NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance consultation

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

1 Recommendations

1.1 Exagamglogene autotemcel (exa-cel) is recommended with managed access as an option for treating sickle cell disease (SCD) in people 12 years and over:

- who have:
  - recurrent vaso-occlusive crises (VOCs) and
  - a β^S/β^S, β^S/β^+ or β^S/β^0 genotype, and
- when haematopoietic stem cell transplant (HSCT) is suitable, but a human leukocyte antigen-matched related haematopoietic stem cell donor is not available.

It is only recommended:

- for people who have had at least 2 VOCs (as defined in section 3.4) per year during the 2 previous years and
- if the conditions in the managed access agreement for exa-cel are followed.

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 exa-cel was not compared with anything else, the number of people in the trial was small and it was not clear how well it works in the long term.

As well as the uncertainties in the clinical evidence, there are several issues with the economic modelling. These include:

- the model structure
- the survival and quality-of-life outcomes used for people having exa-cel and standard care
- how long exa-cel's treatment effect lasts
- how often people withdraw from exa-cel treatment before having the infusion
- the characteristics at the start of treatment of people having exa-cel
- the frequency of complications.

But, more uncertainty and a higher cost-effectiveness estimate than NICE normally considers to be a cost-effective use of NHS resources is acceptable because of:

- the health inequalities experienced by people with SCD
- the innovative nature of the technology and
- its uncaptured benefits for the quality of life of carers.

Taking this into account, exa-cel has the potential to be cost effective compared with standard care. But the cost-effectiveness estimates are highly uncertain. This is because of the uncertainty about exa-cel's long-term effects and its impact on quality of life, and about the outcomes for people having standard care. Some of the most likely cost-effectiveness estimates are higher than what NICE normally considers an acceptable use of NHS resources, even when accounting for exa-cel's potential impact on health inequalities. So, exa-cel is not recommended for routine use in the NHS.

Collecting more data through a managed access agreement may resolve some uncertainty in the evidence. So, exa-cel is 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 per treatment for a single dose of exagamglogene autotemcel is £1,651,000.

2.4 The company has a commercial arrangement. This makes exagamglogene autotemcel available to the NHS with a discount. The size of the discount 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

Sickle cell disease

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. This causes a constant shortage of red blood cells. SCD can result in a range of acute and chronic complications such as acute chest syndrome and multi-organ failure. 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 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. The 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 3.19).

SCD mainly affects people from ethnic minority backgrounds. In the UK, most people with SCD are from Black African and Caribbean groups (see section 3.19). In response to consultation, NICE received a large number of comments from the public, healthcare professionals, carers and people with SCD. They explained that SCD has a significant negative social,

emotional, psychological, physical and financial impact on people with SCD and also their families and carers (see section 3.22). They described how every day is significantly disrupted by a life-limiting, debilitating, unpredictable and progressive condition. They felt that the severity and long-term organ damage from SCD had not been fully appreciated and that people felt abandoned and forgotten. The committee acknowledged the many testimonies that highlighted the constant fear that people with SCD live with. The fear of the next crisis, the next hospitalisation and the shortened life expectancy, which they described as looming over their daily lives. The testimonies described that SCD is traumatic for all involved and that many people with SCD have never known a pain-free life. The patient experts also said that as people with SCD get older, VOCs can become more painful and serious. The time it takes to recover from the physical and mental effects of VOCs can also be longer than the pain episode itself. A survey by the Sickle Cell Society 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. The patient experts stated that consideration should not only be given to the number of VOCs and hospital admissions per person, but also 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 the same as a VOC, and vaso-occlusion 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 few 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 patient experts added that SCD is much more than VOCs and its complications, and there is a lack of understanding of the reality of daily life for people with SCD. The committee took into consideration the patient and clinical perspectives and the comments received in response to consultation, 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 adequate hydration, preventing infections, regulating body temperature and treating pain, with or without hydroxycarbamide. People with SCD may need regular blood transfusions and so may also need iron chelation therapy. The clinical experts highlighted that there are very few treatments to stop symptoms and that those that are available often have intolerable side effects. The 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 a high burden of symptoms. They described how current standard care had reduced the frequency of VOCs, but had caused them to have more painful and severe crises, which increased their risk of complications.

In response to consultation, NICE received comments that described a high unmet need for an effective, well-tolerated treatment. Comments highlighted that current treatments offer only temporary relief and do not address the underlying cause of SCD. There was patient testimony explaining that pain relief often fails, and that this is worsened by delays in treatment, poor care, and conflict with healthcare professionals (see

section 3.19). Improvements in standard care have improved survival rates, but many people with SCD continue to have a reduced life expectancy because of complications (see section 3.8). This was supported by many consultation comments that emphasised that SCD significantly reduces life expectancy by around 2 to 3 decades compared with the general population.

For people who are fit enough and have an available matched related donor, allogeneic haematopoietic stem cell transplants (HSCTs) are a potential cure. The clinical experts noted that in the UK, it is common to search for a matched donor early in the treatment pathway. They 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 population with severe SCD who are not able to have an HSCT. 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. The patient experts highlighted that people with SCD want choice and empowerment in managing SCD. They want 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. The clinical experts and comments received during consultation noted that exa-cel could offer:

- a chance of disease-free life
- improved organ function and QoL
- reduced healthcare resource use
- fewer symptoms such as VOCs, and
- less clinical, social and economic burden for people with SCD and their families.

But, the clinical experts 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 the consultation responses and the 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 most people with SCD.

Treatment positioning of exa-cel

3.3 The company positioned exa-cel for SCD in people 12 years and over:

- who have recurrent VOCs
- who have the β^S/β^S, β^S/β^+ or β^S/β^0 genotype
- for whom HSCT is appropriate, and
- for whom a human leukocyte antigen-matched related haematopoietic stem cell donor is not available.

This is aligned with its marketing authorisation (see section 2.1). The company defined recurrent VOCs in line with its clinical trial, CLIMB SCD-121 (see section 3.4). It 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. The treatment process involves collecting blood stem cells from the person having exa-cel. At a manufacturing facility, 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 process for collecting stem cells already exists in the NHS and, if recommended, exa-cel would only be delivered at units accredited by JACIE (Joint Accreditation Committee International Society for Cell and Gene Therapy-Europe and European Society for Blood and Marrow Transplantation). The clinical experts explained that the first stage of the treatment pathway involves a strict screening process. So, people would only be eligible for exa-cel if:

- they have severe SCD,
- they have recurrent VOCs but no severe, irreversible complications, and
- they are fit enough to have an HSCT.

The committee acknowledged the difficulty in assessing the severity of SCD (see section 3.1) and that recurrent VOCs would be identified in clinical practice based on visible VOC episodes, as 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 had severe SCD with a β^S/β^S, β^S/β^0, or β^S/β^+ genotype, and did not have a suitable human leukocyte antigen-matched related donor. Severe SCD was defined as at least 2 VOCs per year during the 2-year period before screening, while having best supportive care. Severe VOCs during the screening period 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 needing hospital treatment 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 data cut, the trial had recruited 43 people. Of these, 29 had been followed for at least:

- 16 months after exa-cel infusion and
- 14 months after the last red blood cell transfusion for support after exa-cel infusion or SCD management.

This data was used in the economic model (see section 3.6). The latest data cut presented during the evaluation (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. This is a phase 3 long-term follow-up study, in which people will be monitored for up to 15 years. The primary outcome measure in CLIMB SCD-121 was the proportion of people with 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 support after exa-cel infusion or SCD management. Out of 29 people, 28 (96.6%) who were followed for 16 months or more after exa-cel infusion had no severe VOCs for at least 12 months. They 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 had no hospitalisations for at least 12 months. Of all the people who had exa-cel, 86.0% had no VOCs and 97.6% had no hospitalisations for between 1.3 months and 43.6 months. CLIMB SCD-121 was 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 lifetime effectiveness was based on clinical opinion, so robust long-term evidence needs to be collected from more people with longer follow up. The patient experts highlighted that the need for more data must be balanced against withholding a treatment that stops VOCs. But, they also recognised that the long-term effects of exa-cel, and whether people would have any complications in future, were uncertain. 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 treatment in SCD (see section 3.20). At the latest data cut, 44 people had exa-cel and 30 people had at least 16 months follow up (see section 3.4). The 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 questioned the generalisability of the trial results. First, because CLIMB SCD-121 only included 1 UK centre and a small number of people from the UK. Second, while the trial and UK SCD population is mainly people from African and Caribbean groups, this is a genetically varied group. The company stated that clinical practice and treatment guidelines for SCD are consistent across the UK, US and Europe (the countries included in CLIMB SCD-121). The clinical experts supported this and explained that although SCD populations are heterogeneous, 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 was generalisable to the NHS population and practice. The EAG

acknowledged these similarities, but noted that extrapolating a 12-month effect size from the clinical trial to a lifetime time horizon remains speculative. The committee considered CLIMB SCD-121 to be generalisable to the target UK SCD population and clinical practice. It thought that the results showed promise of potentially life-changing outcomes for people with severe SCD. It also noted that more data on the long-term effectiveness of exa-cel would reduce the uncertainties around the durability of the treatment effect (see section 3.27).

Economic model

Company's modelling approach

3.6 The company submitted an economic model that it described as a 'Markov cohort state transition model'. It assumed a lifetime time horizon, a cycle length of 1 month and a starting age of 21.2 years, based on the mean age in CLIMB SCD-121 (see section 3.4). The model compared the effectiveness of exa-cel with that of 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 (see section 3.9). This only accounted for people who had an exa-cel infusion and did not include those who withdrew before the infusion (see section 3.16). The remaining 3.4% were assumed to have the same outcomes as people who have standard care. VOC frequency in the standard-care arm was assumed to be constant throughout the model, based on the trial baseline VOC rate (4.2 per year; see sections 3.4 and section 3.13). After consultation, the company's model included non-mutually exclusive health states for the following 8 acute SCD complications (see section 3.10):

- acute chest syndrome
- acute infections
- acute kidney injury

- gallstones
- leg ulcers
- pulmonary embolism
- stroke
- VOC.

It included the following 7 chronic SCD complications:

- avascular necrosis
- chronic kidney disease
- heart failure
- neurocognitive impairment
- severe stroke
- pulmonary hypertension
- 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 was to reflect the potential effects of SCD before exa-cel and pretransplant conditioning. In the first committee meeting, 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. In this company model, a person in the standard-care arm could have multiple complications that independently added to the risk of dying. The EAG stated that the company's model was structurally flawed and did not have the methodological requirements for a Markov model (mutually exclusive health states). The EAG accepted that a person with SCD could have multiple complications per cycle. But, by applying mortality rates independently to complications, the model assumed that people can die more than once, and total deaths exceeded 100%. The EAG stated that this was mathematically incorrect and

logically impossible. It also stated that the structural problems were likely to invalidate the cost-effectiveness results.

Alternative modelling approach

3.7 During technical engagement, NICE's Decision Support Unit (DSU) did an independent review of the company's original model to clarify whether its structure was appropriate. The DSU agreed with the EAG that the company's modelling approach likely overestimated 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 had implications for the credibility of the modelled estimates of survival, costs and quality-adjusted life years (QALYs) and mostly affected the standard-care arm. This was because people in this arm were assumed to continue to have VOCs and complications. The model was designed to capture all of the healthcare-resource-use costs associated with a person with SCD having standard care for the duration of their life (time horizon). 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 were resolved, it would be necessary to check that the predicted complication rates were plausible. This was because they substantially affected the costs and QALYs in the standard-care arm (see section 3.10). 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 biased complication rates and possibly overestimated rates of the most severe events. This had a large effect on the standard-care arm, which drove the cost-effectiveness results.

In response to technical engagement, the company did 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 survival outputs from its original model 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 was not confident 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 evaluation. The committee agreed that the company's alternative model structure 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 section 3.7). But it noted that this model did not estimate standard-care mortality in line with the company's unpublished UK BOI study (see section 3.11). The DSU highlighted that the mortality estimate from the BOI study was based on very small numbers (40 out of 1,117 people) and included people who died as young as 8 years old. This suggested that the mortality estimate reflected a population with SCD that was more severe than would be eligible for exa-cel. Using the alternative model structure, the company estimated mortality by applying SMRs derived from literature by Desai et al. (2020) and a US Institute for Clinical and Economic Review report on gene therapies for SCD (2023). The EAG did not accept the company's proposed SMR values. This was primarily because the data was collected from a young population (mean age 15.7 years), which means that all deaths captured would have happened at a younger age. So the mean

age of death would be lower than the age of the overall population with SCD, and using this in the model would have overestimated the death rate.

The EAG considered that not enough evidence was provided to determine the most accurate life expectancy for people with severe SCD. This was because the company had not done a systematic literature review. The EAG ran a non-systematic search for additional external evidence, but reported difficulties in finding data to match the evaluation population. It found data from 6 real-world studies that suggested life expectancy was between 43 years and 55 years. The EAG used 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) better represented 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 were for the entire SCD population, not specifically the severe SCD population being evaluated. The company stated that people with severe SCD die at a younger age than people without severe SCD. At the committee meeting, the company said it believed the life expectancy of people with severe SCD to be between 39 years and 43 years, based on a literature search. So it stated Jiao et al. (2023) was not relevant for decision making. The clinical experts highlighted that there was limited data available to validate model inputs because evidence is often incomplete and outdated. Literature mortality estimates were 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. The mean standard-care survival estimates produced by the company's and EAG's preferred SMRs were 50 years and 53 years, respectively. The clinical experts commented that people with SCD with recurrent VOCs have a life expectancy of 40 to 50 years. 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 and why it had not done a systematic literature review. It also asked why further validation using a body of evidence was not presented to reduce uncertainty. It considered that the company's SMRs were more representative of the severe SCD population than the EAG's SMRs. But it concluded that further validation was needed to establish an accurate life expectancy estimate 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 had 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 it was optimistic because the treatment effect duration was 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. The 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 was needed. But, they noted that the clinical trial results suggested that after exa-cel treatment, fetal haemoglobin has a large effect on disrupting the polymerisation of sickle haemoglobin. 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 with measuring SCD severity using countable VOC episodes

(see section 3.1). Instead, maintaining 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 was highly predictive of long-term durability. The clinical experts at the committee meeting said that if the treatment effect was consistent for 5 years, they would be reassured that it would not wane. This aligned with cure assumptions in other disease areas.

There were no scenarios presented around the durability of exa-cel's treatment effect. The committee 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. In response to consultation, clinical experts explained that pain events after exa-cel are not necessarily evidence of exa-cel not working. Instead, these events are common in people who have experienced chronic pain or have a history of high opioid use. 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 was 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. The 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 have exa-cel (see section 3.3). The committee noted uncertainty about the long-term treatment effects of exa-cel because of the relatively short-

term follow up of CLIMB SCD-121. It understood from the 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 was plausible, but that this should be explored further with additional data collection (see section 3.27).

Complication rates

VOCs as a predictor of SCD complications

3.10 The company originally modelled 14 non-mutually exclusive SCD complications. The risk of developing each complication was predicted by the frequency of VOCs. The EAG acknowledged that VOCs are associated with poor outcomes in people with SCD, but stated that using VOCs to predict complications was not supported by evidence. It also highlighted that inconsistencies in the company's original model were causing an overestimation of complication rates. For example, the EAG noted that 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 complications. The EAG said that, by definition, they did not remain 'functionally cured', and the assumption that VOCs predict complications was 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 they were adjudicated VOCs, based on the definition of a VOC in CLIMB SCD-121 (see section 3.4). To reduce the structural uncertainty in the modelled complications, the EAG preferred to model complication rates directly from the literature and include VOC as an independent complication of SCD. It assessed the effect of using different complication rates and found that the incremental cost-effectiveness ratio (ICER) was sensitive to how complications were modelled. The clinical experts in the first meeting noted that there were some significant complications missing from the model, such as priapism and acute multi-organ failure. The EAG modelled complications using the

population with severe SCD from Brousse et al. (2023), because this was thought to be equivalent to the exa-cel target population. At the first meeting, the committee concluded that VOCs should not be used to estimate complications, but should instead be an independent acute complication. It also concluded that directly estimating complications from the literature was most appropriate.

Source of complication rates

3.11 At the second committee meeting, the company provided the following 2 sources to model complication rates:

- a combined literature source using complication data from 7 different studies, including Brousse et al. (2023), and
- the company's unpublished BOI study.

The BOI study was a real-world retrospective study that looked at the clinical burden of SCD in England for people aged between 1 and 86 years with recurrent VOCs. To enter the study, people needed a SCD diagnosis and at least 2 VOCs per year during the 2 previous years (aligned with CLIMB SCD-121; see section 3.4). VOCs were defined as an acute chest syndrome or a primary or secondary diagnosis of SCD with crisis or priapism. The study followed people for an average of 4.69 years and recorded data for the following age subgroups:

- 0 to 11 years
- 12 to 17 years
- 18 to 35 years
- 12 to 35 years and
- 36 years and over.

In the company's base case, it preferred to use the BOI study to estimate complication rates. It said that it was a more robust and relevant population than the combined literature source. This was

because it reported data for all complications and did not rely on assumptions about the length of follow up. Its VOC rate definition and study criteria also aligned with CLIMB SCD-121.

The EAG also preferred the BOI study, but noted that the company did not perform a systematic literature review to source the data to model complication rates. It was concerned that the BOI study may reflect outcomes from a population with more severe disease than the population in the trial. The EAG noted that people in the BOI study and the CLIMB SCD121 trial differed in age, VOC rates and history of complications before having exa-cel. For example, the BOI study population had a follow-up VOC rate of 5.8 per year, compared with 4.2 VOCs per year at baseline in CLIMB SCD121 (see section 3.4). It also included people who had baseline complications and were under 12 years and over 35 years. The marketing authorisation indication for exa-cel is for people aged 12 years and over (see section 2.1). The EAG noted that the model assumed that the only baseline complications were 14% retinopathy and 3% neurocognitive impairment. It said that applying complication rates from the BOI study may have overestimated the complication risk in the evaluation population. The EAG explained that a more robust way to model complications using the BOI study data would be to match to the CLIMB SCD121 data. This would avoid overestimating the benefits of exa-cel.

The clinical experts noted that the baseline VOC rate in the model was likely to be underestimated because many people do not attend hospital when they have a VOC (see section 3.13). They said that in clinical practice, the VOC rate may be more aligned with rates reported in the studies presented. The committee thought that in the absence of a systematic literature review, the BOI study was the most suitable source to model complications. But it was concerned that the

population did not reflect the model population, and about the impact this would have on estimated complications.

After the second meeting, the DSU did a review to provide guidance on which of the available sources of complications was the most appropriate. It also assessed whether using this source would over- or underestimate the long-term risk of complications in SCD. It explained that using the BOI study complication rates in the model assumed that the population in the BOI study reflected the population eligible for exa-cel. It also assumed that the observed exa-cel treatment benefit from CLIMB SCD121 was applicable to a population with more severe SCD than in the trial. The DSU highlighted that the overlap between the BOI study and CLIMB SCD121 was not reported, so it was not possible to see if matching these populations was feasible. It stated that it was unclear if the population in the BOI study or population in the CLIMB SCD121 trial better represented the decision problem population of exa-cel.

The committee asked the clinical experts which population it thought best represented the population that would have exa-cel in NHS practice. The clinical experts responded that there are some people who would be eligible for exa-cel that were not included in the trial. For example, people aged 35 years and over. The committee noted that the average age in the trial and in the model was 21.2 years. But, the equivalent population in the BOI study (people aged 12 to 35 years, who met the CLIMB SCD-121 inclusion criteria) was older (average age 23.4 years). The committee recalled that the clinical experts had said that the UK is beginning to see an older SCD population (see section 3.8). It questioned how old the average person having exa-cel would be in clinical practice, considering that people eligible for exa-cel could be older than the trial population. The clinical experts explained that many people are now being referred for stem cell transplantation at

an older age. People also often delay transplantation because of concerns around fertility after having an HSCT (see section 3.19). The company's clinical advisory board stated that it may initially prioritise treating younger people. But, the clinical experts at the committee meeting expected that the treated population would also include older people, both initially and in the future. The patient experts supported this, noting that people of all ages would want treatment with exa-cel. The committee agreed that if available, people of all ages could have exa-cel, including those over 35 years, if they met the criteria for HSCT. It was uncertain what age, baseline complications and VOC rate would represent the true exa-cel NHS population (see section 3.13). The committee decided that without further evidence, the BOI study was an appropriate source to use for estimating complications. It also considered the current model assumptions about age, baseline complication and VOC rates to be acceptable. It was aware that these assumptions had the potential to affect the cost-effectiveness results. The committee concluded that further data should be collected on the NHS exa-cel population to inform model baseline characteristics, such as age, baseline complications and annualised VOC rate (see section 3.27).

Method of applying complications

3.12 After the first committee meeting, the company's preferred base case applied complication rates from the BOI study, using the overall population data (from now, referred to as the 2 years and over subgroup). The EAG preferred to use a BOI study subgroup of people aged 12 to 35 years (from now, referred to as the 12 to 35 years subgroup). This was because it was more aligned with the CLIMB SCD-121 age criteria (12 to 35 years). But it noted that this subgroup still had a VOC rate that was higher than in the trial, and so represented a more severe disease than in the evaluation population (see section 3.11). The EAG also removed the cost and outcomes of the independent complication of acute chest syndrome from its base case. This was because it noted in the first

meeting that acute chest syndrome was also included in the VOC definition in CLIMB SCD-121 (see section 3.4) and the literature sources used in the model (for example the BOI study, Brousse et al. 2023). So, the cost and disutilities associated with this event were being double counted. The committee agreed that the cost and outcomes of acute chest syndrome as an independent complication should be excluded.

After the second committee meeting, the company stated that the 12 to 35 years subgroup data did not reflect the marketing authorisation (12 years and over, see section see section 2.1). It added that using it to model complications significantly underestimated the lifetime severity of SCD. This was because the 12 to 35 years subgroup complication rates were applied as a constant rate throughout the model's lifetime horizon. This meant that when people in the model turned 36 years old, complications developed at a lower rate than they would otherwise. The company reiterated that the number and severity of SCD complications increase as people age and progress (see section 3.1). At the third committee meeting, the company updated its approach to modelling complications. It combined the complication rates of the 12 to 35 years subgroup and the 36 years and over subgroup (from now, referred to as the 12 years and over subgroup). It did this by weighting the mean complication rates by the proportion of people in each age group in the BOI study. It said that this subgroup matched the decision problem population (12 years and over) and more accurately reflected lifelong SCD-related morbidity. The EAG noted several issues with this approach:

- The BOI study baseline age distribution (12 to 17 years: 9.9%; 18 to 35 years: 48.3%; 36 years and over: 22.3%) was not aligned with CLIMB SCD-121 (12 to 17 years: 27.9%; 18 to 35 years: 72.1%). The EAG stated that weights applied should reflect the model and trial population composition.
- The 12 years and over subgroup rates were applied as a constant rate in the model. This amplified the overestimation of complications in

earlier cycles of the model (where the population and potential bias was largest because of discounting) and downplayed the underestimation in later cycles.

- The 12 to 35 years and 36 years and over subgroups should not have been treated as data from a single population that was followed up from 12 years until 36 years and over. This was because it was unknown if the 2 subgroups were only different because of age and not any other uncontrollable factors. For example, people alive at 35 years and over may be healthier than those alive at 20 years, because people with more severe disease may die younger. This meant that combining the rates as if they were from 1 longitudinal cohort may have introduced uncontrollable biases and increased uncertainty.

  The EAG stated that it still preferred to use the 12 to 35 years subgroup population, noting the mean age of this subgroup was similar to that of the model starting cohort (23.6 years compared with 21.2 years). In its second independent review, the DSU agreed with the EAG that the company's 12 years and over subgroup may inflate the risk of complications for younger people in the model. It also agreed with the company that the 12 to 35 years subgroup data did not account for complications increasing with age. It noted that around 82% of the standard-care arm were predicted to survive beyond 36 years. The DSU noted that the BOI study recorded age at baseline (cross-sectional data) and complications over time (longitudinal data), but not the age at which complications happened. This meant that further statistical modelling of the BOI data to predict the risk of complications by age could not be done. It noted that ideally the statistical relationship between complications and age would be modelled. But to do this, the data would need to be broken down into narrower age bands and re-analysed according to the age at which complications happen. Instead, the DSU ran analyses to further explore the impact of age-specific complication rates. It did this by applying different complication rates for

specific age bands once people reached a particular age in the model. It ran 4 age-dependent scenario analyses:

- DSU scenario 1: 12 to 35 years subgroup rates applied to people modelled until age 36, then 36 years and over rates applied for all subsequent model cycles.
- DSU scenario 2: 18 to 35 years subgroup rates applied to people modelled until age 36, then 36 years and over rates applied for all subsequent model cycles.
- DSU scenario 3: 12 to 17 years subgroup rates applied to people modelled until age 22, 18 to 35 years subgroup rates applied to people modelled aged 23 to 41 years, then 36 years and over rates applied for all subsequent model cycles.
- DSU scenario 4: 18 to 35 years subgroup rates applied to people modelled until aged 41 years, then 36 years and over rates applied for all subsequent model cycles.

DSU scenario analyses 3 and 4 included a 5-year lag to applying complication rates in the model to account for the follow-up time in the BOI study (see section 3.11). These analyses attempted to align the age of people in the BOI study with the appropriate time point in the model. The DSU noted that none of the available options for incorporating complication rates into the company's model were ideal. Its preferred analysis was either DSU scenario 3 or 4. This was because they allowed complications to increase with age, and better reflected the age at which the complications happened in the BOI study. But the DSU did note that its scenarios also had limitations. For example:

- they relied on broad age groups that may hide the true relationship between age and complications
- the exact age at which complications happened was still unknown, so the time lag could lead to inaccuracy in the model predictions, and

- if more age bands are used, the number of people informing the rates is smaller.

The company stated that including a time lag added uncertainty and made the complication estimates even more conservative. This was in addition to the model not including all relevant chronic complications and the literature likely underreporting complications. The company said it was committed to addressing some of these uncertainties, including providing more granular data on complications for the BOI study. The DSU explained that if a lag is not applied, there would be a mismatch in the model. This is because the correct time at which complications happen was not captured and so people would be misallocated in the model.

The committee thought that none of the suggested complication rates were ideal. It recalled that no systematic literature review was done to identify the most appropriate rates to model standard-care complications, as is best practice (see section 3.11). It was also aware that the clinical experts had said that some key manifestations were missing from the model (see section 3.10). The committee thought that complications should be modelled with age-dependent rates to reflect the increased risk of complications as people age. It considered whether the DSU scenarios with or without a lag were most appropriate and highlighted that there were advantages and disadvantages with both options. But it was concerned that the age at which complications happen was still unknown, so applying the lag could be conservative. The committee considered that data on the age at which complications happen, along with a systematic literature review and a model that incorporates all relevant SCD complications, would be needed in any managed access agreement (see section 3.27). It concluded that it would not apply a lag and that DSU scenario 2 was the most appropriate. This was because it used subgroup data that was mostly

aligned with the model's starting age (21.1 years). But it still considered there to be substantial uncertainty in the complication rates modelled.

Definition of VOC

3.13 In the company's model, VOCs were defined as all VOCs that needed treatment in a hospital (inpatient or outpatient; see section 3.4). In the first committee meeting, the EAG highlighted that inconsistencies in the model were causing complications to be overestimated (see section 3.10). This included inconsistency in the VOC definition used in CLIMB SCD-121 and literature used to estimate complications in the company's original model (VOCs that lead to inpatient hospitalisation). So, the EAG said that the company's VOC rate was too high (4.2 VOCs per year) and caused excessive estimated complication rates. The EAG preferred to use the inpatient 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 the 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; see section 3.10).

At the first meeting, the committee concluded that the inpatient hospitalisation VOC definition was the most appropriate for decision making. In response to consultation, the company stated that the inconsistencies in VOC definitions in the model were resolved, and that the most appropriate definition to use was all VOCs treated in a hospital (4.2 per year). It explained that there is no biological difference between a VOC needing inpatient hospitalisation or needing treatment in a day unit. All VOCs impact QoL, complications, life expectancy, healthcare resource use and long-term outcomes. The reasons someone would be admitted to hospital rather than being seen as an outpatient is related to many factors. The committee recalled from the first meeting that many people with SCD avoid seeking hospital treatment (see section 3.1). This was supported by

consultation comments from healthcare professionals and people with SCD. They explained that people try to manage painful crises at home and avoid seeking treatment because of previous negative experiences, stigmatisation and discrimination. They said that because of this, data on VOCs needing hospital treatment will underestimate the frequency of pain and its effect on people's lives. The company acknowledged that its preferred rate (4.2 VOCs per year) likely underestimated the true number of VOCs experienced by people with SCD. This was supported by the clinical experts based on their experience in clinical practice. The EAG highlighted that most literature studies defined VOCs based on inpatient hospitalisation and kept this rate in its base case (2.6 per year). It noted that the literature used in the model (CLIMB SCD-121 and company's BOI study) came from a more severely affected population than the evaluation population (see section 3.11). So, the treatment effect of exa-cel could have been overestimated. The committee considered the reasons people avoid going to hospital and that the CLIMB SCD-121 baseline VOC rates may have been underestimated. It concluded that the most appropriate definition was all VOCs needing treatment in hospital (a rate of 4.2 per year). But it would like further data collected on the most appropriate VOC rate to apply in the model (see section 3.27).

Utility values

3.14 Health state utility values in the model were based on CLIMB SCD-121 EQ-5D-5L data that was mapped to the EQ-5D-3L. Baseline EQ-5D utility value (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 thought that a baseline EQ-5D utility value of 0.81 may be high, considering the impact of the condition. But it noted that in the model this value would reduce over time because of complication events. The company and EAG had considered using the EQ-5D appropriate in their base-case analyses. 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 the EQ-5D in this population.

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 value from baseline to month 24 (0.11). The EAG highlighted that at month 24, the EQ-5D was measured in fewer people than at baseline and so could be affected by selection bias. It said that the EQ-5D values recorded earlier in the trial (0.88), which were not affected by loss to follow-up bias, should be used. Because of the company's 'functionally cured' assumption (see section 3.9), the choice of utility value could affect the cost-effectiveness results. The committee 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 this group 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 QoL.

In response to consultation, the company provided additional evidence showing standard-care utility values over the modelled time horizon. It stated that when disutilities associated with complications were accounted for, the QoL was accurately captured in the model using the 0.81 baseline utility value. It also provided a post hoc analysis that excluded a proportion of people who reported perfect health (EQ-5D of 1) in the trial (the results are confidential so cannot be reported here). The company said that this analysis showed that the 0.11 value was conservative for the potential QoL gains people could have from exa-cel. The EAG noted that this analysis approach violated established methodology. This was because it arbitrarily selected trial data, and using this approach would

create an inconsistency between the utility values and efficacy rates used in the model. The company claimed that the EQ-5D has significant ceiling effects and does not accurately capture the QoL impact of SCD. This is because some people reported the highest EQ-5D health value (1). It explained that it was unrealistic that someone would be willing to trade off perfect health for a burdensome transplant with an experimental treatment. The EAG suggested that the high baseline utility values could instead be because the CLIMB SCD-121 population was relatively healthier than most people with severe SCD. The committee noted that the model applied a disutility at baseline to account for comorbidities, so the utility value at the start of the model would not be equal to perfect health for any patient.

A patient expert asked if data was collected about the time that had passed between a person's most recent VOC and the EQ-5D measurement. They explained that the high EQ-5D values observed in the trial may be reported by people who had not had a VOC recently. The expert described that people with SCD can appear to be healthy one day, but could have severe debilitating pain the next. The company said that the timing of the most recent VOC event in relation to the EQ-5D measurement was not recorded in the trial. The committee asked whether people who reported a low EQ-5D value at baseline had recently had a VOC. This was because additional disutilities for VOC complication events were applied throughout the model. So this could be a source of double counting if the impact of a VOC was already captured in the health state utility value of standard care. The clinical experts highlighted that people who recently had a VOC were unlikely to be well enough to complete the EQ-5D. They explained that the high baseline values were likely a result of adaptation to SCD. That is, because people have had SCD since birth, they cannot compare their life with a life without SCD. A patient expert supported this, explaining that a day at full health after their allogeneic HSCT is not comparable to a day at full health with SCD. They described

that before the HSCT, they had not experienced a time without pain and that they now felt better than they thought was possible. They explained that they had not fully appreciated the mental burden of factoring SCD into every decision and the impact it has on everyday life. A patient expert still living with SCD noted that this post-HSCT experience is unrecognisable, when compared with the daily challenges of SCD. They said that whether someone has many VOCs or not, SCD affects everything. Consultation comments described how the EQ-5D overestimates QoL in long-term conditions. They said that it fails to account for managing pain at home, the days missed from work and education and the reduction in life opportunities because of SCD. They explained how the value given to QoL does not correlate with the reality of living with SCD and that people get used to a health state that would be considered restrictive by people without SCD.

The committee acknowledged the difficulties of measuring QoL in a long-term condition such as SCD, which is associated with multiple unpredictable VOCs and other complications. It considered the consultation comments and the evidence from the company, clinical and patient experts and was satisfied with how utility was modelled over the time horizon once disutilities were accounted for. It recognised that the EQ-5D may not fully capture the QoL of people with SCD, particularly given the episodic nature of SCD crises and the effect of the timing of measuring health-related QoL. It also considered the impact of the highly uncertain complication rates on the utility values and the potential double counting of VOC disutility.

The company stated that the impact of SCD on carer QoL had not been quantitatively captured in the model (see section 3.22). But the committee concluded that it would consider it qualitatively by accepting a higher level of uncertainty associated with the model. The committee concluded that utility values of 0.81 and 0.88 for the standard care and exa-cel arm,

respectively, were acceptable for decision making. But, uncertainties remained about the most appropriate utility values to use.

Adverse events

3.15 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 happen 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 events related to exa-cel would be double counting healthcare resources. The clinical experts supported this. The committee concluded that adverse events for exa-cel infusion did not need to be included in the model.

Treatment withdrawals

3.16 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 and outcomes for people who withdraw and go on to have standard care should be accounted for. At the first meeting, the committee concluded that the costs and outcomes of treatment withdrawal should be accounted for in the model. In response to consultation, the company reiterated that it was unreasonable to include the outcomes of people who did not have exa-cel, as it artificially diluted the efficacy. The company explained that most of the withdrawals from CLIMB SCD-121 were because of the nature

of SCD, or related to the clinical trial, rather than because of the treatment. For example, reasons for withdrawing included:

- the experimental nature of the trial
- the health inequalities experienced and mistrust in healthcare professionals (see section 3.19)
- the economic and psychosocial burden of having a transplant and
- the difficultly collecting cells in people with SCD.

The company claimed that many of the withdrawals in CLIMB SCD-121 would not happen in clinical practice. This was because expertise on apheresis is increasing, as is the support for centres that provide it. The clinical experts supported this, explaining that there is ongoing work to provide psychological support for people who have HSCTs. They expect that this will reduce the number of HSCT withdrawals in the future. The EAG and clinical experts stated that it is difficult to predict the number of people who will withdraw from treatment in clinical practice. The EAG noted that withdrawal was not related to access inequalities, but because some people who provided cells for manufacturing did not have enough cells for editing. The EAG's position remained that costs and outcomes for all people who start the treatment pathway should be modelled. This is the point at which people have screening to determine the suitability of HSCT, defined as the intention-to-treat (ITT) population. It explained that including costs and outcomes is a fundamental requirement of health economic analysis. Removing the outcomes of people who withdraw would conflict with basic health technology assessment principles of using the ITT efficacy. The company's model started at the point of exa-cel infusion and so efficacy was based only on people who have an exa-cel infusion. The committee agreed that 19% of people in the ITT population were not treated and so would continue to have standard care in NHS. It concluded that it was appropriate to include costs and

outcomes for people who withdraw from treatment, to reflect the full treatment pathway and the ITT population.

Non-reference-case discount rate

3.17 The company believed that exa-cel met the criteria for the non-reference-case discount rate of 1.5%. The committee noted that all of the following criteria in section 4.5.3 of the NICE health technology evaluations 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 reported a mean age of death for people with severe SCD of 40 years. The EAG thought that the company did not provide robust and validated estimates of survival (see section 3.8). In response to consultation, the company provided 5 literature studies that showed that the mean age of death for people with severe SCD is 40 to 44 years old. The EAG believed that this data included people who had more severe SCD than in the evaluation population. Responses to consultation highlighted that some people die before they reach adulthood. Data from the UK National Haemoglobinopathy Registry showed that as many people with SCD die aged between 19 to 45 as those over 46 years.

The committee noted that the company's and EAG's base cases used a utility value of 0.81 at baseline to represent health-related QoL for people with severe SCD (see section 3.14). In the company's submission, it said that 0.81 was lower than the average UK population QoL, indicating that

SCD impairs QoL. The committee expected this QoL difference between SCD and the general population to be larger if it caused a very severely impaired life. In response to consultation, the company presented data to show that the modelled utility in the standard-care arm over the time horizon appropriately accounted for the disutilities associated with chronic and acute SCD complications (see section 3.14). The patient experts and responses to consultation from people with SCD, carers, family and the public, explained the substantial effect SCD has on people's lives, and that its effects worsen as people age (see section 3.1). In particular, that there is a fundamental misunderstanding about the nature, severity and impact of SCD on QoL. They said that most data does not fully capture the clinical severity, mortality and morbidity risk of the QoL impact from SCD. People felt like a higher 'burden of proof' was needed for the SCD community to be taken seriously about the severity of the condition. A joint survey done by Anthony Nolan and the Sickle Cell Society showed that 82% of people say that SCD has a negative or very negative impact on their QoL. The clinical experts agreed, and explained that QoL is difficult to capture in conditions present from birth and described SCD as a condition that fluctuates in severity (see section 3.1). 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 in QoL measurement in SCD. It also recognised that there were substantial uncertainties in the estimation of utilities (see section 3.14).

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 that the patient and clinical experts 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. A testimony from the first person to have exa-cel described that they no longer have pain, need treatments or go to hospital, and they are living a life free of SCD.

The company argued 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 of the clinical trial (see section 3.5). The EAG highlighted that CLIMB SCD-121 showed that the possibility of a VOC relapse remains a relevant clinical question. The clinical experts and the company suggested that these reported VOCs were likely to be episodes of pain, similar to those expected after a curative HSCT (see section 3.9). The EAG argued that the trial follow up was insufficient to robustly support the assumptions of a total cure, eradication of VOCs and any relevant longer-term outcomes and SCD complications. The clinical experts had stated 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 met. This is because the company and experts had shown that people would otherwise die or have a severely impaired life.

When considering the second criterion, the committee noted considerable uncertainty about the likelihood of exa-cel returning people to full or near-full health. It understood from the clinical 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 concluded that the second criterion was not met with the available data. It felt that it was plausible that exa-cel could return people

to full or near-full health. But it felt that the uncertainty was compounded by the short-term follow up of the clinical-effectiveness evidence and that further data could demonstrate that this criterion was met. So, it would like to see this explored with further data collection (see section 3.27).

The committee concluded that the third criterion was also not met. It was plausible that exa-cel benefits were sustained over a long period, but this was highly uncertain given the limited follow up of clinical evidence. So the committee would like to see this explored with further data collection (see section 3.27). The committee concluded that not all of the criteria were met, so a 3.5% discount rate should be used. It considered that it was plausible that all criteria could be met after further data is collected.

Severity

3.18 The severity modifier allows the committee to give more weight to health benefits in the most severe conditions. Absolute and proportional QALY shortfall should be calculated in line with section 6.2.17 of the NICE's health technology evaluations manual and DSU technical support document 23. The company estimated that a weight of 1.7 should be applied to the QALY increments. But, in its calculation the company used a 1.5% discount rate (see section 3.17) to calculate the shortfalls. Section 6.2.17 of the NICE health technology evaluations manual stipulates that shortfall calculations should include discounting at the reference-case rate (3.5%). So the severity thresholds were not suitable when different discount rates were used. Using the same reference-case discount rate across evaluations ensures that the assessment of severity is applied consistently and fairly. The committee noted that the company's revised 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-case estimates did not meet the criteria for a severity modifier weight. The company base case (with a 3.5% discount rate) estimated absolute and proportional QALY shortfalls of 12.10 and 54% respectively. The EAG's base case estimated absolute and proportional

QALY shortfalls of 11.53 and 51% respectively. The company and EAG base cases did not include the committee's preferred method of applying complication rates (see section 3.26). Using the committee's preferred assumptions, the severity modifier threshold was met (absolute and proportional QALY shortfalls of 12.11 and 54% respectively). The committee concluded that a severity weight of 1.2 should be applied.

Health inequalities

Identified health inequalities

3.19 The company, stakeholders, consultation comments and patient and clinical experts raised concerns about health inequalities for people with SCD. This is because SCD mainly affects people from ethnic minority backgrounds. In the UK, most people with SCD are from Black African and Caribbean groups (see section 3.1). Comments in response to consultation highlighted that this population is more likely to experience poverty, discrimination and barriers to accessing healthcare. The company added that this population disproportionately experiences health inequalities and is more likely to live in more deprived areas of the UK. It noted that in its unpublished UK BOI study, most 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). 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 among 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 highlights issues of inequity, discrimination, racial bias, stigmatisation, inequalities in accessing treatment, and the lack of understanding and prioritisation of people with SCD. The committee noted that this was also reflected in the large number of comments received in response to consultation. The comments highlighted that people with SCD

feel like they are silently living in agony, often not believed, and their pain often disregarded. People have had to learn how to cope with their daily lives and adapt to being unsupported because of the lack of education and knowledge about SCD. The patient and clinical experts supported this, noting 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 the condition.

The clinical experts explained that, in their view, services are under resourced in terms of staff and facilities and that there is inequality in the commissioning process. The patient experts described how there are large inconsistencies in the care offered in different areas (see section 3.1). This means that some people avoid seeking treatment, even when the pain severity would need hospitalisation. They highlighted that available treatment should not be so varied, and that if exa-cel were to be recommended, it would be important that people could access it wherever they live. The company said that it would try to ensure that exa-cel is equitably available throughout the country. The patient experts also explained how health inequalities, discrimination and stigmatisation have created a sense of hesitancy, and mistrust in 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. The patient and clinical experts explained that exa-cel provides an opportunity to address some of the issues described and could start to repair relationships between people with SCD and healthcare providers. The committee asked if the evidence gaps seen in this evaluation are because SCD mainly affects people from ethnic minority backgrounds, 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, the clinical experts highlighted that high-quality data in SCD is very limited and that it is plausible that people with SCD may be less likely to engage with research. They emphasised that caution is needed so that current health inequalities are not worsened by a conservative approach to decision making being taken based on an assumption of lack of data.

Stakeholders and consultation comments 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 younger and older than the age group in the CLIMB SCD-121 trial (aged 12 to 35 years). People highlighted that under the NHS commissioning criteria, unlike children, adults can only have an HSCT from a fully matched sibling donor. The clinical experts had said that only 15% of people have suitable donors for an allogeneic HSCT (see section 3.2). The committee was aware that the marketing authorisation indication did not include an upper age limit for exa-cel treatment.

The committee understood that the following health inequalities were relevant to consider:

- SCD in the UK mainly affects people from Black African and Caribbean ethnic groups.
- People with SCD are more likely to live in more deprived areas, 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

3.20 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 someone living in an area of high deprivation compared with someone living in an area of low deprivation. 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 health technology evaluations manual does not 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 a DCEA. But, taken together, NICE's health technology evaluations manual, 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 about the inputs of the company's DCEA, including how ethnic background was 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 of exa-cel treatment 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, the estimated uptake appeared to be disappointingly low. The committee noted that SCD is not a rare disease and many people could be eligible for treatment. So it questioned why there was limited evidence and why the CLIMB SCD-121 sample size and anticipated uptake was small. 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. The clinical and patient experts supported this. They explained that the same fears and barriers were felt when hydroxycarbamide and transfusions were first introduced, but 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 by younger people with SCD. So, there is hope that if offered, exa-cel would be accepted by many of those eligible. At the second committee meeting, a patient expert explained that even people who are eligible to have exa-cel, but are in good health now, would still choose to have it. This is because they are aware that in several years, a significant complication could develop that further affects their QoL.

The committee noted that stigma could be a factor in engaging with treatments such as pain management in SCD. But the committee was not clear on the extent of this issue or its impact on QoL or costs. It was aware of the need to consider this aspect, as outlined in NICE's principles, to account for health inequalities. The patient experts stated that the main concern for people will be whether it is a safe treatment to have now and whether it will be safe in the long term. 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 were to have exa-cel, the treatment would not address the inequalities experienced by most people. The committee considered that the company's evidence and testimony from stakeholders, experts and comments received through consultation gave 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 health technology evaluations manual and NICE's principles to account for health inequalities.

It recalled section 6.2.36 of the NICE health technology evaluations manual, which states that additional considerations can be made by the committee, especially when they are broader social considerations. It noted 1 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 experiences 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 clinical experts stated that social and structural barriers may prevent the generation of high-quality evidence. This could be because of 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 and in the modelling of utility, complications and mortality. It also concluded that an appropriate and reasonable adjustment to account for health inequalities was to adjust its acceptable ICER (see section 3.25). 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 that adjustments to the acceptable ICER would need to be carefully considered.

Other factors

Innovation

3.21 The company, patient and clinical experts, and consultation comments explained that exa-cel is an innovative treatment. This is because it provides a potential cure for people who do not have sufficiently effective treatments available to them. They added that exa-cel is a one-time infusion 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. Consultation comments highlighted concern that research and development for such innovative treatments for SCD would stop if NICE did not recommend the treatments. They hoped that exa-cel would encourage the development of new treatments for a disease area that has previously had a lack of equity and funding (see section 3.20). 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 because of the inability to randomise participants. It also noted comments from the patient experts, consultation comments and the company that people can be reluctant to engage in research for innovative and complex treatments (see section 3.20). So, the committee was willing to accept a higher degree of uncertainty in the clinical-effectiveness evidence for exa-cel.

Carer quality of life

3.22 The company, patient experts and consultation comments highlighted the substantial impact that SCD has, not just on people with SCD, but also on carers (see section 3.1). SCD affects carers' ability to maintain employment, causes higher degrees of depression, anxiety and stress, and significantly lowers health-related QoL compared with people not caring for people with SCD. A study from Besser et al. (2022) showed that the mean EQ-5D-5L value for UK SCD carers was 0.62. The company explained that some benefits of exa-cel in SCD, such as improved mental and physical health and QoL of carers, were not captured in the economic modelling. It asked that the maximum acceptable ICER threshold (see section 3.25) should take this into account. The committee acknowledged that SCD has an impact on the QoL of carers, but that this had not been quantified by the company. The committee concluded that it would consider carer QoL qualitatively in its decision making, by accepting a higher level of uncertainty associated with the model.

Equalities

3.23 The committee recognised that equalities issues had been raised during the evaluation. Several issues were identified by stakeholders:

- SCD mainly affects people from Black African and Caribbean ethnic groups.
- People from Black African and Caribbean ethnic groups are more likely to experience poverty, discrimination, barriers to accessing healthcare and poorer health outcomes.
- Consideration needs to be given to the ethnic, faith-related and cultural needs of people offered exa-cel.
- There is a socioeconomic imbalance among people with SCD.
- Ethnic minority groups who already face health inequalities, stigmatisation and prejudice, also face racial discrimination.
- The impact of limited 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.
- Adults, unlike children, can only have an allogeneic HSCT from a fully matched sibling donor, but only 15% of people have a suitable donor available.
- There is likely to remain an unmet need for some 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 discussed in section 3.19. 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. For example, it recognised the potential barriers to generating high-quality evidence because of health inequalities and it accepted some evidence despite the significant uncertainty (see section 3.20). This included:

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

The committee also increased the acceptable ICER at which exa-cel would be considered cost effective (see section 3.25).. It concluded that its recommendations would 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

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

- the source of complications
- the inclusion of acute chest syndrome as an individual complication
- the utility value for the exa-cel 'functionally cured' population
- 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 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 3.25).

Acceptable ICER

3.25 NICE's health technology evaluations manual 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, health inequalities and uncaptured carer QoL benefits. The committee considered the options available to it to account for these additional factors. It recalled its conclusion about the innovative and complex nature of exa-cel and the carer QoL benefits, meaning it was willing to accept a higher degree of uncertainty in the evidence and the model (see section 3.21 and section 3.22). 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 would be between £30,000 and £35,000 per QALY gained.

Committee's preferred assumptions

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

- using the company's alternative model structure (see section 3.7)
- using the company's preferred SMR (see section 3.8)
- using the 'all VOCs treated at hospital' baseline rate (see section 3.13)
- estimating complications directly from the literature using the BOI study (see section 3.10 and section 3.11) and using age-dependent rates from DSU scenario 2 (see section 3.12)
- excluding acute chest syndrome as an individual complication (see section 3.11)
- using a health state utility value of 0.81 for the standard-care population (see section 3.14)

- using a health state utility value of 0.88 for the exa-cel 'functionally cured' population (see section 3.14)
- excluding adverse events for exa-cel (see section 3.15)
- including the effect and costs of exa-cel treatment withdrawals (see section 3.16)
- using a 3.5% discount rate (see section 3.17)
- that the 1.2 severity modifier was met (see section 3.18).

The committee noted significant uncertainties with some of its preferred assumptions. It considered these uncertainties when determining its acceptable ICER (see section 3.25). The committee's preferred assumptions gave an ICER that was above the range considered to be cost effective (see section 3.24). The committee concluded that it could not recommend exa-cel for routine use. The committee thought that some differing assumptions were plausible. It considered an optimistic scenario that included a 1.5% discount rate (see section 3.17). It also considered a pessimistic scenario that included:

- the cost of exa-cel for people who withdrew from exa-cel pre-infusion (see section 3.16)
- complications estimated using the DSU scenario 3 rates (see section 3.12)
- model starting age and sex distribution aligned with the BOI study 12 to 35 years subgroup that was aligned with the CLIMB SCD-121 exclusion criteria (23.36 years and 51.6% female; see section 3.11).

The ICER for the pessimistic scenario was above the committee's preferred cost-effectiveness range. The ICER for the optimistic scenario was below the committee's preferred cost-effectiveness range. The committee considered that further data collection would likely help to identify different appropriate assumptions. So, it agreed that exa-cel demonstrated plausible cost effectiveness.

Managed access

Consideration of managed access suitability

3.27 Having concluded that exa-cel could not be recommended for routine use (see section 3.26), the committee then considered if it could be recommended with managed access for treating SCD. It noted that a recommendation with managed access (section 6.4.6 of the NICE health technology evaluations manual) could be considered when:

- the medicine has not been recommended, and it has the plausible potential to be cost effective at the currently agreed price, but the evidence is too uncertain, and
- 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 medicine in clinical practice, and
- this data could feasibly be collected within a reasonable timeframe (up to a maximum of 5 years) without undue burden.

The committee 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
- baseline characteristics of people having exa-cel, including age, sex, prior complications and annual VOC rate
- mortality and life expectancy for exa-cel and standard care.

It compared this with the data the company intended to collect according to its updated managed access proposal:

- 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 the 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, especially those relating to the standard-care arm. It also noted the limitations of the managed access timeframe, and that some uncertainties, such as life expectancy, were unlikely to be resolved. The committee also discussed the plausible potential for exa-cel to be cost effective at the current price. The committee considered its preferred assumptions (see section 3.26). It considered the range of ICERs, and agreed that the optimistic scenario was plausible and within the range considered an acceptable use of NHS resources (see section 3.25).

Recommendation

3.28 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 and to account for health inequalities. It also decided to accept a higher degree of uncertainty in the model and the clinical-effectiveness evidence because of the innovative and complex

nature of exa-cel and because of uncaptured carer QoL benefits. The committee concluded that exa-cel met the criteria to be considered for a recommendation with managed access and that the managed access proposal from the company had the potential to reduce the outstanding uncertainties. It recommended exa-cel for use if the conditions in the managed access agreement are followed. It recommended it as an option for SCD in people 12 years and older with recurrent VOCs (at least 2 VOCs per year during the 2 previous years), 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. When the guidance is next reviewed, the company should use the committee's preferred assumptions (unless new evidence indicates otherwise), as set out in section 3.26. Also, it should provide systematically gathered evidence for SCD complications and mortality, and a model that more accurately models SCD complications and mortality (see section 3.7 and section 3.12).

4 Implementation

4.1 When NICE recommends a treatment as an option for use with managed access, NHS England will make it available according to the conditions in the managed access agreement. See section 4f of The Innovative Medicines Fund Principles. Funding for this treatment will be available from the point of marketing authorisation, or from the release of positive draft guidance, whichever is later. This means that, if a patient has sickle cell disease and the healthcare professional responsible for their care thinks that exagamglogene autotemcel is the right treatment, it should be available for use, in line with NICE's recommendations and the criteria in the managed access agreement.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use with managed access. When a NICE technology appraisal guidance recommends the use of a

drug or treatment, or other technology, for use with managed access, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 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. 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.

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