

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Exagamglogene autotemcel for treating severe sickle cell disease in people 12 years and over

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using exagamglogene autotemcel in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the [committee papers](#)).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using exagamglogene autotemcel in the NHS in England.

For further details, see [NICE's manual on health technology evaluation](#).

The key dates for this evaluation are:

- Closing date for comments: 11th April 2024
- Second evaluation committee meeting: 8th May 2024
- Details of the evaluation committee are given in [section 4](#)

1 Recommendations

- 1.1 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 β^S/β^S , β^S/β^+ or β^S/β^0 genotype, when a haematopoietic stem cell transplant (HSCT) is suitable and a human leukocyte antigen-matched related haematopoietic stem cell donor is not available.

Why the committee made these recommendations

Standard care for SCD includes hydroxycarbamide, blood transfusions and iron chelation therapy to remove excess iron in the blood. People who are well enough can have an HSCT if available. When an HSCT is suitable but there is no available human leukocyte antigen-matched donor, exa-cel is a possible cure.

In SCD, damaged red blood cells can block blood flow to parts of the body, depriving them of oxygen and causing severe pain. This is often called a VOC. Evidence from a clinical trial suggests that exa-cel can result in people not having VOCs. But this is uncertain because the treatment was not compared with anything else, the number of people in the trial was small and it was not clear how well it will work in the long-term.

NICE requires more information to address the uncertainties in the clinical and economic evidence. There were several issues with the economic modelling, including:

- the model structure
- the survival estimates
- quality-of-life estimates
- how long the treatment effect with exa-cel lasts
- how often people withdraw from exa-cel treatment before having the infusion
- the frequency of complications.

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. Also, the cost-effectiveness evidence suggests that exa-cel is not likely to be cost-effective. So, exa-cel is not recommended for use with managed access.

2 Information about exagamglogene autotemcel

Marketing authorisation indication

2.1 Exagamglogene autotemcel (Casgevy, Vertex) is indicated for ‘the treatment of sickle cell disease in patients 12 years of age and older with recurrent vaso-occlusive crises who have the β^S/β^S , β^S/β^+ or β^S/β^0 genotype, for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available’.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the [summary of product characteristics for exagamglogene autotemcel](#).

Price

2.3 The list price for exagamglogene autotemcel is commercial in confidence.

3 Committee discussion

The [evaluation committee](#) considered evidence submitted by Vertex, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The condition

Details of condition

- 3.1 Sickle cell disease (SCD) is the name for a group of hereditary blood disorders. It is characterised by unpredictable episodes of severe pain (also known as vaso-occlusive crises [VOCs]), chronic haemolytic anaemia, widespread organ damage and shortened life expectancy. SCD is caused by a gene mutation that causes red blood cells to become irreversibly sickle shaped. This can cause problems because the cells can block blood vessels and do not live as long as healthy red blood cells, which causes a constant shortage of red blood cells. This can result in pain and a range of acute and chronic complications such as acute chest syndrome and multi-organ failure. Life expectancy for people with SCD is reduced, particularly for people with severe disease. People with SCD are also more likely to develop other illnesses such as stroke, kidney failure and heart conditions. Patient experts described the burden of SCD as all-consuming and said that it has significant negative emotional, social and quality-of-life (QoL) effects for people with SCD and their families. They highlighted that the most common symptoms are pain in multiple body parts, chronic fatigue and intense localised pain at crisis sites. The committee heard that the complications affect people's mental health and daily activities, in particular their ability to work, go to school, to exercise, to travel and to live with spontaneity. This is particularly the case when the number of symptoms increase and become more severe. Patient experts explained that the severity of pain often requires hospitalisation, but that some people avoid seeking hospital treatment. This is because there is a large variation in the care offered from one hospital and region to another and people with SCD often feel stigmatised by healthcare professionals (see [section 3.17](#)). The committee was aware that SCD mainly affects people from ethnic minorities. In the UK, most people with SCD are from Black African and Caribbean ethnic groups. The committee heard that as people with SCD get older, VOCs can become more painful and serious, and the time it takes to recover from their physical and mental effects can

be longer than the pain episode itself. The Sickle Cell Society survey showed that in the past 2 years:

- 45% of people with SCD had more than 8 VOCs
- 66% needed emergency care and support at least 2 to 3 times, and
- 24% spent 1 to 2 weeks in hospital.

The 2019 Sickle Cell World Assessment Survey also found that chronic pain was present on average 4 days out of every week. Respondents reported that SCD has a significant effect on work, with 76% reducing hours and 58% having to stop work. Patient experts stated that consideration should not only be given to the number of VOCs and hospital admissions per person, but that it is necessary to look at the daily effect of SCD. They noted that they could not remember a day without pain, whether that be mild, moderate or severe. Clinical experts supported this by explaining that pain is not directly the same as a VOC. Vaso occlusion is the process by which SCD develops, and happens constantly, even if a person does not feel pain. They acknowledged that measuring the severity of SCD is difficult and using the frequency of physical complications, in particular VOCs, is one of the only ways to do this. But, they said that this type of measurement has limitations in determining severity, and underestimates the full effect of SCD. The committee took into consideration the patient and clinical perspectives and concluded that SCD is a debilitating and life-limiting condition. It also concluded that there is high unmet need for effective treatments that improve outcomes and QoL.

Clinical management

Treatment options

- 3.2 Usual treatment for SCD includes ensuring adequate hydration, preventing infections, regulating body temperature and treating pain, with or without hydroxycarbamide. Regular blood transfusions may be required, which also means iron chelation therapy may also be

considered. Clinical experts highlighted that there are very few therapies available to stop symptoms and that those that are available often have intolerable side effects. Patient experts supported this, highlighting that 30% of people with SCD say that existing treatments do not manage their condition very well. One patient expert said that they felt like they had reached the ceiling of what current treatments can offer, yet they continue to experience severe symptoms. The committee was aware that improvements in standard care have improved survival rates, but many people with SCD continue to have a reduced life expectancy because of complications. For people who are fit enough and have an available matched-related donor, allogeneic haematopoietic stem cell transplants (HSCTs) are a potentially curative treatment option. Clinical experts noted that in the UK, it is common to search for a matched donor early in the treatment pathway. Clinical experts highlighted that only around 15% of people with SCD have suitable donors available. So, given the small numbers that can have an allogeneic HSCT, exa-cel could provide a cure to a wider population with severe SCD. They also highlighted that HSCTs can lead to graft versus host disease. But, because exa-cel is an autologous HSCT (people receive their own edited cells), there is no risk of this. Patient experts highlighted that people with SCD want choice and empowerment in managing SCD and to resolve symptoms to the point where they have no significant effect on day-to-day life, prospects and opportunities. They added that exa-cel could drastically change the lives of people with SCD, significantly improve QoL and provide much needed hope. Clinical experts noted that exa-cel could offer a chance at disease-free survival, improved organ function, reduced symptoms such as VOCs and reduced healthcare use. But, they noted that people with mild SCD and few VOCs are less likely to derive benefit from exa-cel and the treatment risks may outweigh any benefit. The committee agreed with clinical and patient experts that there are limited effective and tolerable treatments available for SCD. It concluded that there is a significant unmet need for curative treatment options for the majority of people with SCD.

Treatment positioning of exa-cel

3.3 The company positioned exa-cel to be a treatment for SCD in people 12 years and over, with recurrent VOCs who have the β^S/β^S , β^S/β^+ or β^S/β^0 genotype, for whom HSCT is appropriate and a human leukocyte antigen matched-related haematopoietic stem cell donor is not available. This is aligned with its marketing authorisation (see [section 2.1](#)). It defined recurrent VOCs in line with its clinical trial, CLIMB SCD-121 (see [section 3.4](#)). The company explained that exa-cel reactivates the expression of gamma-globin mRNA. This increases fetal haemoglobin levels in red blood cells, stops the effects of sickle haemoglobin in SCD and prevents the polymerisation of sickle haemoglobin (see [section 3.1](#)). The treatment process involves collecting blood stem cells from the person having exa-cel and sending them to a manufacturing facility. There, the CD34+ cells are isolated and the CRISPR associated protein 9 is used to edit the BCL11A gene before the cells are frozen. The edited cells are returned to the body in a single infusion. The committee was aware that the process for collecting stem cells already exists in the NHS and that if recommended, exa-cel will only be delivered by JACIE (Joint Accreditation Committee International Society for Cell and Gene Therapy-Europe and European Society for Blood and Marrow Transplantation) accredited units. The committee was also aware that exa-cel would only be available to people with severe SCD who have recurrent VOCs. It acknowledged the difficulty in accessing the severity of SCD (see [section 3.1](#)) and heard that recurrent VOCs would be identified in clinical practice based on visible VOC episodes, as used in the trial (see [section 3.4](#)). The committee concluded that exa-cel could potentially address the unmet need.

Clinical effectiveness

CLIMB SCD-121 trial

3.4 The main clinical evidence for exa-cel is from CLIMB SCD-121. This was a multiphase (1, 2 and 3), single-arm, open-label trial. It investigated the

efficacy of a single dose of exa-cel in people aged 12 to 35 years, who have severe SCD with a β^S/β^S , β^S/β^0 , or β^S/β^+ genotype, and do not have a willing and healthy human leukocyte antigen matched-related donor. Severe SCD was defined in the trial as someone who had at least 2 VOCs per year during the 2-year period before screening, while having best supportive care. Severe VOCs during the screening period for the trial were defined as any of the following (documented by a visit to a medical facility):

- an acute pain event
- acute chest syndrome
- priapism lasting at least 2 hours
- splenic sequestration.

At baseline, the mean rate of severe VOCs per year was 4.2 and the mean rate of inpatient hospitalisations for severe VOCs per year was 2.6. The trial was done across multiple sites globally, including 1 UK site. At an April 2023 datacut, the trial had recruited 43 people and 29 had been followed for 16 months or more after exa-cel infusion and for at least 14 months after the last red blood cell transfusion for post-HSCT support or SCD management. This data was used in the economic model (see [section 3.6](#)). The latest datacut presented during the appraisal (June 2023) included 1 more person. After exa-cel infusion, people were followed for up to 2 years in the CLIMB SCD-121 trial and then asked to join the CLIMB-131 trial, a phase 3 long-term follow-up study, where people will be monitored for up to 15 years. The primary outcome measure in CLIMB SCD-121 was the proportion of people achieving an absence of severe VOCs for at least 12 months after exa-cel infusion. The key secondary outcome measure was the proportion of people free from inpatient hospitalisation for severe VOCs, for at least 12 months after exa-cel infusion. Both outcomes were measured from 60 days after the last red blood cell transfusion for post-HSCT support or SCD management. 28 out of 29 (96.6%) people who had been followed for

16 months or more after exa-cel infusion were severe VOC-free for at least 12 months and remained VOC-free for an average of 20.7 months of follow up (range: 13.6 months to 43.6 months). All 29 (100%) people were hospitalisation-free for at least 12 months. Of all the people who had exa-cel, 86.0% were VOC-free and 97.6% were hospitalisation-free for between 1.3 months and 43.6 months. CLIMB SCD-121 is a single-arm trial, so it did not collect efficacy data on standard care. The company stated that the baseline VOC rate recorded (4.2 per year), reflected the efficacy of standard care. This was used to model standard care (see [section 3.6](#)).

Clinical trial evidence

3.5 The clinical effectiveness evidence for exa-cel was based on 30 people, who were followed up for an average of 20.1 months (see [section 3.4](#)). The EAG highlighted that the assumption of a lifetime effectiveness is currently based on clinical opinion, so robust long-term evidence needs to be collected from more people who are followed up for longer. Patient experts highlighted that the need for more data must be managed against withholding a treatment that stops VOCs. But, they also raised concerns about the long-term effects of exa-cel and whether people would have any complications in future. They said that people with SCD would want the medium- to long-term effects to be explored so that they can make an informed decision about choosing to have exa-cel. The company responded that the trial sample size was prespecified for adequate statistical power (n=45), and that it can be challenging to recruit people for a novel medicine in SCD (see [section 3.18](#)). At the latest datacut, 44 people had exa-cel and 30 people had at least 16 months follow up (see [section 3.4](#)). Clinical experts said that the trial sample size was sufficient to be able to understand the immediate safety and efficacy signals and to show a true effect size. The EAG also questioned the generalisability of the trial results. First, because CLIMB SCD-121 was only conducted in 1 UK centre and included a limited number of people from the UK. Second, the trial and UK SCD population is mainly people of

African and Caribbean ethnicity, which is a genetically varied group. The company stated that clinical practice and treatment guidelines for SCD are consistent across the UK, the US and Europe (the countries included in CLIMB SCD-121). Clinical experts supported this and explained that while the SCD populations are heterogeneous, the SCD biology has not been shown to differ. There is also no evidence to suggest that the UK population is so genetically diverse that there will be a difference in treatment effect. They confirmed that the trial population is generalisable to the NHS population and practice. The EAG acknowledged these similarities, but noted that extrapolation of a 12-month effect size from the clinical trial to a lifetime horizon remains speculative. The committee considered CLIMB SCD-121 to be generalisable to the target UK SCD population and clinical practice. It also thought that the results showed promise for potentially life-changing outcomes for people with severe SCD. It also noted that more data collection to establish the long-term effectiveness of exa-cel would reduce the uncertainties around durability of the treatment effect.

Economic model

Company's modelling approach

3.6 The company submitted an economic model that they described as a 'Markov cohort state transition model'. It assumed a lifetime horizon, a cycle length of 1 month and a starting age of 21.2 years. The model included VOC frequency as a health state to capture the effectiveness of exa-cel, compared with standard care, based on the absence or frequency of VOCs. Based on the CLIMB SCD-121 primary outcome results (see [section 3.4](#)), the company assumed that 96.6% of people who have exa-cel would be 'functionally cured' and have no severe VOCs, based on the primary outcome measure at 12 months in the clinical trial (see [section 3.9](#)). The remaining 3.4% were assumed to have the same outcomes as those who have standard care treatments. VOC frequency in the standard-care arm was assumed to be constant, based on the trial

baseline VOC rate (4.2 per year; see [section 3.4](#)). The model included non-mutually exclusive health states for the following 7 acute SCD complications:

- acute chest syndrome
- acute infections
- acute kidney injury
- gallstones
- leg ulcers
- pulmonary embolism and
- stroke.

And the following 7 chronic SCD complications:

- avascular necrosis
- chronic kidney disease
- heart failure
- neurocognitive impairment
- post-stroke
- pulmonary hypertension and
- sickle retinopathy.

Mortality in the ‘functionally cured’ population was modelled by applying a 1.25 standardised mortality ratio (SMR) to age- and gender-specific general UK population mortality rates. This is to reflect the potential effects of SCD before exa-cel and pretransplant conditioning. For people having standard care, the company used complication-specific mortality rates in addition to SCD mortality rates. The company stated this was to account for an increased risk of death from SCD complications (see [section 3.10](#)). In the company’s model, a person in the standard-care arm could have multiple complications that independently add to the risk of dying. The EAG stated that the company’s model is structurally flawed and does not have the methodological requirements for a Markov model (mutually exclusive health states). It accepts that a person with SCD could

have multiple complications per cycle. But, by applying mortality rates independently to complications, the model assumes that people can die more than once, and total deaths exceed 100%. The EAG stated that this is mathematically incorrect, logically impossible and the structural problems are likely to invalidate the cost-effectiveness results.

Alternative modelling approach

3.7 NICE's Decision Support Unit (DSU) gave an independent review of the company's model during technical engagement to clarify whether its structure was appropriate. The DSU agreed with the EAG that the company's modelling approach likely overestimates complication-related mortality risks. This was because complications were independently associated with an increased mortality risk, despite happening at the same time in the same people. This has implications for the credibility of the modelled estimates of survival, costs and quality-adjusted life years (QALYs) and mostly affects the standard-care arm. This is because people in this arm were assumed to have continued VOCs and complications. The DSU suggested that a more simplistic and robust approach would be to remove complication-related mortality risks, and to model SCD all-cause mortality using SMRs. The EAG and DSU both highlighted that once the model structure and mortality issues are resolved, it would be necessary to check that the predicted complication rates are plausible. This is because they are a key driver of costs and QALYs in the standard-care arm (see [section 3.11](#)). The EAG noted that this could not be done within the company's original model structure. The EAG and DSU stated that, regardless of the mortality approach, not estimating complications in a conditional way biases complication rates and possibly overestimates rates of the most severe events. This has a large effect on the standard-care arm, which drives cost-effectiveness. In response to technical engagement, the company provided a scenario analysis using an alternative model structure, aligned with the DSU's suggestion of applying a SCD-specific death rate, independent from model complications. The company compared the mean standard care

survival estimates from its original model (44 years) and the alternative model (50 years) to data from the company's unpublished UK Burden of Illness (BOI) study (40 years). The company stated that its original model survival outputs had better external validity and so were used in its base case, despite the limitations. The EAG reiterated that the company's original model was structurally flawed, and it could not have confidence in the results it produced. The EAG explained that the company's alternative model, although still significantly flawed, was the only proposed structure that did not pose a challenge to the validity of the appraisal. The committee considered that the alternative model structure presented by the company was the only model structure appropriate for decision making, but it acknowledged that it was also associated with uncertainties, including the plausibility of modelled mortality rates and risks of acute and chronic complications.

Standard care mortality modelling

3.8 The company acknowledged that the alternative model structure addressed the uncertainties raised about mortality modelling in the original model (see [section 3.6 and 3.7](#)). But it noted that this model did not estimate standard-care mortality in line with the company's unpublished UK BOI study. Mortality was estimated by applying SMRs derived from literature by [Desai et al. \(2020\)](#) and the [US Institute for Clinical and Economic Review report \(2023\)](#). The EAG did not accept the company's proposed SMR values, primarily because the data was collected from a young population (mean age 15.7 years), which means that all deaths captured will occur at a younger age. So the mean age of death would be lower than the overall population with SCD and using this within the model would have overestimated the death rate. It considered that not enough evidence was provided to determine the most accurate life expectancy for people with severe SCD. The EAG ran a non-systematic search for additional external evidence but reported difficulties in finding data to match the appraisal population. It found data from 6 real-world studies that suggested life expectancy is between 43 years and

55 years. The EAG chose to use the mortality rates from [Jiao et al. \(2023\)](#) (life expectancy of 55 years) in its base case. This was because the cohort (mean age 26.6 years) could better represent mortality across the age range of people with SCD. The company and clinical experts highlighted that the mortality rates from the Jiao et al. (2023) paper are for the entire SCD population, not specifically the severe SCD population being appraised. The company stated that people with severe SCD die at a younger age. At the committee meeting, the company said it believed this to be between 39 years and 43 years, based on a literature search. So it stated Jiao et al. (2023) is not relevant for decision making. Clinical experts highlighted that there is limited data available to validate model inputs because evidence is often incomplete and outdated. Literature mortality estimates are based on a younger population, but the UK is beginning to see an older SCD population. The committee agreed that this demonstrated the degree of uncertainty around the mortality estimates. It considered that the mean standard-care survival estimates produced by both the company and EAG's preferred SMRs were 50 years and 53 years, respectively. Clinical experts commented that the life expectancy for people with SCD with recurrent VOCs is in the fifth decade of life. The company explained that its own SMRs overestimated survival in the severe SCD population. The committee questioned why the company only provided 1 paper (company's unpublished BOI study) to validate the modelled survival estimates. It also asked why further validation using a body of evidence was not presented to committee to reduce uncertainty. It considered that the company's SMRs were more representative of the severe SCD population, but concluded that further validation is needed about the most accurate life expectancy for people having standard care.

Long-term treatment effects

- 3.9 A 'functional cure' was assumed in 96.6% of people in the exa-cel arm, based on the primary outcome of CLIMB SCD-121 (see [section 3.4](#)). This assumption meant that people with no severe VOCs carry no risk of

complications for the duration of the lifetime time horizon. Although the EAG used this assumption in its base case, it highlighted that this was optimistic because the treatment effect duration is unknown because of the limited follow up (see [section 3.5](#)). The company stated that there is no known biological mechanism that could reverse the genetic edit, which supports the durability of the exa-cel treatment effect. The committee asked the clinical and patient experts whether being VOC-free results in a cure and no further complications. Clinical experts noted that the absence of VOCs does not translate directly to a cure but that there is evidence that frequent VOCs are a marker of severe disease and early death. They agreed with the company's rationale, but still had some concerns about whether the treatment effect would wane, so agreed that longer follow up is needed. But, they noted that the clinical trial results suggest that the fetal haemoglobin after exa-cel has a large effect on disrupting the polymerisation of sickle haemoglobin (see [section 3.1](#)). They explained that if fetal haemoglobin is maintained at around 40% across every red blood cell, then this would be expected to stop the process of vaso-occlusion. But it would not necessarily stop all acute pain events, which may fall under the definition of a VOC. They reiterated that this is a problem associated with measuring SCD using countable VOC episodes (see [section 3.1](#)). Instead, the maintenance of fetal haemoglobin levels would provide reassurance of a 'functional cure'. The company agreed, but explained that it was too complex to model this as an endpoint and VOC was used based on the availability of data. It noted that its clinical experts believed that a durable effect at 2-years after exa-cel infusion is highly predictive of long-term durability. Clinical experts at the committee meeting said that if the treatment effect is consistent for 5 years, they would be reassured that it will not wane. This aligns with when a cure is assumed in other disease areas. The committee was aware that there were no scenarios presented around the durability of exa-cel's treatment effect. It noted that the trial suggested that some people may still have episodes of pain. The company and clinical experts explained that VOCs

are often seen after allogeneic HSCTs and people may still have pain events, particularly for the first year after the HSCT. To reflect this, the company applied baseline VOC rates to the entire exa-cel arm for the first year after infusion. The EAG highlighted that these were adjudicated VOCs in the trial and that acute pain is part of the trial definition of VOCs (see [section 3.4](#)). The committee also questioned the effect of pre-existing complications on the 'functionally cured' status. A patient expert who had had an allogeneic HSCT confirmed that they have had no further complications. But they added that the damage SCD had already caused was still there after their HSCT. Clinical experts supported this, explaining that if someone had a pre-existing organ-specific complication, the effects were unlikely to be reversed by exa-cel. The company highlighted that people with severe complications would not be eligible to receive exa-cel. The committee considered there to be uncertainty with the long-term treatment effects of exa-cel because of the relatively short-term follow up of CLIMB SCD-121. It understood from clinical experts that the long-term efficacy of exa-cel would be more assured after 2 to 5 years of follow up, but full health may not be restored. So, it concluded that long-term durability of the exa-cel treatment effect may be plausible, but that this should be explored further with additional data collection.

Vaso-occlusive crisis as a predictor of complications

3.10 VOC frequency was used to predict the risk of developing SCD complications in the company's model. For each complication, a hazard ratio for the additional risk of developing a complication after a VOC, was multiplied by the baseline complication risk and the baseline VOC rate (see [section 3.4](#)). The hazard ratios were taken from [Shah et al \(2019\)](#) and were calculated using VOCs defined as VOCs needing hospitalisation. This was different to the definition used by the company in its model and in CLIMB SCD-121, which was all VOCs (hospitalisation or non-hospitalisation; see [section 3.4](#)). The company stated that Shah et al. (2019) shows that VOC is a predictor of complications and deaths. This is because the 'rate of follow-up VOCs' was a statistically significant

predictor for all complications, when included in the regression equation. 'Baseline VOCs' were only significant at predicting death and strokes. The EAG acknowledged that VOCs are associated with poor outcomes in people with SCD, but stated that using VOCs to predict outcomes is not supported by evidence. It stated that because 'baseline VOCs' is not a significant predictor of most complications, then 'follow-up VOCs' would not be either because the variables are correlated. It accepted that VOCs were a significant predictor for mortality and stroke, but did not agree that VOCs should be used as a predictor for all 14 complications in the model. The EAG preferred to model VOC as an independent complication of SCD. The company stated that its estimated complication rates were consistent with external data from its UK BOI study, which had a severe SCD population. The EAG disagreed (see [section 3.11](#)), explaining that several inconsistencies throughout the model were causing an overestimation of complications. First, using VOCs as a predictor of complications is contradicted by Shah et al. (2019). Second, the model assumes 'functionally cured' people are VOC-free and so have no complications (see [section 3.9](#)). CLIMB SCD-121 showed that 3 people in the 'functionally cured' population had VOCs after exa-cel, but were assumed to have no risk of developing complications. The EAG said that, by definition, they did not remain 'functionally cured', and the assumption that VOCs predict complications is applied inconsistently between the exa-cel and standard-care arms. The company and clinical experts explained that these were likely to be pain events, but the EAG highlighted that these were adjudicated VOCs, based on the definition of a VOC in CLIMB SCD-121 (see [section 3.4](#) and [section 3.9](#)). Another inconsistency was the different definitions of VOCs used in CLIMB SCD-121 and Shah et al. (2019). By applying the Shah et al. (2019) hazard ratios to VOCs in the model, all VOCs were assumed severe enough to lead to hospitalisation. So the EAG explained that the baseline VOC rate incorporating all VOC events was too high and caused excessive estimated complication rates. The EAG preferred to use the

hospitalisation VOC definition and equivalent baseline VOC rate from CLIMB SCD-121 (2.6 per year; see [section 3.4](#)). It said that this reduced the chance that model estimates were affected by interpretation bias and ensured consistency in the VOC definition throughout the model. It also reduced the need to model a relapse rate (most VOCs reported after exa-cel did not need hospitalisation). The EAG noted that if the model uses the trial baseline VOC rate, it should be applied as a mean rate and not as a probability, which was how the company had applied it. The committee considered the definitions of VOCs and the inconsistencies highlighted and concluded that the hospitalisation VOC definition was the most appropriate for decision making.

Complication rates

3.11 The company modelled 14 non-mutually exclusive SCD-complications, each associated with increased mortality, decreased QoL and increased healthcare resource use and costs (see [section 3.6](#)). The EAG highlighted that many of the inputs for these complications were based on assumptions. It explained that a model should be based on evidence and that most clinical parameters should be based on data, complemented by a few logical assumptions when data is lacking. They stated that when certain clinical endpoints have no evidence base they should be excluded from the model. The company acknowledged that including assumptions introduces uncertainty, but removing these complications, based on assumptions, had a minor effect on cost effectiveness. It also stated that the rates of modelled complications were aligned with those observed in a UK severe SCD cohort. The EAG stated that the company's cumulative complication rates were calculated incorrectly and only captured part of the time horizon. The company said it was up to the point of the average life expectancy of 44 years in the company's original model (see [section 3.6](#)). During the committee meeting, the company provided alternative rates of complications to those the EAG had corrected. The EAG stated that the company's rates only captured part of the time horizon and that it should reflect the entire time horizon. The EAG's external validation found

that the complication rates were much higher than those reported in the literature, particularly for chronic events and VOCs. This is partly because of the uncertainty associated with the company's original model (see section 3.6). The model estimated a substantial disease burden for people with SCD, with an average of 15 acute and 5 chronic complications per person, per lifetime. This was because of how the rates were calculated and the data inconsistencies in the model (see [section 3.10](#)). The EAG assessed the effect on the incremental cost-effectiveness ratio (ICER) of using different complication rates, including directly modelling those from the literature (including [Brousse et al. 2023](#), [Shah et al. 2019](#) and the company's BOI study). It found that the ICER was sensitive to how complications were modelled. Clinical experts reviewed the complications from the literature and said that they were plausible. But they noted that there were some significant complications missing from the model, such as priapism and acute multi-organ failure. During the committee meeting, the EAG raised an additional issue. It stated that acute chest syndrome was modelled as an independent complication, but was also included within the company's definition of a VOC (see [section 3.4](#)). So, the cost and disutilities associated with this event were being double counted. The company stated that it had not had time to consider a response to this query. To reduce the structural uncertainty in modelled complications, the EAG base case directly estimated complication rates from the literature. It chose to use the most severe population from Brousse et al. (2023), because this was considered to be equivalent to the exa-cel target population. The committee concluded that directly estimating complications from the Brousse et al. (2023) severe population was most appropriate but that there was uncertainty associated with the estimated frequency of SCD complications.

Utility values

- 3.12 Health state utility values in the model were based on CLIMB SCD-121 EQ-5D-5L data that was mapped to EQ-5D-3L. Baseline EQ-5D (0.81) was used for the standard-care arm (representing SCD without

complications). Disutilities for acute and chronic SCD complications were also applied to model the effect of these events in the standard-care arm. The committee considered that a baseline EQ-5D utility value of 0.81 may be considered relatively high, considering the impact of the condition. But it noted that in the model this value would reduce over time because of complication events. It was aware that both the company and EAG had considered the use of the EQ-5D appropriate in their base case analysis. The committee noted that, to understand the modelled impact of SCD, it would like to see further analysis of the utility value assumed at different time points for the standard-care arm. It also requested further comments on the use of EQ-5D in this population (see [section 3.15](#)). For people assumed to be ‘functionally cured’, the company used a health state utility value of 0.92 in its model. This was based on a mean change in EQ-5D score from baseline to month 24 (0.11). The EAG highlighted that at month 24, EQ-5D was measured in fewer people than at baseline and so could be affected by selection bias. It said that EQ-5D values recorded earlier in the trial (0.88), which are not affected by loss of follow-up bias or are not statistically different, should be used. At the committee meeting, the EAG mentioned that there was an error in the model. At points in the model, SCD-specific utility values were replaced by age-specific general population utilities that reach 0.94. This inflated the total QALYs gained in the exa-cel arm. The company responded that it had not had time to consider a response to this query. The committee was aware that because of the company’s ‘functionally cured’ assumption (see [section 3.9](#)), the choice of utility value could potentially effect the cost-effectiveness results. It asked the company if there were any differences in baseline utilities between people with and without 24-month follow up. The company responded that the 0.11 value used was based on the subset that reached 24 months and that they had a baseline EQ-5D value of 0.77. The committee noted that the difference in baseline utility values suggested that people were not missing at random and that this selected population had more opportunity to improve their health-related quality of

life. The committee had concerns about using the 0.11 mean change from baseline value and the resulting 0.92 utility value in the exa-cel arm. It concluded that a health state utility value of 0.88 for the exa-cel 'functionally cured' population should be used. It also requested that, if necessary, a fix for any potential errors in the model should be accounted for. It further requested additional information on utility values over time in the standard of care arm in the model and comments on the use of the EQ-5D in this population.

Adverse events

3.13 The company did not explicitly model any adverse events related to exa-cel. It stated that all adverse events for people who have exa-cel would occur during the hospital stay as part of the HSCT procedure. It assumed that the effect of these would be captured in the model's transplantation or transplant-related hospitalisation costs and disutilities. The EAG stated that the NHS transplant reference cost cannot account for adverse events of a product that is not yet used in clinical practice. The company highlighted that the NHS cost includes inpatient management of adverse events related to autologous HSCT. So, separately accounting for adverse event related to exa-cel would be double counting healthcare resources. Clinical experts supported this. The committee concluded that adverse events for exa-cel infusion do not need to be included in the model.

Treatment withdrawals

3.14 In CLIMB SCD-121, 19% of people withdrew and did not complete exa-cel treatment. In the model, only people who had an exa-cel infusion were included. To account for those who withdrew, the company included one-off premobilisation, mobilisation and apheresis costs equal to the proportion of people who withdrew. It did not include the outcomes for this population and noted that this would have a large effect on the ICER. The EAG stated, and the clinical experts agreed, that costs (including the cost of manufacturing for those that do not obtain enough cells for infusion)

and outcomes for people who withdraw and go on to have standard care should be accounted for. The committee concluded that cost and outcomes of treatment withdrawal should be accounted for in the model.

Non-reference case discount rate

3.15 The company believed that exa-cel met the criteria for the non-reference case discount rate of 1.5%. The committee acknowledged that all of the following criteria in [section 4.5.3 of the NICE health technology evaluations: the manual](#) must be met for a 1.5% discount rate to be used:

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

The company argued that the first criterion was met because SCD is characterised by unpredictable episodes of severe pain, widespread organ damage, a shortened life expectancy and has a substantial effect on health related QoL (see [section 3.1](#)). The company's BOI study reports a mean age of death for people with severe SCD of 40 years. The EAG considered that robust and validated estimates of survival were not provided by the company (see [section 3.8](#)). The committee noted that the company's and EAG's base cases use a utility value of 0.81 at baseline to represent health related QoL for people with severe SCD (see [section 3.12](#)). In the company's submission, it said that 0.81 was lower than the average UK population QoL, which indicates that SCD impairs QoL. The committee expected this QoL difference between SCD and the general population to be larger if a condition caused people to have a very severely impaired life. But the committee was aware that disutilities were applied over the model time horizon to the standard-care arm to account for the effect of chronic and acute SCD complications. The committee had heard from the patient experts about the substantial effect SCD has on people's lives, and that the effects of SCD worsen as people get older

(see [section 3.1](#)). The committee noted that the baseline EQ-5D value suggests that people with severe SCD experience a reasonable QoL, relative to the general population. It asked if the EQ-5D measure did not fully or accurately capture QoL for people with SCD at the start of the trial or if survival is overestimated (see [section 3.8](#)). Clinical experts agreed, and explained that QoL is difficult to capture in congenital conditions and described SCD as a condition that fluctuates in severity. They noted that only once the negative effects are removed (that is, through an HSCT), can the true QoL effect be understood by people with SCD. The committee acknowledged and understood these difficulties surrounding QoL measurement in SCD. The company explained that the second criterion was met because exa-cel increases survival, improves QoL, reduces the risk of complications and comorbidities and eliminates the need for treatment. It explained that the persistent increased fetal haemoglobin from the exa-cel infusion restores people to near-normal health (see [section 3.9](#)). The committee recalled discussion from patient and clinical experts who said that some effects of having had SCD and SCD complications cannot be reversed (see [section 3.9](#)). But it noted that people with severe complications would not be eligible for exa-cel treatment. The company considered that the third criterion was met because there is no biological mechanism or reason for exa-cel to lose its treatment effect. The EAG agreed, but noted that plausibility is not sufficient to demonstrate a prolonged benefit. It said that it is not possible to establish with certainty that benefits are likely to be sustained for a very long period because of the relatively short follow up (see [section 3.5](#)). The EAG highlighted that CLIMB SCD-121 shows that the possibility of a VOC relapse remains a relevant clinical question. Clinical experts and the company suggested that these reported VOCs were likely to be episodes of pain that are expected after an HSCT (see [section 3.9](#)). The EAG argued that, based on this data, the trial follow up is insufficient to provide robust evidence to support the assumptions of a total cure, eradication of VOCs and any relevant longer-term outcomes and SCD complications.

The committee had heard that a durable effect for between 2 to 5 years could indicate a cure. The committee concluded that the first criterion for using a 1.5% discount rate was not met because there was insufficient evidence to show that people would otherwise die or have a severely impaired life. This is because there is uncertainty around the life expectancy for people with severe SCD (see section 3.9) and no evidence was presented to suggest that the EQ-5D does not fully capture QoL for people with SCD. The committee requested further exploration of why the EQ-5D may not adequately capture the QoL of people with severe SCD and further analysis showing the modelled effect in the standard-care arm of baseline utility and disutilities due to SCD complications over time (see [section 3.12](#)). It also requested longer-term follow up QoL data from CLIMB SCD-121. When considering the second criterion, the committee noted considerable uncertainty with the likelihood of exa-cel returning people to full or near-full health. It understood from experts that exa-cel would reduce the risk of complications, but it was not clear whether persistent damage from complications and comorbidities would be reversed. The committee considered the second criterion was not met, concluding that it may be plausible that exa-cel returns people to full or near full-health. But, it noted the uncertainty was compounded by the short-term follow up of the clinical-effectiveness evidence and that further data could allow the committee to consider if this criterion was met. So, it would like to see this explored with further data collection (see [section 3.23](#)). The committee considered the third criterion was not met, concluding that it may be plausible that exa-cel benefits were sustained over a long period. But it noted that this was highly uncertain given the limited follow up of clinical evidence. So it would like to see this explored with further data collection (see [section 3.23](#)). The committee concluded that not all of criteria were met, so a 3.5% discount rate should be used.

Severity

3.16 The severity modifier allows the committee to give more weight to health benefits in the most severe conditions. Absolute and proportional quality-

adjusted life year (QALY) shortfall should be calculated in line with [section 6.2.17 of the NICE's process and methods guide](#) and [NICE Technical Support Document 23](#). The company estimated that a weight of 1.7 should apply to the QALY increments. But, in its calculation the company used a 1.5% discount rate (see [section 3.8](#)) to calculate the shortfalls. Section 6.2.17 of the NICE process and methods guide stipulates that shortfall calculations should include discounting at the reference-case rate (3.5%). The committee was aware that the severity thresholds were not suitable when calculations using different discount rates were made. Using the same reference-case discount rate across appraisals ensures that the assessment of severity is applied in a consistent and fair manner. The committee noted that the company base case QALY shortfall estimates calculated using a 3.5% discount rate met the criteria for a 1.2 severity modifier weight. But, the EAG's base estimates did not meet the criteria for a severity modifier weight. The company base case (with 3.5% discount rate) estimated an absolute and proportional QALY shortfall of 14.12 and 63% respectively. The committee recalled that the company's base case did not include all of the committee's preferred assumptions (see [section 3.23](#)). The EAG base case estimated an absolute and proportional QALY shortfall of 9.94 and 44% respectively. The committee noted that this estimate did not include its preferred standardised mortality ratio (see [section 3.8](#)), but this change would unlikely result in the estimates meeting the severity modifier thresholds. The committee recalled the powerful testimony of the patient and clinical experts on what it is like to live with the condition and the impacts on families and carers (see [section 3.1](#) and [section 3.2](#)). It considered whether the identified uncertainties in the evidence could have impacted the calculations of QALY shortfall. The committee also considered any impact from health inequalities. It noted that the condition disproportionately affects people from areas with higher levels of deprivation and considered how this could bias the estimates. It was reassured that this would not lead to an

underestimate of the QALY shortfall. The company argued that the severity modifier:

- discriminates against conditions that get progressively worse over time
- will only be accepted in conditions with an immediate mortality risk instead of mortality that increases over time.

The committee was aware that section 6.2.17 of the NICE process and methods guide includes consideration of both absolute and proportional shortfall. It understood that the use of both measures of shortfall widens the consideration beyond conditions with an immediate mortality risk. The committee took into account the quantitative estimates and any possible changes to these estimates due to uncaptured benefits and uncertainties. It did not consider that the threshold for a severity modifier was met but noted the uncertainty in modelled mortality and complications.

Health inequalities

Identified health inequalities

3.17 The company, stakeholders, and patient and clinical experts raised health inequality concerns for people with SCD. This is because SCD mainly affects people from ethnic minority backgrounds. The committee heard that in the UK, most people with SCD are of Black African and Caribbean ethnicities (see [section 3.1](#)). The company highlighted that this population disproportionately experiences health inequalities and are more likely to live in more deprived areas of the UK. It noted that in its unpublished UK BOI study, the majority of people aged 12 to 35 years with recurrent VOCs identified as being in 2 of the most deprived quintiles, according to the Index of Multiple Deprivation (IMD). The committee heard that people from the most socioeconomically deprived areas are more likely to have suboptimal clinical outcomes and are at highest risk of hospital readmissions and in-hospital mortality. This suggests that there are significant inequalities in healthcare access and health outcomes amongst

people with SCD. The committee was aware of the [Sickle Cell and Thalassaemia All-Party Parliamentary Group's 'No one's listening' report](#). The report highlighted issues of inequity, discrimination, racial bias, stigmatisation, inequalities in accessing treatment, and the lack of understanding and prioritisation towards people with SCD. Patient and clinical experts noted that while the function of genes in SCD is understood, little has been done to develop effective treatments and cures. They emphasised that racial bias and condition-related stigma have contributed to a lack of investment in SCD and continue to negatively affect the care offered to people with SCD. Clinical experts explained that services are under resourced in terms of staff and facilities and that there is inequality in the commissioning process. Patient experts described how there are large inconsistencies in the treatment people can have because of the large variation in the care offered around the country (see [section 3.1](#)). This means that some people avoid seeking treatment, even when the pain severity would need hospitalisation. They highlighted that the treatment people can have should not be so varied and that if exa-cel is recommended, it is important that people can access it wherever they live. The company said that it would try to ensure that exa-cel is equitably available throughout the country. Patient experts also explained how health inequalities, discrimination and stigmatisation have created a sense of mistrust and hesitancy around healthcare professionals. The committee noted that exa-cel cannot reduce some of the issues raised, but it may have a role to play in reducing the amount of time needed for hospital visits. Patient and clinical experts explained that exa-cel provides an opportunity to address some of the issues described and could start to repair those relationships between people with SCD and healthcare providers. The committee asked if the evidence gaps seen in this appraisal are because SCD mainly affects people from ethnic minorities, who are likely to be more socioeconomically disadvantaged and less likely to engage with clinical research. The company explained that people with SCD are very willing to engage in research and it did not

anticipate problems following up people from the trial. But, clinical experts highlighted that high-quality data in people with SCD is very limited and that it is plausible that they may be less likely to engage with research. The clinical experts emphasised that caution is needed so that current health inequalities are not worsened by assuming there is not enough data to make a decision on the technology. Stakeholders raised concerns about the effect of required pretreatment and conditioning with busulfan on the fertility of people with SCD. They also noted that there is likely to remain an unmet need for people who are older than the age group in the CLIMB SCD-121 trial (aged 12 to 35 years). The committee was aware that the marketing authorisation did not include a limit on the upper age that people can have exa-cel. The committee understood that the following health inequalities were relevant to consider:

- SCD in the UK mainly affects people from a Black African or Caribbean ethnic group.
- People with SCD are more likely to live in areas with higher levels of deprivation, which generates barriers to access and exacerbates existing variations in care.

The committee concluded that there were clear health inequality concerns that needed to be taken into account in its decision-making.

Accounting for health inequalities in decision making

3.18 The company accounted for health inequalities in its submission by doing a distributional cost-effectiveness analysis (DCEA). This stratified the eligible population by the IMD. The company weighted the benefits and costs in each IMD group using a health inequality aversion parameter to create an equity-weighted ICER. This used information on how much the UK population prefers extending quality-adjusted life expectancy for a poor individual compared with a wealthy individual. The company used an aversion parameter of 11, taken from [Robson et al. \(2017\)](#). But the EAG noted that this was based on the opinion of a single clinical expert. The

NICE technical team clarified that NICE's position is that the methods guide does not currently allow for a quantitative modifier for health inequalities. NICE does not consider that there is sufficiently robust evidence to support using aversion weights as part of DCEA. But, taken together, NICE's process and methods guide, statutory duties, principles and deliberative decision making provide the flexibility to take into account relevant considerations. So, the committee considered the company's quantitative assessments of health inequalities from the DCEA, without aversion weights. The EAG shared concerns around the inputs of the company's DCEA, including how ethnicity is accounted for and the use of IMD data. But the committee did not discuss these concerns in detail. The EAG also noted that the estimated uptake was very small relative to the 1,750 people considered eligible for exa-cel by the company. It said that in the context of the equity concerns, it appeared to be disappointingly low. The committee questioned why there was limited evidence and why the trial's sample size and anticipated uptake was small, given that SCD is not a very rare disease and a large number of people could be eligible for treatment. The company explained that because exa-cel is a complex technology with significant initial side effects, recruiting people to take part in a trial is challenging. Clinical and patient experts supported this, explaining that the same fears and barriers were felt when hydroxycarbamide and transfusions were first introduced, but that these are now established first-line treatment options for most people with SCD. They highlighted that trust is slowly being rebuilt in this disease area and there is a high value placed on a cure from younger people with SCD. So, there is hope that if offered, exa-cel would be accepted by many of those eligible. The committee noted that stigma could be a factor in engaging with treatments for SCD, such as pain management. But the committee was not clear on the extent of this issue or its impact on quality of life or costs. It was aware of the need to consider this aspect, as outlined in [NICE's principles](#) to account for health inequalities. Patient experts stated that the main concern for people will be whether it is a safe treatment to

have now and will be safe in the long term (see [section 3.4](#)). The committee appreciated that exa-cel could be very beneficial for people with SCD. But it was concerned that if only a small number of people have exa-cel, then the treatment would not address the inequalities experienced by most people. The committee considered that the company's evidence and testimony from stakeholders and experts (see [section 3.17](#)) gave it a comprehensive understanding of the health inequalities concerns. The committee gave careful consideration to:

- its obligations under the [Health and Social Care Act 2012](#)
- the options available to it in the [NICE process and methods guide](#) and [NICE's principles](#) to account for health inequalities.

It recalled section 6.2.36 of the [NICE process and methods guide](#), which states that additional considerations can be made by the committee, especially when they are broader social considerations. It noted one such consideration is NICE's social value judgement principle 9, which aims to reduce health inequalities. It states that NICE must give due regard to reducing inequalities and produce guidance that aims to reduce and not increase identified health inequalities. The committee concluded that the eligible population for exa-cel experience health inequalities and exa-cel would likely reduce or mitigate them. So, it considered what reasonable adjustments it could make to avoid disadvantaging this population. The committee heard from experts that social and structural barriers may prevent the generation of high-quality evidence. This could be due to a lack of funding for research and barriers to participant engagement in research. So, the committee was willing to accept a higher degree of uncertainty in the clinical effectiveness evidence for exa-cel. It concluded that an appropriate and reasonable adjustment to account for health inequalities was to adjust its acceptable ICER (see [section 3.21](#)). But the committee was mindful of the opportunity cost of doing so. This would mean displacing resources for care for others in the NHS. So, it concluded

adjustments to the acceptable ICER would need to be carefully considered.

Other factors

Innovation

3.19 The company, and patient and clinical experts explained that exa-cel is an innovative treatment. This is because it provides a potential cure for people who have no very effective treatments available to them. They added that exa-cel is a one-time infusion treatment that uses cutting-edge gene therapy. The company also considered that exa-cel will substantially reduce the need for contact with the healthcare system, which is a significant challenge for some people with SCD to engage with. The committee concluded that exa-cel is an innovative treatment and recognised that its innovative and complex nature made generating high-quality evidence more difficult. This could be because of small sample sizes in clinical trials and restrictions on trial design due to the inability to randomise participants. It also noted comments from the patient experts and the company that people can be reluctant to engage in research for innovative and complex treatments (see [section 3.18](#)). So, the committee was willing to accept a higher degree of uncertainty in the clinical effectiveness evidence for exa-cel.

Equalities

3.20 The committee recognised that equalities issues had been raised during the evaluation. These issues, identified by stakeholders, are:

- SCD mainly affects people from Black African or Caribbean ethnic groups.
- There is a socioeconomic imbalance among people with SCD.
- Racial discrimination of ethnic minority groups who already face health inequalities, stigmatisation and prejudice.
- The impact of funding within services and available treatment options for people with SCD.

- SCD is not widely understood, including among healthcare professionals, which often results in poor hospital care and stigma around seeking pain relief for VOCs.
- Treatment with exa-cel may require treatment with busulfan (or other drugs), which may affect fertility.
- There is likely to remain an unmet need for a cohort of people, especially those older than the studied age group (12 to 35 years).

The committee was mindful that most of the equality issues raised were closely related to the health inequalities issues it previously considered (see [section 3.17](#)). It discussed whether the equalities issues had fully been taken into account in the evaluation. It felt that the equalities issues had been fully captured in the evidence, economic modelling and committee considerations. It concluded that equality and health inequality issues with this condition had been fully taken into account when developing its recommendations. The committee noted the reasonable adjustments that it had made. Recognising the potential barriers to generating high-quality evidence due to health inequalities, it accepted some evidence despite the significant uncertainty (see [section 3.18](#)). This included:

- the clinical evidence for exa-cel
- the modelling of complications and mortality

The committee also increased the acceptable ICER at which exa-cel would be considered cost effective (see [section 3.21](#)). The committee considered the equality issues, noting that its recommendations apply to all people within the marketing authorisation indication for exa-cel for SCD. It concluded that its recommendations do not have a different impact on people protected by the equality legislation than on the wider population.

Cost-effectiveness assumptions

Company and EAG cost-effectiveness estimates

3.21 The company and EAG's base case differed on several assumptions:

- the model structure
- the standard-care mortality
- the calculation of complications
- the definition and rate of VOC
- the inclusion of treatment withdrawals
- the discount rate, and
- the severity modifier.

The deterministic cost-effectiveness results included the confidential list price for exa-cel. So, the exact results cannot be reported here. The company's and EAG's deterministic base-case ICER for exa-cel compared with standard care was above the range that NICE normally considers a cost-effective use of NHS resources (see [section 3.21](#)).

Acceptable ICER

3.22 [NICE's process and methods guide](#) notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including difficulties with evidence generation for innovative and complex technologies, and health inequalities. The committee considered the options available to it to account for these additional factors. It recalled its conclusion regarding the innovative and complex nature of exa-cel, meaning it was willing to accept a higher degree of uncertainty in the evidence (see [section 3.19](#)). It also recalled its conclusion on health inequalities and the reasonable adjustments to its acceptable ICER (see

[section 3.18](#)). So, taking these into account, the committee concluded that the acceptable ICER range was between £30,000 and £35,000 per QALY gained.

Committee's preferred assumptions

3.23 The committee concluded that its preferred assumptions for the cost-effectiveness modelling of exa-cel compared with standard care were:

- the company's alternative model structure (see [section 3.7](#))
- the company's preferred standardised mortality ratio (see [section 3.8](#))
- hospitalisation baseline VOC rate (see [section 3.10](#))
- complications estimated directly using the [Brousse et al. \(2023\)](#) severe population (see [section 3.11](#))
- to use a health state utility value of 0.88 for the exa-cel 'functionally cured' population (see [section 3.12](#))
- excluding adverse events for exa-cel (see [section 3.13](#))
- Including the effect of exa-cel treatment withdrawals (see [section 3.14](#))
- a 3.5% discount rate (see [section 3.15](#))
- that the severity modifier was not met (see [section 3.16](#))

The committee noted significant uncertainties with some of its preferred assumptions. It considered these uncertainties when determining its acceptable ICER (see [section 3.21](#)). The committee's preferred assumptions gave an ICER that was above the range considered cost-effective (see [section 3.21](#)). The committee concluded that it could not recommend exa-cel for routine use.

Managed access

Recommendation with managed access

3.24 Having concluded that exa-cel could not be recommended for routine use (see [section 3.23](#)), the committee then considered if it could be recommended with managed access for treating SCD. The committee considered whether a recommendation with managed access could be made. It identified the key uncertainties where additional data collection would be useful:

- data on the durability of the treatment effect of exa-cel (relapse rate)
- if people return to full or near full health after exa-cel or if complications persist
- utility values for exa-cel and standard care
- the rates of complications for exa-cel and standard care
- the number of exa-cel treatment withdrawals
- mortality and life expectancy for exa-cel and standard care.

The committee compared this with the data the company intended to collect according to its current managed access proposal:

- 3 years of additional data for CLIMB SCD-121 from the CLIMB-131 follow-up study
- additional exa-cel safety and effectiveness data from the European Society for Blood and Marrow Transplantation Registry.

The committee agreed that the trial data would provide additional follow up on people who have had exa-cel. It thought that it would reduce the uncertainty about durability of treatment effect, particularly if data for people being followed for longer than 2 years was captured. It also thought it would reduce uncertainty about whether people return to full or near full health or have any complications. The committee acknowledged that it may be difficult to collect data on all of its uncertainties within a managed access timeframe. But it concluded that it would like the

company to consider these in an updated managed access proposal. The committee also discussed the plausible potential for exa-cel to be cost effective at the currently agreed price. The committee concluded that exa-cel did not meet the criteria to be considered for a recommendation with managed access. This is because it does not have the plausible potential to be cost effective at the currently agreed price. Also, it was because the company's current managed access proposal would not collect data to address many of the committee's uncertainties. The committee concluded that it would like to see an updated managed access proposal from the company with more detail on how its identified uncertainties would be addressed.

Recommendation

3.25 The committee recalled the uncertainties it identified with the company's cost-effectiveness evidence. It considered that the alternative model still had uncertainties and that more evidence was needed to generate more robust cost-effectiveness estimates. It recalled that both the EAG's and company's base cases were associated with high uncertainty. But it decided to assess the cost-effectiveness estimates with reasonable adjustments to its acceptable ICER because of the innovative and complex nature of exa-cel and to account for health inequalities. The committee noted, even when taking this into account, the cost-effectiveness estimates were still considerably above the range NICE would consider a cost-effective use of NHS resources. So, it did not recommend exa-cel for SCD in people 12 years and older with recurrent VOCs who have the β^S/β^S , β^S/β^+ or β^S/β^0 genotype, when an HSCT is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available.

4 Evaluation committee members and NICE project team

Evaluation committee members

This topic was evaluated as a single technology evaluation by the [highly specialised technologies evaluation committee](#). Because of this, some members of the technology evaluation committees were brought in to provide additional expertise to the committee. The highly specialised technologies evaluation committee and the 4 technology evaluation committees are standing advisory committees of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The [minutes of each evaluation committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel

Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical and a project manager.

Cara Gibbons

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Alan Moore

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