and praying to one day wake up from this terrible nightmare of a life."

"1 in 16 people with SCD die before age of 18"

"Nothing could have prepared me for the sheer magnitude of their [child] suffering"

"All we want is a better quality of life, a pain free life, a long and healthy life"

"It's like a relentless storm that never lets up, slowly wearing you down until you feel like you can't go on. And it's not just the physical toll; it's the toll it takes on your spirit, your hopes, your dreams. I sometimes feel like I want to give up just for the pain to end"

Anthony Nolan and the Sickle Cell Society

Link to discount rate, utilities, severity

250+ responses from patients, parents, family members, clinicians and others

"This [exa-cel] would have been literally life saving for people like me who are suffering with this dreadful condition"

"Prospect of Exa-cel gives me hope, a glimmer of light in the darkness of my condition"

"Having SCD is like a death sentence because it comes with daily excruciating bone pain"

"It's difficult to convey as this is an invisible condition. Little awareness. Often, we are misbelieved"

"Patients have learnt to cope with their daily lives because of the lack of education and knowledge surrounding the illness due systemic racism, we've adapted to being unsupported"

"Only 50% of patients with SCD survive beyond their fifth decade"

"Sickle cell sufferers are living in agony in silence, we are not believed, [and] our pain is often disregarded"

"It's discerning when you have to be faced with how much others just don't care"

"[People with SCD] get used to QoL that would be considered restrictive by normal people"
"How I rate my QoL doesn't correlate with the reality of it"

"2013 study (sickle cell anaemia): average life expectancy of 42 years for women and 38 years for men"

"I am always in pain most times and am unable to work, or even enjoy my life"

"Its heart reaching to see the volume of pain they are in and knowing there isn't anything you can do to help them!"

"Severe cases frequent experience excruciating pain, debilitating fatigue, and increased susceptibility to infections and organ damage"

"Whenever we go to the hospital, we are treated differently, sometimes even being sworn at and told to be quiet during a painful sickle cell crisis."

Consultation responses: 2 patient experts

Understanding SCD

- Fundamental misunderstanding about nature, severity, and impact of SCD on QoL - lack understanding of treatment potential or reality for people with SCD
- VOCs understood but SCD is so much more than VOCs and its complications

EQ-5D is not suitable

- EQ-5D is not suitable, effective, or accurate in measuring SCD QoL - need a better suited tool
- Only fully understand dramatic difference between having SCD and not post-transplant

Allogeneic SCT experience

- It has changed my life hugely - my blood doesn't sickle, QoL difference is drastic - reality of being fitter, healthier, pain-free and able to do what I want is still a huge adjustment for me
- I am still dealing with legacy of SCD and organ damage that accompanies it

Current treatment options

- Lack of SCD treatments - current SoC offers improvements, but they are temporary and cumbersome
  - E.g., Hydroxyurea gave less frequent, but more painful and severe crises = increased complication risk

Wider considerations

- Consideration given to fact that SCD mainly affects black people of African origin, but equality considerations are not compatible with having a curative option
- There are funding discrepancies between SCD and similar conditions

Abbreviations: SCD, sickle cell disease, QoL, quality of life, VOC, vaso-occlusive crisis; SoC, standard of care; SCT, stem cell transplant

Consultation responses: 2 clinical experts

Disease severity

- In danger of failing this patient group once again - failing to acknowledge disease severity and impact and failing to provide a low risk, effective cure for those most severely affected
- Most data does not fully clarify clinical severity, mortality and morbidity risk or QoL impact

EQ-5D is not suitable

- EQ-5D is not appropriate for chronic lifelong disorders
- Fails to account for those who manage pain at home and days missed from work / education and reduction in life opportunities due to their underlying condition
- Does not account for long term benefits of reduction/removal of the polymerisation of sickle haemoglobin

Acute pain after exa-cel

- Acute pain can happen infrequently within the first year after allogeneic SCT e.g., people with frequent acute / chronic pain, history of high / frequent opioid use → likely similar reasons after exa-cel
  - Complicated - takes time to recover from acute/chronic pain and opioid reduction pain similar to SCD
  - Not lack of response and wrong to assume all pain is vaso-occlusion driven
- Pain diary studies: 1/3rd people report pain daily and most pain happens outside healthcare setting

Mortality

- Life expectancy studies give different results but there is no argument that people with SCD have a life expectancy that is around 2-3 decades less than general population

Return to near or full health

- Uncertain if exa-cel will reverse all chronic organ damage present before conditioning but seems unlikely.
- Exa-cel could enable near normal health, massive reduction in pain and prevent irreversible complications

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

Consultation responses from professional groups

NICE has received responses from the British Society for Haematology General Haematology Guidelines Task, Cell and Gene Therapy Catapult, UK Forum on haemoglobin disorders, Royal College of Pathologists

Mortality and disease severity

- Medical literature: clear evidence for reduced life expectancy, severely impaired QoL, and accumulation of complications and co-morbidities with age
- Some studies suggest improved life expectancy, but reality for UK clinicians is a peak in deaths after 40 years

Unmet need

- For a large group of people with SCD, there is no current therapy option (e.g., 10-20% cannot be transfused)
- Not considering exa-cel due to fears of little uptake reinforces current inequity and ongoing failures within our health systems for this much ignored community

EQ-5D is not suitable

- EQ-5D Overestimates QoL in long-term conditions such as SCD, must be taken as highly conservative
  - ↳ EQ-5D does not fully capture experience of people with severe SCD due to ceiling effects
- Other measures e.g., ASQ-ME, FACT-BMT, Pain NRS, are more validated assessment of SCD QoL

Return to near or full health

- People eligible will be treated before irreversible complications - exa-cel could return people to near normal health, life expectancy and QoL, and prevent future complications (as shown with allogeneic SCT)

Long-term treatment effect

- No biological plausibility that edit will not be permanent - first exa-cel patient still VOC-free after 5 years
- Underrepresentation of ethnic minorities in clinical trials = difficulty producing high quality data

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

Equality considerations

ACM1 committee conclusions:

- willing to accept a higher degree of uncertainty in the clinical effectiveness evidence for exa-cel
- an appropriate and reasonable adjustment to account for health inequalities is to adjust its acceptable ICER
- the acceptable ICER range was between £30,000 and £35,000 per QALY gained

Equality issues raised during consultation:

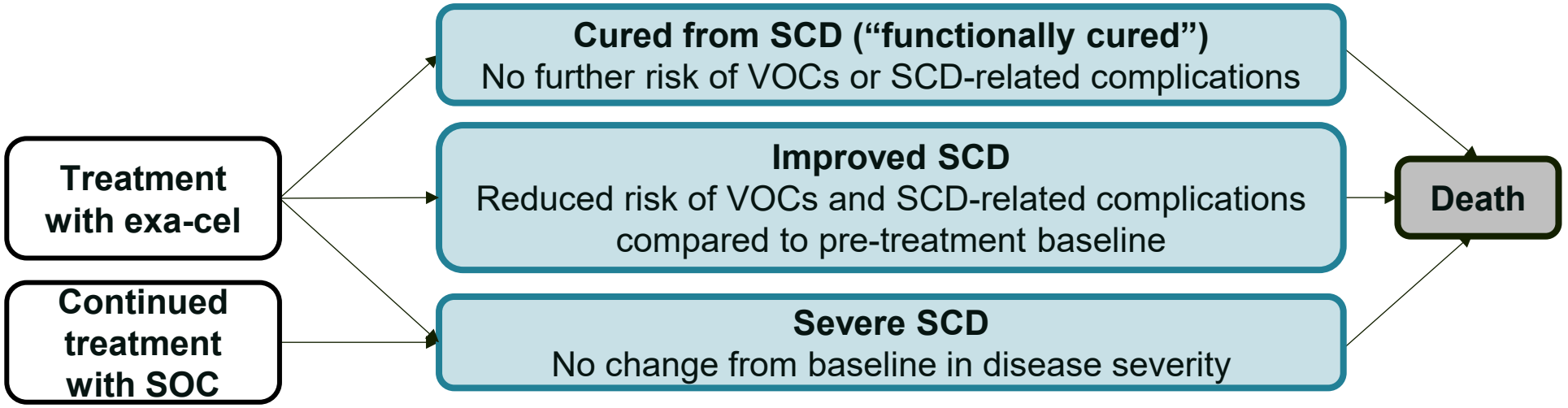
- Most UK SCD patients are of Black African and Caribbean heritage – more likely to experience poverty, discrimination, barriers to accessing healthcare and poorer health outcomes
- SCTAPPG 'No one's listening' report: highlighted issues of inequity, discrimination, racial bias, inequalities to access treatment, stigmatisation and a lack of understanding and prioritisation towards SCD patients
- Careful consideration needs to be given to the ethnic, faith and cultural needs/aspects of individuals who are being offered this treatment
- Recommendation disadvantages people with SCD who do not have suitable stem cell donor so cannot receive HSCT
- Recommendation disadvantages adults with SCD – NHS commissioning criteria allows children to receive HSCT using any donor e.g., matched unrelated donors. Most adults do not have fully matched sibling donor
- Need pre-treatment or conditioning with busulfan before exa-cel, which may affect fertility

Abbreviation: SCD, sickle cell disease; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; HSCT, hematopoietic stem cell transplant; SCTAPPG, All-Party Parliamentary Group for Sickle Cell and Thalassaemia

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model (updated post ACM1)



Input	Source / method
Time horizon, cycle length	Lifetime (model start age: 21.2), 1 month (half-cycle correction)
Discount rate	1.5%. (3.5%)
Treatment waning	No. If 12 months VOC-free, assumed "functionally cured" (96.6%)
Annual VOC frequency	CLIMB SCD-121 baseline VOCs (all VOCs): 4.2 a year (hospitalisation VOCs: 2.6 a year)
Acute and chronic complications	Modelled independently based on disease status Source: Udeze et al (2023) / Brousse et al (2023) severe population
Mortality	Exa-cel (cured): general population mortality + SMR SoC: SMR (Desai et al [2020] and ICER report [2023])

Complications

Acute (last one cycle)

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

Chronic (permanent)

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

Key **Committee preference at first committee mtg**

Note: model accounts for SoC healthcare costs across time horizon (lifetime)

Abbreviations: VOC, vaso-occlusive crisis; SCD, sickle cell disease; SMR, standardised mortality ratio; SoC, standard of care; ICER report; institute for clinical and economic review

Key issue: Exa-cel treatment withdrawal in the model (1)

Company removed treatment withdrawal outcomes and exa-cel cost from base case

ACM1 conclusions

- Costs and outcomes of treatment withdrawals (19%) after apheresis and before exa-cel infusion should be included in model

Company

- Acknowledge other ATMPs companies have accepted modelling of cost and outcomes of cell collection
- Model applies cost uplift equal to the proportion of patients who withdraw to pre-transplant costs
  - Removed outcomes - unreasonable to include as it artificially dilutes exa-cel efficacy
- [redacted]
- Withdrawals mainly due to nature of SCD e.g., difficulty collecting cells, rather than treatment related
  - ↳ Many reasons clinical trial related e.g. experimental nature led to consent withdrawal → less likely now
- Uncertainty about proportion who will have cell collection but do not have treatment in clinical practice – knowledge and expertise on apheresis is increasing, as is the support for centres providing it
  - Company scenario: Company scenario: include outcomes (but not exa-cel cost) for [redacted]% ([redacted]) of withdrawals – accounts for those who do not have exa-cel due to inability to manufacture drug product. Expect other withdrawal issues would not occur in clinical practice

Abbreviations: ATMP, advanced therapy medicinal product; SCD, sickle cell disease

Key issue: Exa-cel treatment withdrawal in the model (2)

EAG believe that including costs and outcomes for all that start treatment pathway is a fundamental health economic requirement

EAG comments

- Company added unusable functionality to incorporate costs and outcomes, substantially reduced drop-out rates without justification ([redacted]%) and assumed no costs for exa-cel
- Withdrawal reasons not related to access inequalities, but instead technical reasons
  - ↳ All participants provided biological material, but some did not reach minimum requirements
- [redacted]
- Removing outcomes would violate basic HTA principle of using ITT population efficacy
  - In any cost-effectiveness problem, outcomes for people who do not remain compliant to treatment always remain part of the ITT, regardless of the reason for non-compliance.
- Company's model functionality assumes no consequences for people that withdraw and does not consider increased costs / impact of disutilities and fatalities after apheresis
- Impossible to predict who in clinical practice will remain compliant and who will not have sufficient cells

Other considerations

- RCP: Hard to predict exact figures in practice - 19% is much higher than other conditions
  - May be due to nature of SCD, inequalities, way people interact with health care system
- NHP: in clinical practice - 22% decide not to have SCT despite approval, 76% proceed to treatment

Does committee change its position of including costs and outcomes for people who withdraw from exa-cel?

NICE

Abbreviations: SCD, sickle cell disease; RCP, Royal College of Pathologists; ICER, incremental cost-effectiveness ratio; NHP, National Haemoglobinopathy Panel; ITT, intention to treat; HTA, health technology assessment

Key issue: Complication – estimation, source and ACS (1)

Company prefer to use Vertex BOI study (Udeze, 2023) to model SCD complication rates

ACM1 conclusions

- Estimating complications from Brousse et al. (2023) severe population is most appropriate but there is uncertainty associated with estimated frequency of SCD complications
- **EAG:** acute chest syndrome was modelled as an independent complication, and included within definition of a VOC - cost and disutilities associated with acute chest syndrome double counted

Company

Estimation

- Claim error in EAG calculations → corrected = more realistic predictions (peak prevalence ~ 42-45 years)
  - EAG did not appropriately incorporate baseline prevalence into point prevalence calculations = invalid results (peak complication prevalence 25-27 years) = clinically unrealistic

Source

- Preferred base case: Vertex unpublished UK BOI study (Udeze et al, 2023) severe SCD population (≥2 VOCs per year ≥2 consecutive years) – more robust, relevant population:
  - Brousse does not report data for 6 complications, Udeze reports data for all modelled complications
  - Udeze incidence reported as rate per 100 person-years, so not reliant on assumptions regarding follow-up duration (EAG assumed 7-year follow-up as Brousse did not report average follow-up)
  - Definition and study criteria of VOC rate in Udeze aligns with CLIMB SCD-121
- Alternative base case: 'Literature' (committee preferred source), complications derived from multiple literature sources, e.g. Brousse et al (2023) severe population

ACS: Corrected double counting of ACS, only applies if BOI study source for complications data used

Abbreviations: VOC, vaso-occlusive crisis; SCD, sickle cell disease; SoC, standard of care; BOI, burden of illness; ACS, acute chest syndrome

Key issue: Complication – estimation, source and ACS (2)

Both complications rates may reflect outcomes from a more severe population

EAG comments

Estimation

- Accept changes but model remains structurally affected by double counting of events and mortality = inflated complication rates
  - All chronic complications calculations are not calculated conditionally to mortality in same cycle
  - Baseline prevalence should not be incorporated in forward rates estimation
- EAG not attempted to correct errors - model estimates are unreliable
- Reiterate original recommendation: model should be rebuilt using correct heath economic methodology

ACS

- Sources used in appraisal (CLIMB SCD-121; Udeze, 2023; Brousse, 2023) include ACS in VOC definition
  - ↳ Cost and outcomes already captured so should exclude from model. Company's base case did not exclude

Source

- 'Literature' = literature-derived data from 7 studies including Brousse et al (2023) and Shah (2019)
  - Complication rates lower than Udeze (2023), despite similar severity inclusion criteria
  - Literature far from accurate data to allow EAG to identify rates best matched to decision population
  - Rates mostly Brousse 2023 → hospitalisation VOCs align with trial, but rates by age not provided for most outcomes

Abbreviation: VOC, vaso-occlusive crisis; SoC, standard of care; SCD, sickle cell disease; ICERs, incremental cost-effectiveness ratio; ACS, acute chest syndrome

Key issue: Complication – estimation, source and ACS (3)

EAG prefer to use Udeze (2023) 12-35 years subgroup data to calculate complications

EAG comments continued

Udeze population is more severe than CLIMB SCD-121

- Baseline VOC rate in severe population double CLIMB SCD-121 (8.6 vs 4.2 per year)
- Includes people below 12 years (20%) and over 35 years (23%) – drives complication rates
- 12-35 group (all severity) has 50% higher baseline VOC (6.4 per year vs 4.2 per year)
- No hospitalisation VOC data reported
- Company has not matched Udeze data to CLIMB SCD-121 population

Udeze data may lack predictive validity for decision problem population (sicker than eligible population)

- Baseline comorbidities not comparable:
  - Model: assumes none except 14% retinopathy and 3% neurocognitive impairment
  - Udeze: unclear if baseline comorbidity is not reported or is much higher than model
- Udeze complication rates calculated with people who had other complications at baseline – reasonable to assume risk of new event higher if have history of other complications
  - ↳ Overestimates complication risk in model for appraisal population who had no baseline comorbidity

Immediate solution: use Udeze et al (2023) 12–35 years subgroup population

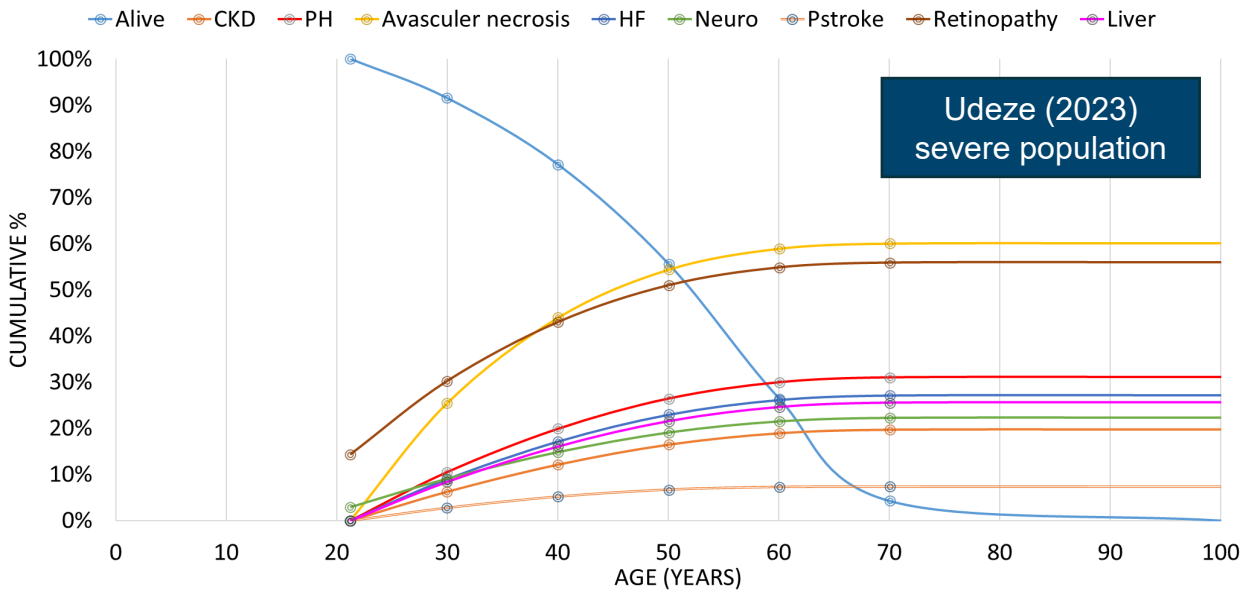
- Complications still uncertain because subgroup more severe = overestimate burden averted by exa-cel
- More robust solution: match Udeze 12-35 data to CLIMB SCD-121 by age and baseline VOC rate – should reproduce almost baseline complication free population

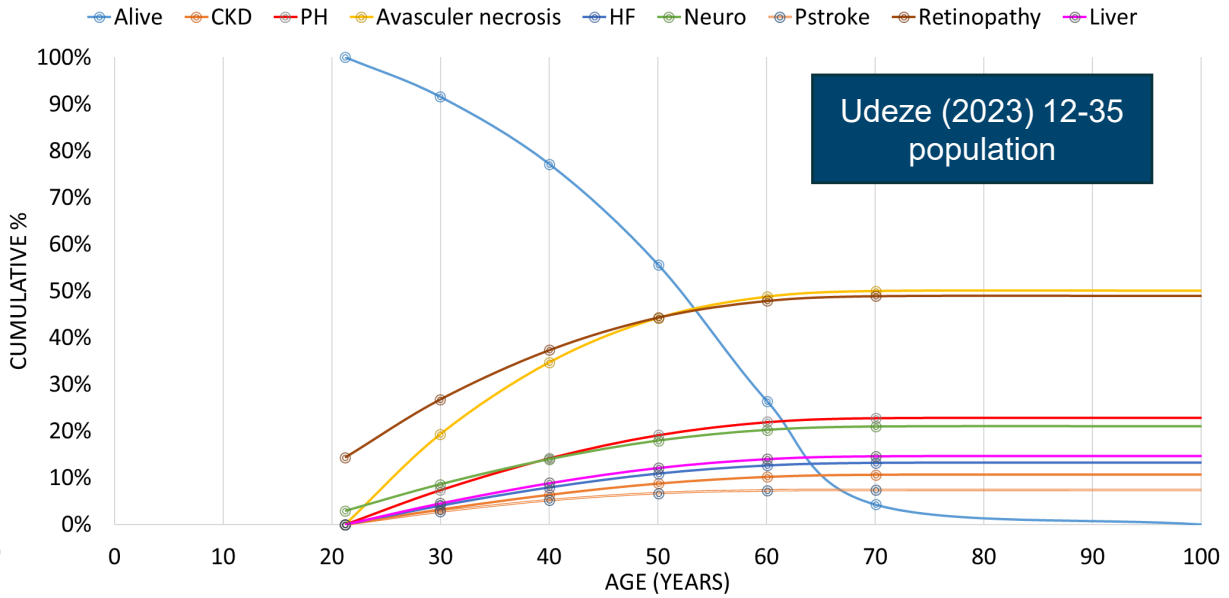
NICE

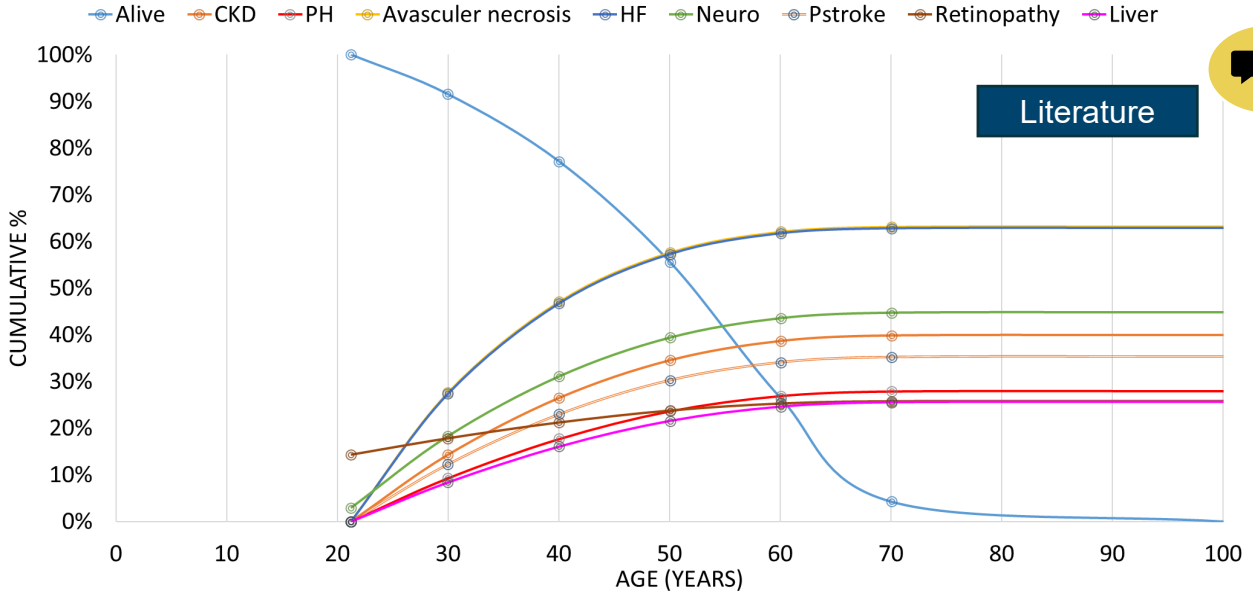
Abbreviation: VOC, vaso-occlusive crisis; SoC, standard of care; SCD, sickle cell disease; ACS, acute chest syndrome

Key issue: Complication – estimation, source and ACS (4)

Graphs of the proportion of people with chronic complications over the time horizon







- Has committee's preferred complication source changed from Brousse et al (2023) severe population ('literature') to Udeze et al (2023)?
- If Udeze, which population – severe, or 12-35 years?
- If Udeze, should the data be matched to trial population?
- Are complications estimated appropriately? Should ACS cost and outcomes be excluded?

Abbreviation: SCD, sickle cell disease; CKD, chronic kidney disease; HF, Heart failure; Pstroke, post stroke; PH, Pulmonary hypertension; ACS, acute chest syndrome

Key issue: Baseline VOC definition (1)

Company believe all VOCs definition should be included in the economic model

ACM1 conclusion

- CLIMB SCD-121 VOC definition: all VOCs treated in hospital (inpatient / day case) (baseline rate: 4.2 per year).
- Alternative definition: VOCs that lead to inpatient hospitalisations (baseline rate: 2.6 per year)
  - EAG prefer - removes need to model exa-cel relapse rate and allows consistency throughout model
- Committee: hospitalisation VOC definition is the most appropriate for decision making

Company

- Inconsistencies related to baseline VOC definition are now resolved
- Non-hospitalised VOCs after exa-cel are not a relapse as HbF %, Hb concentration and allelic editing is stable
- No biological difference between VOC needing in-patient hospitalisation or needing a day unit
- All VOCs impact QoL, complications, life expectancy, health care resources, and long-term outcomes
- Hospitalisation related to multiple factors, and many avoid it - DG 3.1: "*Patient experts explained that the severity of pain often requires hospitalisation, but that some people avoid seeking hospital treatment…because there is a large variation in the care offered…and people…often feel stigmatised by healthcare professionals*"
- Most mortality and complication data in model come from unselected populations and aligns with trial definition

Abbreviations: VOC, vaso-occlusive crisis; Hb, haemoglobin; HbF, fetal haemoglobin; QoL, quality of life

Key issue: Baseline VOC definition (2)

EAG prefer to use hospitalisation VOC rate

EAG comments

- EQ-5D captures impact of VOCs that do not lead to hospitalisations, i.e., pain episodes
  - ↳ EQ-5D directly and explicitly includes pain score → adding correction for pain would double count
- Data used in model should be similar to appraisal population so can extrapolate data through time horizon (e.g., similar study inclusion/exclusion criteria and observed number of VOCs at baseline)
  - E.g., Udeze data meets ≥2 VOC inclusion criterion, but baseline VOC not equal (8.6 vs 4.2 per year)
- Most literature studies use a definition of VOCs based on hospitalisations or hospitalisation codes
- Data in model is more severe than model population → much higher baseline VOC rates than CLIMB SCD-121 = extrapolating rates overestimates treatment effect
  - Trial efficacy may not be representative of efficacy for people with a much higher VOC rate – applying this may bias model results and may increase uncertainty in the cost-effectiveness

Other considerations (RCP, patient expert, web comments):

- Most people try and manage painful crises at home and avoid seeking treatment due to previous negative experiences, stigmatisation and discrimination
- Data on hospitalisation will inevitably underestimate the frequency of pain and its effect on patients' lives

Does the committee change its preferred VOC rate definition from hospitalisation VOCs to all-event VOCs?

Abbreviations: VOC, vaso-occlusive crisis; RCP, royal college of pathologists; BOI, burden of illness

Utility values (1)

Company explain that without treatment, QoL would continue to deteriorate as people age and accumulate further co-morbidities.

ACM1 conclusions

- SoC utility value (SCD without complications): 0.81 (based on CLIMB SCD-121 baseline EQ-5D score)
  - ↳ Need further exploration of modelled SoC baseline utility and disutilities over time in the model
- Exa-cel "functionally cured" utility: 0.88 (not 0.92 based on 0.11 change from baseline to 24 months)

Company:

SoC utility

- QoL has been accurately captured in model (Baseline utility: 0.81, accounting for disutilities: [redacted])
  - Captured at point exa-cel given, before people develop significant complications that characterise SCD
- Baseline value includes [redacted]% with EQ-5D = 1 (perfect health) = significant ceiling effects
  - EQ-5D fails to fully capture QoL impact of SCD = unrealistic that someone would be willing to trade off perfect health for a burdensome transplant with an experimental treatment
  - Post-hoc scenario analysis excluding those with baseline utility of 1: [redacted]

Exa-cel utility

- Exa-cel exceeded minimal clinically important difference across all QoL measures in CLIMB SCD-121
- Literature supports the QoL gains at 24 months, particularly if no post-HSCT complications e.g., GVHD
  - E.g., Brien et al (2009): severe SCD pre-HSCT utility 0.70; post-HSCT 0.95
- Post-hoc scenario analysis (excluding utility values = 1), utility gain from baseline to 24 months: [redacted]
  - Consistent throughout follow-up, not affected by sample bias and shows 0.11 change is conservative

Abbreviation: SoC, standard of care; SCD, sickle cell disease; QoL, quality of life; GVHD, graft vs host disease; HSCT, hematopoietic stem cell transplant

Utility values (2)

Graph showing the modelled SoC utility, accounting for complication disutilities

Abbreviation: SoC, standard of care

Utility values (3)

EAG prefer to use the committee's preferred utility for exa-cel of 0.88

EAG comments

- Prefer committee's 'functionally cured' utility of 0.88, company's value (0.92) still affected by selection bias
- High baseline utility values may not be a ceiling effect, could be due to trial population being relatively healthier than general severe SCD population
  - Other indicators of this misalignment e.g., prognostic data, mortality data and complication data
- Post-hoc analysis – unclear what data this offers, bias in utility gain is larger than original bias
  - Very risky approach - implies arbitrary selection of data from the clinical trial to fit the decision problem at hand. Such approach violates established methodology.
  - Using these values creates inconsistency between efficacy rates (for entire trial population) and utility values (selected to reflect relatively most severe population)
  - Baseline VOC rate likely to differ between the whole sample and the selected sub-sample

Scenario	SoC utility	Change from baseline (months)	"Functionally cured" utility
Committee ACM1 preference (EAG base case)	0.81	0.07 (12)	0.88
1 (company base case)	0.81	0.11 (24)	0.92
2	0.81	[redacted] (24)	[redacted]
3	[redacted]	0.11 (24)	[redacted]
4	[redacted]	[redacted] (24)	[redacted]

Abbreviation: SoC, standard of care; SCD, sickle cell disease; VOC, vaso-occlusive crisis

Utility values (4)

Link to additional patient, family and carer testimonies

EQ-5D is not suitable, appropriate, effective, or accurate in measuring QoL in SCD

Other considerations from patient and clinical experts and groups and web comments:

- EQ-5D does not fully capture the experience of patients with severe SCD due to ceiling effects.
  - Overestimates QoL in long-term conditions such as SCD - must be taken as highly conservative
  - Other measures e.g., ASQ-ME, FACT-BMT, Pain NRS, are more validated assessment of SCD QoL
  - Fails to account for those who manage pain at home and days missed from work / education and reduction in life opportunities due to their underlying condition.
  - Does not account for long term benefits of reduction/removal of the polymerisation of sickle haemoglobin
- People have learnt to cope with their daily lives - never known a normal life or can compare to what an expected / normal QoL is
- "*When you've lived with SCD your whole life you take for granted adaptations you've made to survive. You get used to a QoL that would be considered restrictive by normal people. You accept the futility of complaining about what can't be changed and just get on with it*."
- "*How I rate my QoL doesn't correlate with the reality of it. In reality, if I was cured of SCD my life would change significantly and it's difficult to conceptualise that for someone looking from the outside seeing an apparently healthy person*."

What utility values should be modelled for the SoC and exa-cel "functionally cured" population?

Abbreviation: SoC, standard of care; SCD, sickle cell disease

Key issue: Non-reference 1.5% case discount rate (1)

Exa-cel did not meet the 1.5% discount rate criteria at ACM1

NICE methods

4.5.3: Committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects, if, in the committee's considerations, all of the following criteria are met:

1. Technology is for people who would otherwise die or have a very severely impaired life
2. It is likely to restore them to full or near-full health
3. The benefits are likely to be sustained over a very long period

ACM1 conclusions

1. Insufficient evidence - need further exploration of modelled SoC baseline utility and disutilities over time
   - uncertainty around the life expectancy for people with severe SCD
   - no evidence presented suggesting EQ-5D does not capture QoL for people with severe SCD
2. Considerable uncertainty with the likelihood of exa-cel returning people to full or near-full health
   - understand exa-cel would reduce risk of complications, but unclear whether persistent damage from complications and comorbidities would be reversed
   - may be plausible, but the uncertainty compounded by the short-term follow up of the clinical effectiveness evidence – further data collection could allow committee to consider if this is met
3. May be plausible that exa-cel benefits are sustained over a long period. But this is highly uncertain given the limited follow up of clinical evidence. Would like to see this explored with further data collection

Abbreviation: QoL, quality-of-life; SCD, sickle cell disease; SoC, standard of care

Key issue: Non-reference 1.5% case discount rate (2)

Company base case applies the non-reference case 1.5% discount rate

Company

1. SCD characterised by unpredictable episodes of severe pain, chronic haemolytic anaemia, widespread organ damage, shortened life expectancy, and associated with substantial impact on HRQoL
- Patient expert (DG, 3.1): "*could not remember a day without pain, whether that be mild, moderate, or severe*"

Early mortality:

- 5 SCD studies (3 UK): mean death age: 42-58 years (all SCD); 40-44 years (severe SCD)
  - Desai et al (2020): mortality incidence, 27.3% are 19-35 years old (model mortality source)
- Life expectancy significantly reduced compared to UK general population (median age: 81.8 years [males]; 85.5 years [females]) - reduction more pronounced in severe UK SCD patients (40.2 years, BOI study)

Severely impacted QoL:

- Complications inevitably worsen with age and are not stopped by current therapies
  - UK severe SCD cohort analysis (n=9,503): average co-morbidities 2.5 over 10-years; 63.2% had 2+
- Agree EQ-5D only partially captures SCD QoL impairment - people adapt and underestimate QoL burden
  - Baseline EQ-5D (0.81) vs UK (18-24 years) population norm (0.93) - reduction significant and clinically meaningful, but not representative of majority of SCD patients
    - ↳ Mean: 0.81 (skewed by [redacted]% in PES reporting full health), minimum: 0.2, ~20% were less than 0.55
  - Literature supports lower EQ-5D values in comparable SCD populations (0.39 – 0.75)
- Yearly hospital visits: 22.2 (UK severe SCD population) vs 2.6 (matched controls) - substantial burden

Abbreviation: HRQoL, health-related quality-of-life; SCD, sickle cell disease; QoL, quality of life; DG, draft guidance; BOI, burden of illness; PES, primary efficacy set

Key issue: Non-reference 1.5% case discount rate (3)

Company base case applies the non-reference case 1.5% discount rate

Company

2. People eligible for exa-cel will not yet have developed significant, irreversible complications
    - First exa-cel patient testimony: "*I no longer have pains…take opioids… have hospital stays or receive blood transfusions. I get to participate with my kids…join them in their activities… cheer them on at their dances… just be here just to play with them, knowing I no longer have to leave them to go to the hospital*"
    - CLIMB SCD-121 shows clear long-term benefits of exa-cel (27/29 remain VOC free)
        - Rapid and persistent HbF increase (40% HbF concentration at 6 months) prevents vaso-occlusion and new complications, halts/reverses existing complications, reduces haemolysis, resolves anaemia
        - Substantial evidence supporting return to full or near-full health in SCD post-HSCT outcomes
    - Exa-cel will return QoL to population norms – clinically meaningful increases in 5 different QoL measures
3. Genetic editing with exa-cel results in a permanent and durable effect (trial: 24m, 15 people with mean HbF % of 42.2%), with long-term amelioration of SCD and no known mechanism to revert edited HSC
    - Small number of acute pain events - do not represent VOC, treatment failure or lack of response
        - Clinical experts: events from people with chronic pain – not related to additional VOC complications
        - Literature: 1 in 5 after SCD HSCT continue to have acute pain events in the 12 months post-HSCT
        - 2 people with acute pain events in trial had sustained HbF % at 24 month – despite pain event, exa-cel is providing durable, stable benefit that allow rapid recovery from complications

Abbreviation: HRQoL, health-related quality-of-life; SCD, sickle cell disease; SoC, standard of care; HSCT, haematopoietic stem cell transplant; HbF, foetal haemoglobin; VOC, vaso occlusive crisis; QoL, quality of life

Key issue: Non-reference 1.5% case discount rate (4)

EAG think that non-reference discounting should not be applied

EAG comments

- Given relatively short follow-up, no certainty that exa-cel benefits are likely to be sustained for long period
- Exa-cel may halt SCD progression, but no evidence, direct or indirect or based on ACM1 clinical opinion, that exa-cel will revert the health of all patients to full health, particularly those with history of SCD complications

Mortality:

- Company think life expectancy 40-44 years - limited studies provided to support this
  - Study populations more severe than decision problem, did not include data for older people (deaths captured will occur at a young age, so mean death age lower than overall SCD population)
  - Company: no data because no deaths – not true e.g., Jiao et al (2023) has age group with mean age 73 years. Company have not included databases where these cases recorded
- Company accepted mortality modelling (mean age 52 years)
- Evidence showing 50 years is a reasonable lower bound for life expectancy for this decision problem

Other considerations from UK Forum on haemoglobin disorders (UKFHD)

- Struggle to comprehend not recognising SCD as a severe condition, with people living severely impaired lives
- Even best-case data has people with SCD dying 20 years before their matched birth cohorts without condition
- Our real-world experience: people die 30+ years before age-matched unaffected population
- UK National Haemoglobinopathy Registry (n=13000, 2020/21 report) confirmed as many people with SCD die aged 19-45 years as do over 46 years. UKFHD clinicians report this to be their real-world experience

Abbreviation: SoC, standard of care; SCD, sickle cell disease; QoL, quality of life; HbF, fetal haemoglobin

Key issue: Non-reference 1.5% case discount rate (4)

Fundamental misunderstanding about nature, severity, and impact of SCD on QoL

"The spectre of a shortened life expectancy looms over me, a grim reminder of the fragility of my existence"

"I am always in pain most times and am unable to work, or even enjoy my life"

Other considerations from patient and clinical experts and groups and web comments:

- Failing to acknowledge disease severity and impact and failing to provide a low risk, effective cure for those most severely affected
- Most data does not fully clarify clinical severity, mortality and morbidity risk or QoL impact
- SCD is a serious condition which detrimentally affects both quality of life and life expectancy of sufferers
  - 82% of people say SCD has either a negative impact or very negative impact on their QoL
  - No question that repeated episodes of pain requiring hospital admission, chronic pain and fatigue, and the increasing risk of morbidities, must severely impair life.
- UK mortality rate for people with SCD is alarmingly high - estimated 1 in 16 die before age of 18
  - People with SCD have life expectancy around 2-3 decades less than general population
  - Reality for UK clinicians is a peak in deaths after 40 years

"Having SCD is like a death sentence because it comes with daily excruciating bone pain"

"It's not just the pain; it's the feeling of being trapped in your own body, unable to escape the torment"

Should a 3.5% (reference case) or 1.5% (non-reference case) discount rate be applied?

NICE

Abbreviation: SCD, sickle cell disease; QoL, quality of life

Link to additional patient, family and carer testimonies

QALY weighting for severity

Link to additional patient, family and carer testimonies

Estimated QALY shortfalls for different base cases

Scenario	General population QALEs	QALYs with SoC	Absolute (proportional) QALY shortfall	Weight
Company base case	22.53	9.91	12.61 (56%)	x1.2
EAG base case	22.53	11.44	11.09 (49%)	x1
Company base case: 'Literature' source	22.53	9.59	12.94 (57%)	x1.2
EAG base case: 'Literature' source	22.53	10.19	12.34 (55%)	x1.2

NICE methods manual 6.2.17: calculate severity weighting using the reference case discount rate (3.5%)

Key for applying severity modifier

QALY weight	Absolute shortfall	Proportional shortfall
x1	Less than 12	Less than 0.85
x1.2	12 to 18	0.85 to 0.95
x1.7	At least 18	At least 0.95

Company:

- Progressive diseases where mortality increases and HRQoL deteriorates substantially over time are unfairly penalised by discounted QALY approach. HST, where undiscounted QALYs are used is more appropriate
- Where case for non-reference discount rate, no discount rate, or 1.5% discount rate should apply in QALY shortfall calculation – in this scenario, 1.7 QALY weight could apply

Other considerations from patient and clinical experts and groups and web comments:

- Strongly feel that the severity of SCD has been misjudged, severity for those living with SCD has not been fully appreciated
- SCD is a severe condition & patients die very prematurely (late 30s / early 40s), even with best available treatment
- There are potential gaps in knowledge and evidence concerning SCD severity and the impact on QoL.

Has the severity modifier been met? If so, which QALY weight should be applied?

NICE

Abbreviations: SoC, standard of care; QALE/Y, quality-adjusted life expectancy/year; SCD, sickle cell disease; QoL, quality of life; HRQoL, health-related quality of life; HST, highly specialised technology

Managed access (1)

Company has submitted an updated managed access proposal

The committee can make a recommendation with managed access if:

- The technology cannot be recommended for use because the evidence is too uncertain
- The technology has the **plausible potential** to be cost effective at the **currently agreed price**
- New evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- Data could feasibly be collected within a reasonable timeframe (≤**5 years**) without **undue burden**

ACM1 conclusions:

- Trial data would provide additional follow up on people who had exa-cel. Would reduce uncertainty about:
  - durability of treatment effect, particularly if data captured people followed for longer than 2 years
  - whether people return to full or near full health or have any complications.
- May be difficult to collect data on all of its uncertainties within a managed access timeframe.
- Exa-cel did not meet criteria to be considered for a recommendation with managed access because:
  - does not have plausible potential to be cost effective at currently agreed price
  - current managed access proposal would not collect data to address many of committee's uncertainties.
- Would like updated managed access proposal with more detail on these uncertainties would be addressed

Abbreviations: RWE, real world evidence; ICER, incremental cost-effectiveness ratio; HRQoL, health-related QoL

Managed access (2)

Company has submitted an updated managed access proposal

Uncertainty	Proposed data collection source to resolve uncertainty	Length of data collection
Durability of the treatment effect of exa-cel (relapse rate)	CLIMB SCD-121, CLIMB-131	Up to 3.5 years
	PASS EBMT Registry	Up to 3 years
Rates of complications for exa-cel	CLIMB SCD-121, CLIMB-131	Up to 3.5 years
	PASS EBMT Registry	Up to 3 years
Whether people return to full health after exa-cel or whether complications persist	CLIMB-131	Up to 3.5 years
	PASS EBMT Registry	Up to 3 years
Number of exa-cel treatment withdrawals before the infusion is given	Vertex Connects™	Up to 3 years
Generalisability of trial population (age)	PASS EBMT Registry – age of post-authorisation patients at pre-mobilisation stage of exa-cel treatment process	Up to 3 years
Mortality and life expectancy for exa-cel	CLIMB SCD-121, CLIMB-131	Up to 3.5 years
	PASS EBMT Registry	Up to 3 years
SoC uncertainties: utility values, rates of complications, mortality and life expectancy	SLR/most relevant and up to date evidence at end of managed access (to be determined)	Up to 3 years

Note: managed access team will review the proposal after ACM2

Abbreviations: SoC, standard of care

Uncaptured benefits

Carer QoL issues raised during consultation:

- Should consider carer QoL in most appropriate ICER threshold, beyond flexibility given to health inequality
- SCD has substantial impact on caregiver QoL e.g., ability to maintain employment and results in higher degrees of depression, anxiety, stress and significantly lower HRQoL relative to those not caring for SCD patients
- Need to account for full social costs associated with lost productivity and QOL for patient and carers
- Barcelos et al (2022): mean UK carer EQ-5D-5L was 0.62
- "*SCD can also take a heavy toll on mental health not just for carriers but parents and carers who are woken up to the sound of their children's screams and cries in the middle of night, watching them suffer in excruciating pain and putting their life on pause to be with their child for weeks in hospital to witness the agony*."

Equality issues raised during consultation:

- Most UK SCD patients are of Black African and Caribbean heritage – more likely to experience poverty, discrimination, barriers to accessing healthcare and poorer health outcomes
- 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
- Careful consideration needs to be given to ethnic, faith and cultural needs/aspects of people offered exa-cel
- Recommendation disadvantages people with SCD who do not have suitable stem cell donor so cannot receive HSCT, particularly adults who need a fully matched sibling (unlike children who can use any donor)
- Need pre-treatment or conditioning with busulfan before exa-cel, which may affect fertility

Abbreviations: SCD, sickle cell disease; QoL, quality of life, HRQoL, health-related QoL; ICER, incremental cost-effectiveness ratio; HSCT, haematopoietic stem cell transplant

Summary of preferences

Issue	ACM1 committee preferences	Company base case (difference to ACM1 cttee preferences)	EAG base case (difference to ACM1 cttee preferences)
Model structure and SoC mortality	Alternative model structure SoC mortality: SMR - Desai et al	-	-
Treatment effect	No treatment effect waning	-	-
Treatment withdrawal	Include exa-cel costs and outcomes	Exclude exa-cel costs and outcomes	-
Baseline VOC rate	Hospitalisation baseline VOC rate (2.6 a year)	All VOC event rate (4.2 a year)	-
Complications	Not predicted by VOC rate Brousse (severe population)	Udeze et al (2023) – severe population	Udeze et al (2023) 12-35 years population
Acute chest syndrome	-	Included	Excluded
SoC utility	0.81	-	-
Exa-cel utility	0.88	0.92	-
Exa-cel adverse events	Excluded	-	-
Severity modifier	1	1.2	-
Discount rate	3.5%	1.5%	-

Abbreviations: VOC, vaso-occlusive crisis; AE, adverse events; SMR, standardised mortality ratio; SoC, standard of care

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include a confidential list price

Key questions for committee

Issues	Key questions	ICER impact
VOC definition	Does the committee change its preferred VOC rate definition from hospitalisation VOCs to all-event VOCs?	Moderate
Complications: estimation, source and ACS	• Has the committee's preferred complication source changed from Brousse et al (2023) severe population ('literature') to Udeze et al (2023)? • If Udeze, which population should be used – severe SCD population, or 12-35 years SCD population? • If Udeze, should the data be matched to the CLIMB SCD-121 population? • Are complications estimated appropriately? Should ACS cost and outcomes be excluded?	Moderate
Health utility (exa-cel and SoC)	What utility values should be modelled for the SoC and exa-cel "functionally cured" population	Moderate
Exa-cel treatment withdrawals	Does committee change its position of including costs and outcomes for people who withdraw from exa-cel?	Large
Discount rate	Should a 3.5% (reference case) or 1.5% (non-reference case) discount rate be applied?	Large
Severity modifier	Has the severity modifier been met? If so, which QALY weight should be applied?	Large

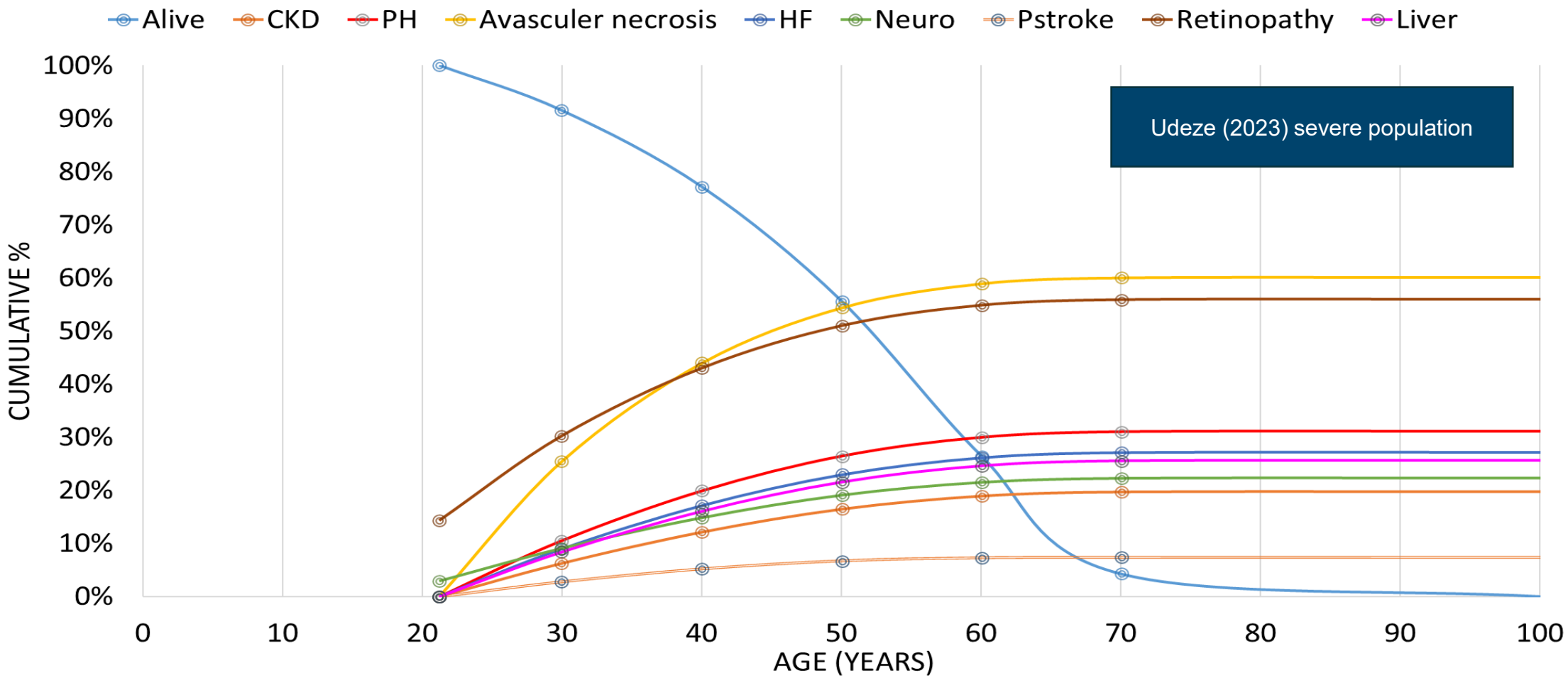
Abbreviations: VOC, vaso-occlusive crisis; SCD, sickle cell disease; SoC, standard of care; QALY, quality-adjusted life year; ACS, acute chest syndrome

NICE National Institute for Health and Care Excellence

Thank you.

Complications (1)

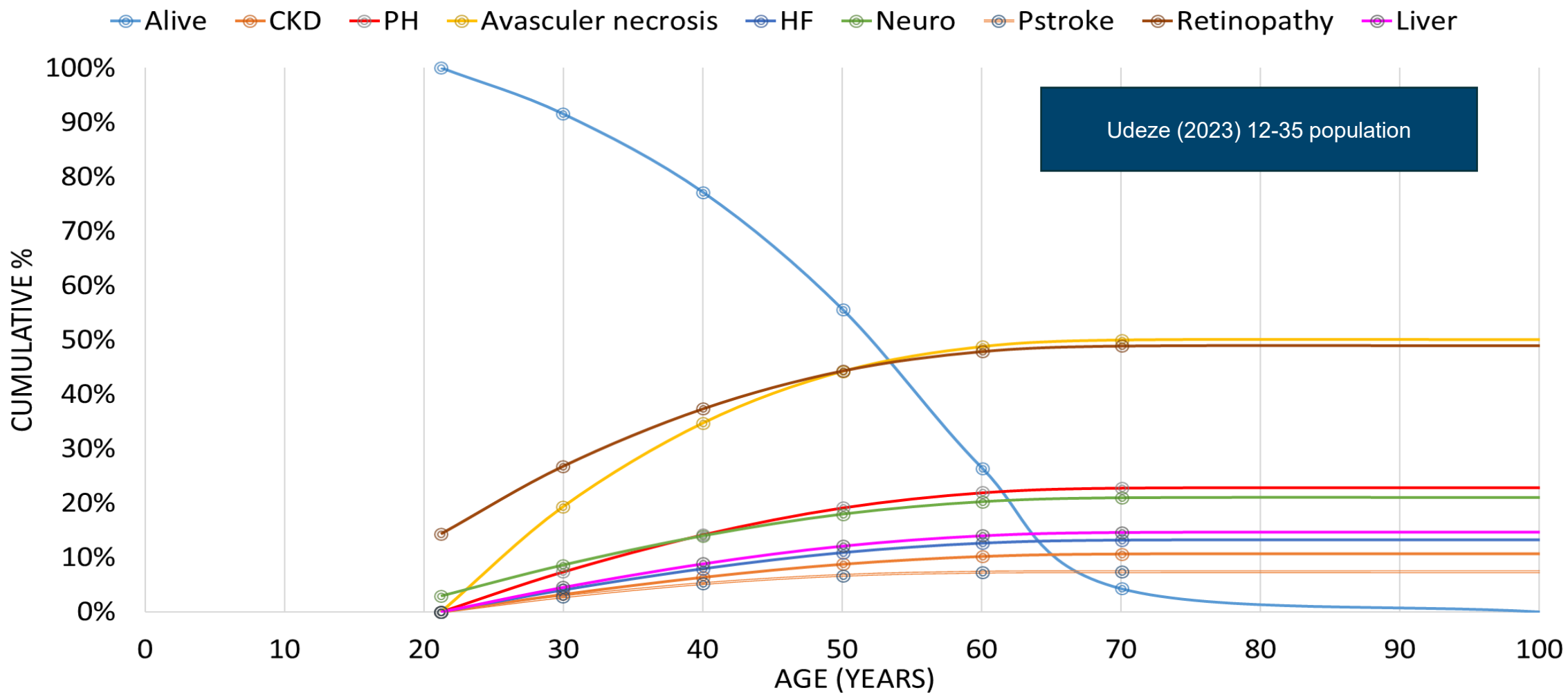
Proportion of chronic complications over time horizon



Abbreviation: CKD, chronic kidney disease; HF, Heart failure; Pstroke, post stroke; PH, Pulmonary hypertension

Complications (2)

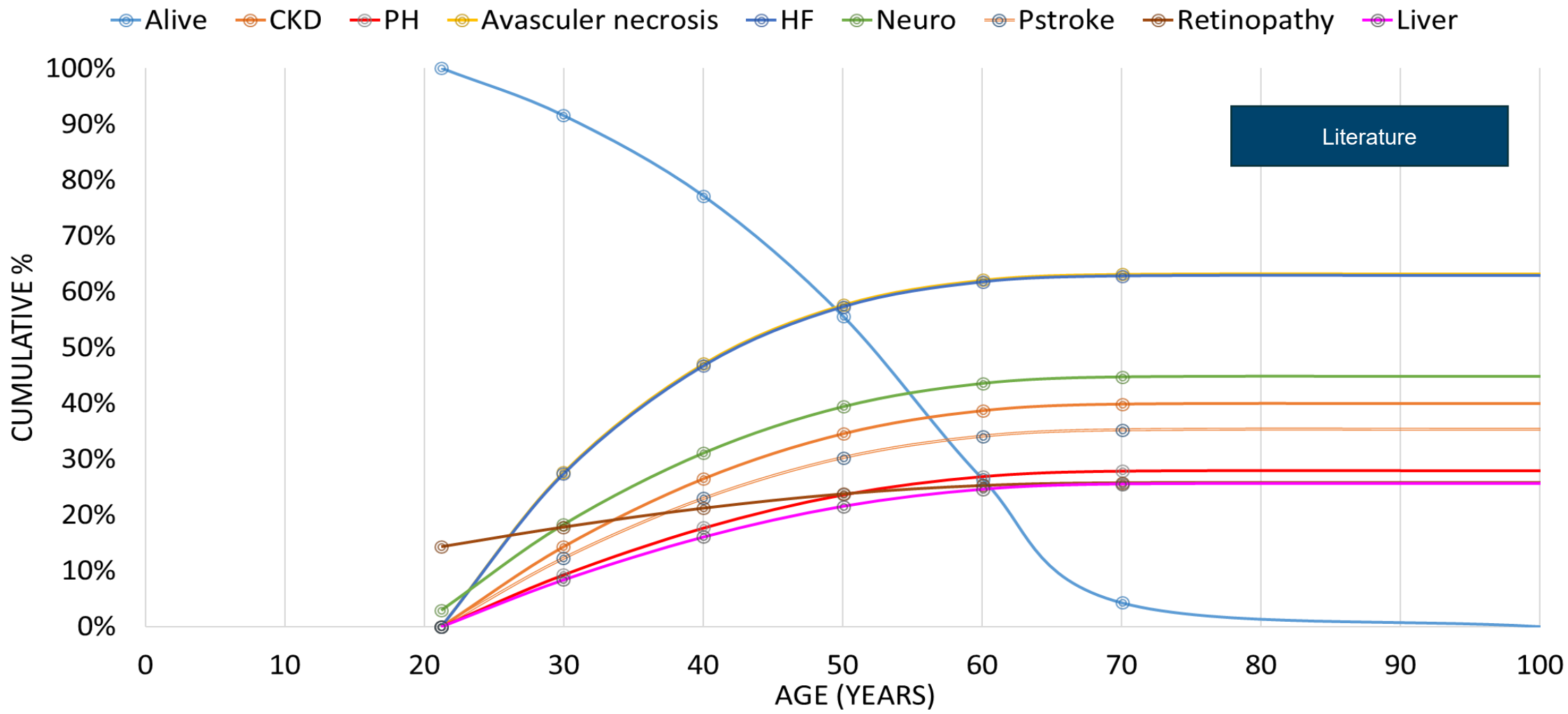
Proportion of chronic complications over time horizon



Abbreviation: CKD, chronic kidney disease; HF, Heart failure; Pstroke, post stroke; PH, Pulmonary hypertension

Complications (3)

Proportion of chronic complications over time horizon



Abbreviation: CKD, chronic kidney disease; HF, Heart failure; Pstroke, post stroke; PH, Pulmonary hypertension

Complications (4)

Udeze severe

Age	Alive	CKD	PH	Avascular necrosis	HF	Neuro	Pstroke	Retinopathy	Liver
21	100.00%	0.00%	0.00%	0.00%	0.00%	2.86%	0.00%	14.29%	0.00%
30	91.54%	6.26%	10.49%	25.40%	8.98%	9.02%	2.76%	30.20%	8.36%
40	77.08%	12.17%	19.89%	44.00%	17.17%	14.83%	5.18%	43.05%	16.06%
50	55.55%	16.50%	26.41%	54.39%	22.97%	19.07%	6.67%	51.01%	21.54%
60	26.41%	18.96%	29.93%	58.92%	26.16%	21.49%	7.24%	54.86%	24.58%
70	4.25%	19.73%	30.98%	60.03%	27.13%	22.24%	7.32%	55.89%	25.51%
100	0.00%	19.80%	31.06%	60.10%	27.20%	22.31%	7.32%	55.96%	25.59%

Udeze 12-35 yr

Age	Alive	CKD	PH	Avascular necrosis	HF	Neuro	Pstroke	Retinopathy	Liver
21	100.00%	0.00%	0.00%	0.00%	0.00%	2.86%	0.00%	14.29%	0.00%
30	91.54%	3.22%	7.36%	19.31%	4.03%	8.56%	2.76%	26.73%	4.52%
40	77.08%	6.38%	14.21%	34.74%	7.94%	13.96%	5.18%	37.33%	8.87%
50	55.55%	8.77%	19.16%	44.20%	10.88%	17.94%	6.67%	44.29%	12.12%
60	26.41%	10.19%	21.94%	48.73%	12.60%	20.21%	7.24%	47.85%	14.01%
70	4.25%	10.65%	22.80%	49.93%	13.15%	20.93%	7.32%	48.86%	14.62%
100	0.00%	10.69%	22.86%	50.01%	13.20%	20.99%	7.32%	48.93%	14.67%

Literature

Age	Alive	CKD	PH	Avascular necrosis	HF	Neuro	Pstroke	Retinopathy	Liver
21	100.00%	0.00%	0.00%	0.00%	0.00%	2.86%	0.00%	14.29%	0.00%
30	91.54%	14.29%	9.27%	27.58%	27.33%	18.23%	12.25%	17.81%	8.36%
40	77.08%	26.50%	17.70%	47.11%	46.77%	31.10%	22.99%	21.22%	16.06%
50	55.55%	34.55%	23.64%	57.65%	57.29%	39.39%	30.26%	23.79%	21.54%
60	26.41%	38.67%	26.90%	62.09%	61.75%	43.56%	34.10%	25.29%	24.58%
70	4.25%	39.84%	27.89%	63.14%	62.81%	44.72%	35.22%	25.77%	25.51%
100	0.00%	39.93%	27.96%	63.20%	62.87%	44.81%	35.30%	25.81%	25.59%

NICE

Abbreviation: CKD, chronic kidney disease; HF, Heart failure; Pstroke, post stroke; PH, Pulmonary hypertension