

Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 11 April 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Vertex Pharmaceuticals Ltd.

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: - the name of the company - the amount - the purpose of funding including whether it related to a product mentioned in the stakeholder list - whether it is ongoing or has ceased.		N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.		None.
Name of commentator person completing form:		
Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.	
1	Executive summary Application of the non-reference discount rate - Vertex maintains that exa-cel qualifies for the non-reference discount rate and demonstrates that each of three criteria are firmly met. Severe SCD has a substantial impact on daily living, quality of life over time, and reduces life expectancy by several decades. Exa-cel provides an irreversible genetic edit that directly addresses the underlying cause of SCD, restoring patients to normal or near-normal health. Severity modifier - Following correction of the errors in the model provided to the committee by the EAG, SCD qualifies for the 1.2x severity modifier, by NICE's preferred methodology. Vertex re-affirms the belief that progressive diseases where mortality increases and HRQoL deteriorates substantially over time are unfairly penalised by the discounted QALY approach. A similar approach to HST, where undiscounted QALYs are used in the calculation is more appropriate here. When using this methodology exa-cel qualifies for the 1.7 modifier. Economic model - Vertex has amended its original model structure and is providing the committee with a new version of the model where the committee's concerns are addressed and therefore uncertainty reduced. Furthermore, several of the committee's preferred assumptions are now reflected in an updated base case. Vertex appreciates the attempt made by the EAG to address the committee's concerns in the previous version of the model; however several inaccuracies have been found e.g. the EAG has inappropriately added a calculation of the costs of treatment withdrawal prior to exa-cel infusion and the prevalence of chronic	

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	complications. We therefore provide an updated model for decision-making, including the committee preferences that Vertex has accepted. We request that the model submitted with this response be used to run all scenarios in future. Uncaptured benefits • SCD has a substantial detrimental impact on QoL, not just for patients but also for caregivers. SCD impacts caregivers' ability to maintain employment, and results in higher degrees of depression, anxiety and stress relative to those not caring for SCD patients. The committee should take this into account when considering the most appropriate ICER threshold, beyond the flexibility in the threshold given for health inequalities. Accounting for patients who do not have exa-cel infusion in the model • In the trial, and model, some patients undergo cell collection but do not go on to have exa-cel treatment. The reasons for this are related to the nature of SCD and systemic health inequalities experienced by patients. [REDACTED] [REDACTED] Equally, treatment effects for those patients that do not have exa-cel infusion should be removed from the exa-cel arm of the model, to ensure model results accurately represent the effect of treatment with exa-cel. Definition of baseline VOCs • Vertex strongly believes that all VOCs that require healthcare attendance should be accounted for in the model. All VOCs are related to SCD complications, and result in a reduction in QoL. Further, issues with VOCs definitions in baseline vs follow up periods are alleviated by the new model structure. Modelling of chronic SCD complications: choice of source • While Vertex maintains the position that frequency of VOCs is a valid predictor of complications over time in severe SCD patients and therefore a hazard rate approach to model the risk of complications is appropriate, Vertex agrees to a new model structure whereby the risk of complications is derived from the literature e.g. from Brousse et al. Vertex presents two scenarios with data on complications derived from Brousse et al (as per committee's request) and data from Udeze et al. The latter provides a more complete source for the relevant population, based on UK data, and will therefore also be useful for the committee to consider. Utility of SoC patients and evolution over time • As requested by the committee, Vertex provides a longitudinal view of how the net utility of SoC patients in the model changes over time, to ensure it is clear that patients experience a severe impact on their quality of life as they grow older. Vertex has also implemented additional scenarios to evaluate the uncertainty related to baseline utility. Choice of utility value following exa-cel treatment • Vertex acknowledges the committee's uncertainty with utility value following exa-cel treatment. Vertex believes that this value reflects the QoL gain experienced with functionally cured SCD

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	patients. However, based on a post-hoc subgroup analysis, which excludes patients with a baseline score equal to 1, Vertex provides an alternative scenario value of [REDACTED]. We hope the below detail adequately addresses questions raised by committee and supports the case for the value of exa-cel, and the severity of SCD, for patients, who have few other options.
2	Application of the non-reference discount rate Vertex maintains that exa-cel qualifies for the non-reference discount rate and demonstrates that each of three criteria are firmly met. Severe SCD has a substantial impact on daily living, quality of life over time, and reduces life expectancy by several decades. Exa-cel provides an irreversible genetic edit that directly addresses the underlying cause of SCD, restoring patients to normal or near-normal health. The overall objective of the 1.5% discount rate is to avoid penalising those treatments with high upfront (undiscounted) costs but where the QALY gain and cost savings accrue over a long time period and are subject to discounting. As described in the ACD, the committee queried whether exa-cel qualifies for the non-reference discount rate, with repeated mentions that uncertainty could be addressed by further data collection. Vertex reiterates that exa-cel qualifies for the non-reference discount rate, satisfying the three qualifying criteria as set out below (and further detailed in this section), and is committed to working in partnership with NICE, as we are currently doing in TDT, to agree a managed access agreement that meets the committee's requirements. • SCD has a substantial, daily impact on patients' & caregivers' QoL, and age at death for severe SCD patients is in the 40s, constituting a reduction of several decades relative to the general population. • Treatment with exa-cel has a transformational impact on outcomes, with no new complications related to SCD expected, and current complications likely to be halted or even reversed, as supported by evidence from HSCT in SCD. • Genetic editing with exa-cel results in a permanent and durable effect, supported by stable HbF %, and allelic editing in patients. • Finally, whilst strongly defending that the totality of evidence supports exa-cel's qualification for the non-reference discount rate, Vertex is committed to a managed access agreement to further demonstrate this. <i>1. Technology is for people who would otherwise die or have very severely impacted life</i> The National Institute of Health defines a severe illness as '<i>a health condition that carries a high risk of mortality AND either negatively impacts a person's daily function or quality of life, OR excessively strains their caregivers.</i>' (1). We provide evidence below that SCD is a severe illness and fulfils all three of these criteria, with further detail on the caregiver burden elaborated in Section 5 'Uncaptured benefits'. SCD is a chronic, life-limiting, and debilitating condition that causes significant morbidity and mortality. In patients with severe SCD (with frequent vaso-occlusive episodes) mortality and morbidity are increased even further. SCD is characterised by haemolytic anaemia, widespread organ damage, unpredictable episodes of severe pain called VOC ('vaso occlusive crisis') and shortened life expectancy (2, 3).

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SCD has significant negative emotional, social and quality-of-life (QoL) effects on patients, but also their families on a daily basis. As described in the ACD (S3.1), '*They [patient experts] noted that they could not remember a day without pain, whether that be mild, moderate, or severe*'. The ACD also reports the findings of the 2019 Sickle Cell World Assessment Survey, in which 76% of respondents reported having to reduce their working hours, and 58% having to stop work entirely (4). This daily impact of SCD was characterised by clinical experts in the ACD, who explained that vaso-occlusion happens constantly, even if a patient is not experiencing a crisis. In view of this, the committee concluded that SCD is a debilitating and life-limiting condition. This conclusion is supportive of qualification for non-reference criterion #1.

Furthermore, it is stated in Section 3.8 of the ACD that '*Clinical experts commented that the life expectancy for people with SCD with recurrent VOCs is in the fifth decade of life*'. When exploring how best to define 'severe' SCD during an advisory board conducted in the UK, advisers were in agreement that any other disease with a median life expectancy in the 40s would be classed as severe as a whole (5). The severity of SCD, seen in both the substantial reduction in life expectancy, and impact on quality of life, is supported by clinical experts, the body of evidence detailed below, and the committee deliberations, as detailed in the ACD.

The committee asked for additional data on mortality and QoL, which we provide below to further demonstrate the severity of SCD, and substantial impact on daily living.

Early mortality

Patients with SCD are affected by a myriad of complications and associated chronic multi-organ comorbidities, which results in a reduction in life expectancy by several decades relative to the general population.

There is extensive recent literature (including studies from the UK) that consistently demonstrates that SCD patients have a significantly reduced life expectancy which is further reduced for patients with severe SCD/recurrent VOCs. These figures are consistent across cultures and over time with a lack of significant improvement over the last few decades even if optimal treatment is available (6). We summarise this data in Table 1, before providing additional detail.

Table 1: Summary of the literature on mortality estimates in SCD

Lead author (year)	Sample size	Mean age, years	Geography	Mean age at death, years (mean)	
				All SCD	Severe SCD*
Udeze <i>et al</i> (2023)	1,117	24.96	UK	NA	40
Piel <i>et al</i> (2021)	9,503 (all) 1,171 (severe)	22.9 (all) 23.4 (severe)	UK	46.7	39.7
Di Mauro <i>et al</i> (2023)	1,069	35 (HbSS) 45 (HbSC)	UK	41.5 yrs (HbSS) 52.5 (HbSC)	NR
Brousse <i>et al</i> (2023)	20,412 (all) 4,270 (severe)	24.0 (all) 21.8 (severe)	France	58 yrs**	44**
Jiao <i>et al</i> (2023)	94,616	26.6	US	52.6 yrs	NR

NR, not reported.

*severe SCD definitions differ by paper, and are summarised in the below text.

**median values.

Increased mortality in patients with severe SCD/recurrent VOCs

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Udeze et al (2023) observed a mean age at death of 40 years in a UK severe SCD population (n=1,117), defined as at least 2 VOCs per year for 2 consecutive years, followed retrospectively between 2008 – 2018 (7).

In another UK SCD cohort followed from 2009-2018, Piel et al (2021) observed a mean age at death of 39.7 years for those with four or more hospital admissions due to sickle cell crises over the two base years (n=1,171) (8). Notably, in this study the mortality rate for the five-year period of 2014 – 2018 (3.2%) was actually higher than that observed between 2009 – 2013 (2.2%), with the number of deaths increasing over time, from 36 in 2009 to 69 in 2018.

Brousse *et al.* (2023) had similar findings with an observed mean age of death of 44 for severe SCD patients between 2012-2018 in France (n=4,270) (9). In this study, severity was defined by 2 vaso-occlusive events in the year preceding index or 4 VOs in the 2 years preceding index for 3,855 of the 4,270 patients, with the definition for the remainder relating to hydroxyurea and transfusion use.

Increased mortality in all patients with SCD regardless of severity

In a recent analysis of data from the southeast London sickle cell gene bank cohort, Di Mauro *et al.* (2023) observed an average age at death of 41.5 years for HbSS (all severities) male SCD patients (n=692) (10).

Brousse et al (2023) had an observed median age at death of 58 years in the total (unselected for severity) SCD patient cohort (n = 2,619) and Piel et al showed a mean age of death of 46.7 in the total patient cohort (9). Similarly, Jiao et al showed a mean age of death of 52.6 years in the total SCD population (11).

The SMRs applied in the economic model and accepted by committee were sourced from Desai et al (2020) (12). Between the period of 2000 – 2013, Desai et al observed a cumulative incidence of mortality of 27.3% in 19–35-year-old patients with SCD in a US Medicaid population (n=44,033), (of which 11,064 were 19-35 years), demonstrating the impact of SCD on survival in even young patients. In those >35 years of age, the cumulative incidence of mortality was substantial, at 45.4%. In this study, higher VOC burden in the preceding year was associated with a considerably increased risk of mortality: 2-4 VOC vs <2 VOC HR 1.62.

In response to the EAG's critique that the Desai mortality rates were obtained from a younger cohort, the SMRs from Desai were stratified by age band. Furthermore, there was no age limit restriction in the eligibility criteria of the Desai study. The reason that there was a lack of older patients in Desai was simply because there were none: the majority had died. The fact that both the US Institute for Clinical and Economic Review (ICER) and the present NICE committee favoured use of the Desai et al. paper to inform mortality estimates for exa-cel provides further support for the Desai mortality estimates and the substantial reduction in life expectancy seen in all patients with SCD (13).

In summary, it is clear from the weight of the literature that life expectancy for SCD patients is reduced by many decades compared to the UK general population (median age at death of 81.8 years for males and 85.5 years for females in 2020 (14)), with this reduction even more pronounced in severe SCD patients, as demonstrated by a mean age at death of 40.2 years in a UK population.

Severely impacted quality of life

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'describing the actual pain I feel is a real challenge – I can say that it feels like being stabbed everywhere repeatedly or having all your bones broken, but the words just don't do the pain justice' – Patient expert, ACM1 slides

Multi-organ damage, co-morbidities and complications

As described consistently in the clinical literature and summarised in the NHS Commissioning Policy, severe SCD is associated with a very significant rate of morbidity and mortality (2, 15-17). The toll of SCD on the patient is considerable. Frequent severe and unpredictable acute pain episodes which often need hospital admission but may be managed at home prevent school and work attendance and cause disruption of normal life for the patient and their family. Patients experience high rates of acute complications including stroke, infection, acute chest syndrome, acute renal failure, respiratory failure. As their disease progresses patients will also experience high rates of chronic organ impairment and reduction in organ function (eg brain, lungs, kidney, heart, spleen, eyes) and high levels of chronic pain. These complications, both acute and chronic, inevitably worsen with age and are not stopped by current therapies (6).

For example, in a 10-year cohort analysis of 9,503 patients with SCD in the UK, using Health Episode Statistics (HES) data, Piel *et al* (2021) examined co-morbidities commonly associated with SCD and 10- year mortality rates compared with the general population (8). The most common acute co-morbidity recorded was acute chest syndrome, which occurred at least once in 53.9% of the most severe SCD patient group. High prevalence of eleven other co-morbidities (including osteonecrosis, sepsis, renal disease, cardiovascular disease and priapism) were also reported in this study. The mean number of co-morbidities per patient over the 10-year study period was 2.5, for severe patients, with 63.2% of patients having two or more co-morbidities.

Substantial impact of SCD on QoL further adds to the severity of the disease

There is robust and extensive evidence showing the impact of SCD on QoL confirming the severity of this condition. SCD patients have an inherited condition and have experienced symptoms since early childhood. Whilst it is clear that baseline EQ-5D in CLIMB SCD-121 is well below age-adjusted population norms, the likely adaptation to their condition and associated underestimation of the burden on QoL means that their experience may not be fully captured by EQ-5D. This is further discussed in the section on utility values in the model (Section 9).

The ACD states that the committee expected the QoL difference between the SCD population and the general population to be greater than stated by the company 'if a condition caused people to have a severely impaired life'. We refute the committee's perspective that the data from the trial indicates the population is not severe.

CLIMB SCD-121 EQ-5D data

We believe that first, the difference in QoL between patients at baseline in the trial and the age adjusted general population norm is significant and does show a severely impaired quality of life. The baseline EQ-5D value in the trial is 0.81, which compares with the UK population norm for an adult aged 18-24 of 0.93, providing us with a difference of 0.12 (18). The minimal clinically important difference (MCID) for EQ-5D is 0.08, so a reduction of 0.12 relative to general population is significant and clinically meaningful. However, the reduction of 0.12 is not representative of the majority of SCD patients and we agree with the committee that this may be because the EQ-5D only partially captures the impairment of QoL in SCD, as evidenced through a more granular view of the CLIMB SCD-121 EQ-5D data:

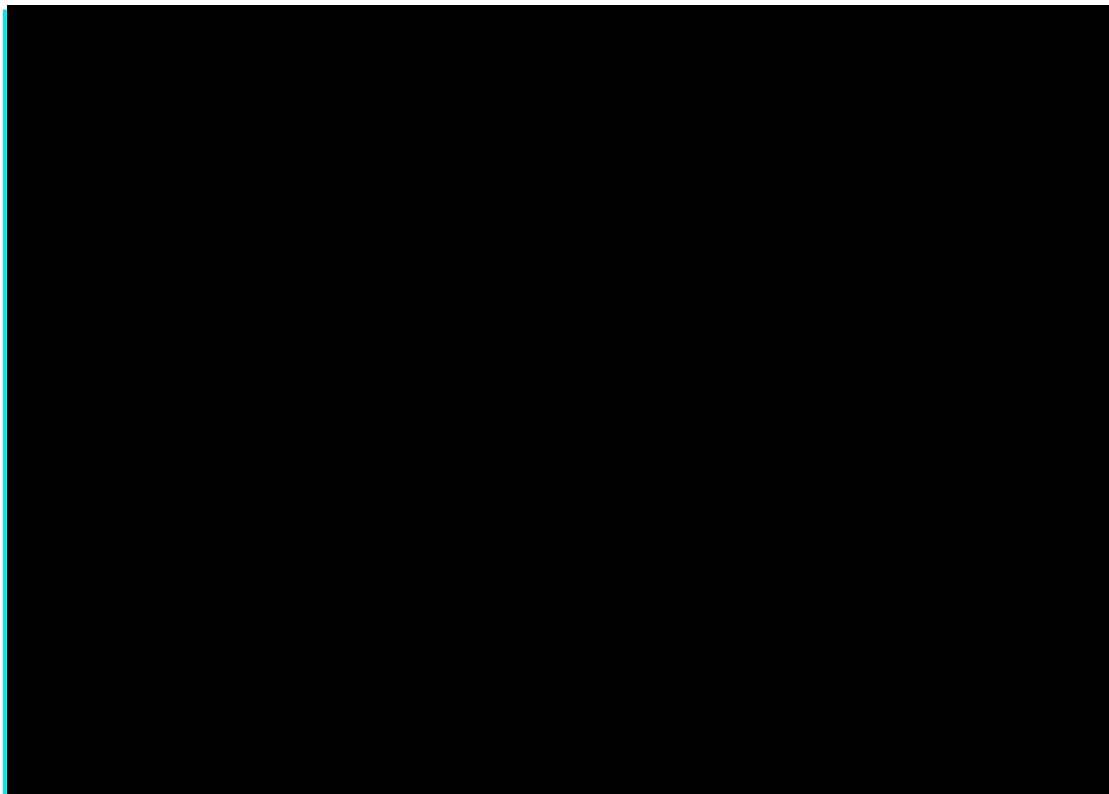
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Figure 1 depicts the distribution of EQ-5D scores in the d120 FAS. Two contrasting observations can be made from the histogram: firstly, while 0.81 represents the mean of the CLIMB SCD-121 cohort, a proportion of patients had extremely low EQ-5D index scores; the minimum EQ-5D value at baseline at d120 in the FAS (n=31) was 0.2 and approximately one fifth of patients had scores less than 0.55. Secondly, the mean of 0.81 represents a value highly skewed by a significant proportion of patients with an EQ-5D utility at full health (over [REDACTED] of patients in the PES and over [REDACTED] of patients in the FAS). When estimating the baseline value for those patients in the FAS and PES not reporting perfect health the mean EQ-5D was [REDACTED] and [REDACTED], respectively. These two contrasting observations support the evidence that patients with SCD have a severely reduced QoL compared with the UK general population, but also that the EQ-5D may not adequately capture the impact of SCD in a significant proportion of patients: the idea that people with perfect health would be willing to trade that for a burdensome transplantation with an experimental therapy clearly lacks face validity.

Figure 1: Histogram of EQ-5D-5L UK Index Scores for all patients at baseline in CLIMB SCD-121 FAS (N=30)



The severity of SCD is further evident when one considers that this lower utility value of 0.81, relative to the age-adjusted general population at baseline, is captured at the point at which exa-cel would be administered before patients go on to develop additional significant complications that characterise their condition. The applicability of this value is evident based on the results presented in Table 8. When using a baseline value of 0.81, the predicted baseline net health state utility (0.71) in the model aligns with the observed baseline utility value [REDACTED] reported by patients ≥ 18 and ≤ 35 with baseline utility < 1 .

It is also clear that their QoL would continue to deteriorate as they grow older and live with multiple co-morbidities. This effect on QoL has been accurately captured in the updated Vertex economic model

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(see Table 8, discussion in Point 9). This is supported by the significant body of evidence on this, which looks at QoL of patients of all ages with SCD disease, detailed in 'summary of QoL data in SCD'.

Further support for this comes from the literature, where lower EQ-5D values have been reported in comparable patient populations (Table 2)

Table 2: Alternative SCD utility values reported in the literature

Source	Sample size	Population	EQ-5D value
Anie <i>et al</i> (2012) (19)	510	SCD patients admitted to hospital, followed to 7 days post-discharge	0.39 - 0.75
O'Brien <i>et al</i> (2009) (20)	N/A	Severe paediatric SCD patients	0.7
Drahos <i>et al</i> (2023) (21)	139	Adults with SCD, including subgroup with a recent VOC	0.48 – 0.59

Summary of QoL data in SCD

It is evidently clear from published literature and from patients' experiences (as illustrated in the APPG No One's Listening report) that SCD severely affects patients' life (22). Multiple studies in various populations all consistently show a reduction of QoL in SCD, and patients with severe SCD (characterised by frequent VOCs) have a more marked reduction in QoL, which, as already demonstrated, is also associated with a further reduction in life expectancy.

A systematic review in 2012 by Panepinto and Bonner found 39 studies of HRQoL in SCD and concluded that adults and children have significantly impaired HRQoL that is comparable to or worse than other chronic diseases (23). The included studies looked at a variety of QoL measures, most commonly SF-36 or PedsQL. Most studies showed that pain has a negative impact on QoL. For example, a large study based on the US Co-operative Study of SCD (Dampier *et al* 2011) looked at 1180 patients (median age 28 years) (24). All individual SF-36 scores were significantly decreased compared to the general US population and the occurrence of VOCs progressively decreased SF-36 scores.

A 2012 UK study measured HRQoL in 510 patients (mean age 28.9 years) using EQ-5D on admission with VOC to the day unit or hospital and repeating this measurement on discharge and at one week post discharge (19). It showed utility values of 0.39 on admission, increasing to 0.65 at discharge and 0.75 one week later. Health scores derived from EQ-5D showed a negative association with pain, with patients reporting EQ-5D well below general population level even after recovery from VOC. A further study from the same lead author (Anie *et al* 2002) included 96 patients (mean age 30.1 years) and showed a significant reduction in all domains of SF-36 compared with the general population (25).

Similar findings were shown by Shafrin *et al* (2021), who enrolled a population of 301 patients (average age 30.1 years) performing EQ-5D twice, once when experiencing a VOC and once when not experiencing a VOC. Results showed a reduced HRQoL at baseline (0.738) reducing further to 0.311 during a VOC, with disease severity strongly predicting worse self-reported HRQoL (26).

A further study by Drahos *et al* (2023) looked at 142 adults from US and Europe and compared various PRO measures in patients who had or had not experienced a recent VOC (within one week). The overall mean EQ-5D-5L health utility US index score among participants with SCD (0.59 [SD: 0.27])

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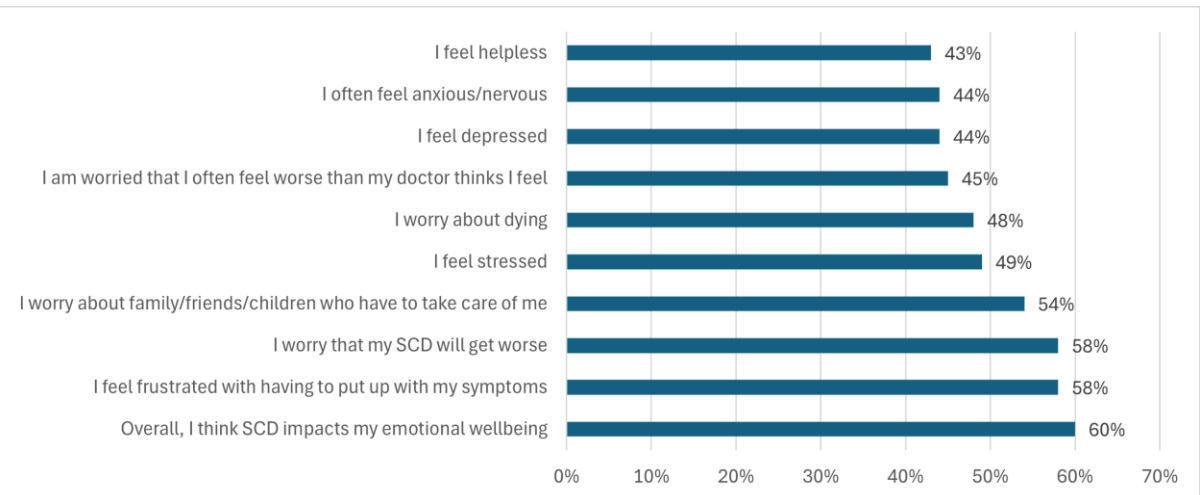
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was much lower than the US general population mean score (0.85 [SD: 0.21]) and even lower (by – 0.11) among participants with SCD who experienced a recent VOC (0.48 [SD: 0.25]). Similar reductions were seen in overall mean FACT-G score and EQ-5D-5L VAS (21).

Further evidence of the impact of SCD on patient reported outcomes has been shown by the SWAY survey (2,145 patients), where a substantial proportion of patients reported that SCD caused a high negative impact on emotions (60%) and school achievement (51%) and a reduction in work hours (53%) (4). Fatigue was the most commonly reported symptom (65%), graded “high severity” by 67% of patients, and this is poorly captured by EQ-5D.

Even among the minority of patients able to work, a separate study found that participants reported missing approximately 9.8 hours in the past week due to SCD (27).

Figure 2: Proportion of patients reporting a high impact of SCD per statement



Source: Figure 1b, Osunkwo *et al* (2021) (4).

The significant burden of complications patients experience has a huge impact on overall health, which translates into a reduction of many decades in life expectancy, as already detailed. Severity of SCD is also demonstrated by considering the resource use associated with severe SCD and the complications patients experience (7, 9). For example, patients with severe SCD in the UK require 22.17 hospital visits per year compared with 2.63 visits per year in matched controls, and receive 31.06 outpatient prescriptions compared with 7.58 in the matched population (28).

In summary, SCD has a substantial, daily impact on QoL, with worries about their condition worsening, lack of understanding from doctors, and fear of dying all posing a substantial burden on patients (Figure 2). This burden is particularly pronounced for patients experiencing recurrent VOCs, the patient population that would be eligible for treatment with exa-cel.

2. Technology is likely to restore them to full or near-full health

Before going into detail on the transformational benefit achieved with exa-cel, and supporting literature, we include testimony from the first ever patient to receive exa-cel as part of CLIMB SCD-121, provided as part of the FDA advisory committee meeting held in October 2023:

“After receiving this treatment, I no longer have pains, I no longer have to take opioids, I no longer have hospital stays or receive blood transfusions. I get to participate with my kids and join them in their activities when they play sports, cheer them on at their dances and just be here just to play with

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	<i>them, knowing I no longer have to leave them to go to the hospital. I now work full time and I contribute to my household and my community. “</i> <u>Clear long-term benefits of exa-cel demonstrated in CLIMB SCD-121</u> The data from CLIMB SCD-121 demonstrates the substantial, transformational and consistent benefit of exa-cel for SCD patients. At baseline, these patients (PES, d120, n=29) were experiencing a mean 3.9 VOCs per year, 2.7 hospitalisations per year, and a mean of 17.4 inpatient hospitalisation days for severe VOCs per year. Following treatment with exa-cel, 96.6% of patients achieved 12 months free of VOCs, with 100% achieving 12 months free of hospitalisation, with patients VOC-free for up to 43.6 months at the time of the d120 data cut (29). Furthermore, we note that 27/29 patients in the PES, (follow-up of 17.8 - 48.1 months after exa-cel infusion) remain VOC free, a substantially clinically meaningful improvement from the rates reported at baseline. <u>Pain</u> As discussed at the previous committee meeting, a small number of patients do experience acute pain after exa-cel infusion. As discussed, these events are not VOCs, and do not represent treatment failure or lack of response to exa-cel. It is important to remember that the VOC definition as per CLIMB SCD-121 protocol was ‘acute pain needing attendance at hospital for opiates/iv NSAIDs, ACS, splenic sequestration or priapism’ (29). This broad definition of acute pain will inevitably include patients who are experiencing acute pain not related to vaso-occlusion. Post-transplant acute pain events (which would be classified as VOCs if trial criteria were used) are observed in the post allo-transplant context, even in patients with 100% chimerism (i.e. only non-sickle red cells). This is more marked in patients with a history of chronic pain and hyperalgesia. Among patients with SCD who undergo HSCT, 1 in 5 patients continue to experience acute pain events during the 12 months post-HSCT period (30). We go into further detail on post-HSCT findings in the relevant sub-section. Of the small number of patients who experienced these acute pain events after exa-cel, none needed hospitalisation (29). There were no episodes of ACS (which is the leading cause of death, responsible for up to 25% of SCD-related deaths) and no priapism or splenic sequestration. When the clinical details of the patients who experienced acute pain post exa-cel are reviewed in detail, it becomes apparent that they all had chronic pain and had reasons other than vaso-occlusion for their pain. This point is substantiated in the section relating to benefits being sustained over a very long period. <u>Other benefits of exa-cel</u> While VOCs have been used as a primary endpoint in the study, they do not capture the systemic impact that exa-cel mechanism of action has on the pathophysiology of SCD. The rapid and consistent increase in fetal haemoglobin (HbF) not only prevents vaso-occlusion but also reduces haemolysis and resolves anaemia and consequently will remove the risk of acute and long-term complications of haemolysis. This is substantiated by the CLIMB SCD-121 clinical results showing a rapid and persistent resolution of anaemia (mean Hb >13.0g/dl from month 12) and reduction in haemolysis: Results presented at ASH 2023 showed that: 1. Lactate dehydrogenase: mean levels normalised by Month 9 and were sustained at normal levels thereafter. Elevated LDH as a haemolytic marker has been independently associated with increased morbidity and mortality in SCD (31, 32) 2. Haptoglobin: all patients had increases in haptoglobin to detectable levels after Month 6, which sustained over time, consistent with resolution of intravascular haemolysis. 3. Absolute reticulocyte count: mean improvement from elevated levels at baseline, with reduction maintained over time, consistent with improvement in haemolysis post exa-cel

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	All of these improvements were durable, with data for 30 patients at month 24, and range of follow-up in the PES from 17.8 months to 48.1 months (29). This normalisation of haemolysis, while shown via surrogate markers, demonstrate the profound effect of exa-cel on addressing the underlying pathophysiology of SCD. <u>Development of new complications is prevented. Existing complications will be halted or reversed by prevention of vaso-occlusion and maintenance of high HbF.</u> As described in the CS, exa-cel's mechanism of action results in an increase in HbF levels. Increases in HbF level ameliorate the clinical manifestation of SCD. Support for this comes from the experience of patients with hereditary persistence of fetal haemoglobin (HPFH), a naturally occurring variation that causes continued persistence of HbF into adulthood (33, 34). Patients with compound heterozygosity for SCD and HPFH experience little or no SCD symptoms, leading to a normal life expectancy, and this is particularly true for those who maintain HbF levels above 20% (34-36). In CLIMB SCD-121, a mean HbF % of 40% was achieved by Month 6, and maintained at this level thereafter, well above the level shown to result in little or no SCD symptoms. Exa-cel therefore has a positive impact on all aspects of SCD: reversing anaemia, haemolysis and vaso-occlusion and stopping crisis due to vaso-occlusion (VOCs). A key factor in eligibility for treatment with exa-cel is the individual patients' fitness to safely undergo myeloablative conditioning with busulfan. As such, while patients treated with exa-cel in CLIMB SCD-121 had severe SCD (i.e. were experiencing recurrent VOCs at baseline), they will not have developed significant, irreversible, complications as this would render them ineligible for myeloablative conditioning. In the real-world patients will be treated in the 'clinical window' after they have developed severe, recurrent VOC but before they have developed severe organ damage, ensuring they are able to return to near-normality after exa-cel treatment. Furthermore, all cases will require approval by the National Haemoglobinopathy Panel which will confirm that all patients meet the eligibility criteria set out in the SmPC including fitness to undergo conditioning. Furthermore, there is evidence from treatment with hydroxycarbamide and transfusion that increasing the HbF and reducing the red cells ability to sickle reduces the development of complications and reverses the severity of complications (37, 38). In addition the contrast between asymptomatic patients with co-inheritance of HbS and genes that cause pancellular increases in HbF (HPFH) and symptomatic patients suggest that, if it were possible to induce high HbF levels in most sickle erythrocytes and if this could be done before organ damage occurs, one might expect the disease to be cured (36). Therefore, the literature supports the view that the sustained high levels of HbF will prevent the development of any new disease-related complications, and halt or reverse the progression of any existing disease-related complications. <u>Post-HSCT outcomes in SCD support the return to full or near-full health</u> The substantial body of evidence gathered in HSCT, the other curative therapy for SCD, indicates that once the sickle phenotype is reversed, there is no recurrent haemolysis, and therefore no further disease-related complications occur. Detailed below are a selection of these studies: 1. Inam <i>et al</i> (2023) (39): Outcomes and long-term effects of hematopoietic stem cell transplant in sickle cell disease Expert opinion provided as part of this article states the following: <i>'HSCT, both allogeneic and autologous gene therapy, in the SCD population reverses the sickle phenotype, prevents further organ damage, can resolve prior organ dysfunction in both pediatric and adult patients.'</i> Specific outcomes detailed in Inam <i>et al</i>:

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- Neurologic outcomes: TCD velocities normalise post-HSCT. By 5 years post-HSCT, evidence of improvement in white matter changes and stable or improved cerebral vessel abnormalities. In general, patients with SCD and prior stroke history are protected from subsequent clinical strokes following successful engraftment and can safely stop secondary prevention with chronic RBC transfusion therapy following HSCT
- Cardiac Function and Pulmonary Hypertension: Following successful HSCT, there are significant improvements in cardiac size and function
- Pulmonary Function: The majority of studies report stabilisation and/or improvement of lung function as measured by pulmonary function testing following transplantation
- Renal Function: Evidence of stable kidney function
- Bone Health: published studies comment on stability of avascular necrosis up to 3-5 years post-HSCT in those with pre-HSCT avascular necrosis

2. Walters et al (2010) (40): Pulmonary, gonadal, and central nervous system status after bone marrow transplantation for sickle cell disease

Prospective study with a median follow-up of 6.5 years (range: 3.0-12.4 years) after transplant in patients <16 years of age to receive a stem cell transplant between 1991 – 2000.

1. After BMT, patients with stroke who had stable engraftment of donor cells experienced no subsequent stroke events after BMT, and brain MRI exams demonstrated stable or improved appearance.
2. After transplantation, most patients also had unchanged or improved pulmonary function. Among the 11 patients who had restrictive lung changes at baseline, 5 were improved and 6 had persistent restrictive disease after BMT.
3. Mahesri et al (2023) (30): VOC-Free Status Among Patients with Sickle Cell Disease Following Allogeneic Hematopoietic Stem Cell Transplant: A Cohort Study of Medicaid Enrollees

Retrospective cohort study of 44,685 patients with SCD in the US, of which 103 had undergone HSCT between 2000 – 2014 and had ≥24 months of follow-up.

- Among patients with SCD who undergo HSCT, 1 in 5 patients continue to experience acute pain events during the 12 months Post-HSCT period. This population-based study provides valuable information regarding long-term acute pain event-free status among patients with SCD who have undergone allogeneic HSCT in routine clinical care.

In summary, the substantial body of evidence for outcomes post-HSCT in SCD demonstrates that patients post-transplant are restored to full or near-full health. Importantly, this benefit is expected to be even more pronounced for exa-cel, because as an autologous therapy there is no risk of graft rejection, or graft-versus-host disease.

Exa-cel will restore QoL to population norms

Review of the full breadth of QoL measurements in CLIMB SCD-121 confirms the impact of SCD on trial participants. For example, the baseline of EQ-VAS (where 100 is best imaginable health and 0 is worst imaginable health) was 69 compared with a population norm of 85. A similar reduction at baseline was seen in the other measures used.

In CLIMB SCD-121, exa-cel resulted in a substantial, clinically meaningful increase in QoL as measured by five different tools, including the disease-specific Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me). As shown in Table 3, exa-cel resulted in improvements above the minimal clinically important difference, across all QoL measures, irrespective of whether these measured general QoL (EQ-5D), pain (NRS Pain Scale), or SCD-specific QoL (ASCQ-Me) (29).

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Table 3: QoL measures tracked in CLIMB SCD-121

QoL tool	Baseline (pop ⁿ norm)	Improvement, M24	MCID
EQ-5D (UK)	0.81 (0.93*)	0.11	0.08
EQVAS	69 (85*)	20	7-10
FACT	73 (80)	22.5	3-7
FACT-BMT	101	26	2-3
NRS Pain Scale	2.5	Reduction of 1.7	Reduction of >1
ASCQ-Me	Various domains	6.6-17.5**	>5

*Age-adjusted population norm. **improvement in all domains except sleep.
Source; D120 report (29).

Precedent supports exa-cel qualifying for this criterion

We also note precedent from HST15, where *'the committee was uncertain about whether most of the people who would have onasemonogene abeparvovec would be considered to have a 'normal or near normal-health'. But believed that a proportion might'*, with this consideration supporting an ultimate decision to apply the non-reference discount rate in HST15.

3. The benefits are likely to be sustained over a very long period

As a CRISPR technology, there is no biological plausibility that exa-cel's genetic edit will not be permanent. There is no known mechanism by which an edited haematopoietic stem cell (HSC) could convert back to a wild-type sequence. Edits to HSCs are permanent and durable. Support for this comes from the latest data from CLIMB SCD-121. The stable proportion of alleles with the intended genetic modification (allelic editing) in peripheral blood and in the CD34+ cells of the bone marrow over time are indicative of the durable engraftment of edited long-term HSCs and reflect the permanent nature of the intended edit (29).

Acute pain events may occur infrequently after allo-SCT and have been reported at low event rates even in subjects with high donor chimerism, who have no cells capable of sickling as all haematopoiesis has been replaced by donor cells (41-43). The interpretation of pain events after HSCT for SCD is complicated, because post-HSCT pain in patients with SCD can be related to factors that may not represent VOC events. Pain events can be due to consequences of pre-existing disease such as exacerbation of chronic pain (e.g., related to pre-existing avascular necrosis), allodynia (pain elicited by normally innocuous, low threshold stimuli) and hyperalgesia (enhanced pain response to noxious stimuli) exacerbated by chronic opiate use.

Clinical experts have stated the reasons for the acute pain events seen after exa-cel in a small number of patients is likely to be similar (5). These events were predominantly in the first year following treatment with exa-cel. Pain, and acute pain events are complex, multifactorial issues in SCD. There is no evidence of microvascular occlusion-related VOC. All the VOCs observed are in patients with chronic pain, and so are not expected to be related to additional VOC complications.

As explained by the clinical expert at committee *'if fetal haemoglobin is maintained at around 40% across every red blood cell, 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 VOC'*. The

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expert went on to attribute this to the problem associated with measuring SCD using countable VOC episodes.

Support for the use of HbF % as a measure of long-term durability comes from the clinical course of the two patients in the PES to experience acute pain events (adjudicated as VOCs) during CLIMB SCD-121.

It is clear from this that despite experiencing acute pain events, exa-cel is providing a durable, stable, benefit, that allow rapid recovery from complications relating to co-morbidities, that would otherwise not be possible in patients with SCD.

Clinical expert feedback obtained as part of this appraisal further supports the expected long-term benefits of exa-cel. It was agreed that clinical experts would like to observe stable HbF levels for at least another 12 months (24 months in total) with at least 10 patients to be confident that exa-cel is providing a sustained treatment effect (5). With additional data available since those discussions, at the D120 data cut there are a total of 15 patients with 24 months of data, with a mean HbF % of 42.2% in those patients, satisfying the required threshold for clinical experts to believe that exa-cel is providing a sustained benefit.

Vertex robustly defend the duration of follow-up in CLIMB SCD-121 as suitable for decision-making - supported by the aforementioned regulatory approvals - and note the overwhelming efficacy of exa-cel, with 29 of 30 patients in the PES achieving VF12. However, to address remaining uncertainty, Vertex re-iterates a commitment to working in partnership with NICE, as we are currently doing in TDT, to agree a managed access agreement that meets the committee's requirements.

Conclusion – non-reference discount rate

In conclusion,

- SCD has a substantial, daily impact on patients' & caregivers' QoL, and age at death for severe SCD patients is in the 40s, constituting a reduction of several decades relative to the general population.
- Treatment with exa-cel has a transformational impact on outcomes, with no new complications related to SCD expected, and current complications likely to be halted or even reversed, as supported by evidence from HSCT in SCD.
- Genetic editing with exa-cel results in a permanent and durable effect, supported by stable HbF %, and allelic editing in patients.

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	Finally, whilst strongly defending that the totality of evidence supports exa-cel's qualification for the non-reference discount rate, Vertex is committed to a managed access agreement to better characterise this.																					
3	Severity modifier Following correction of the errors in the model provided to the committee by the EAG, severe SCD qualifies for the 1.2x severity modifier, by NICE's preferred methodology. Vertex re-affirms the belief that progressive diseases where mortality increases and HRQoL deteriorates substantially over time are unfairly penalised by the discounted QALY approach. A similar approach to HST, where undiscounted QALYs are used in the calculation is more appropriate here. As discussed by committee, shared by patient and clinical experts, and outlined in the Vertex evidence submission to NICE, and in the response above, SCD has a severe impact on patients, reducing life expectancy by many decades. While the committee did not directly conclude whether the severity modifier applied, there was consensus on the fact that SCD is a severe and debilitating disease. Following correction of the errors in the model provided to the committee by the EAG, by NICE's stated methodology, SCD qualifies for the 1.2 severity modifier. Proportional and absolute short fall calculations are provided below. Notwithstanding this, we strongly disagree that the QALYs should be discounted, and this particularly applies where the non-reference case discount rate is used. This is because, the severity modifier calculation performs extremely well in situations where near-term mortality risk is high and/or HRQoL is extremely low at baseline. However, progressive diseases in which mortality increases or HRQoL deteriorates substantially over time, such as SCD, are penalised by the discounted QALY approach and the only way that these diseases would be eligible for a modifier is by decreasing the QALY discount rate. Furthermore, it is notable how, in this respect, the modifier differs between STA and HST. Modifiers in the HST appraisal route are underpinned by undiscounted QALYs. Indeed, it is evident that a number of HSTs would never have been awarded a modifier had it been reliant on discounted QALYs (26). Therefore, from a methodological and consistency perspective, it is clear that either no discount rate, or a lower discount rate of 1.5% should apply in the QALY shortfall calculation where there is a case for the non-reference case discount rate. When this is the case, the severity of severe SCD is appropriately recognised, and severity weighting of 1.7 applies (see Table 4). Table 4: Severity modifier calculations based on updated model <table border="1"> <thead> <tr> <th>Severity Modifier</th><th>Value</th><th>Weight</th></tr> </thead> <tbody> <tr> <td>General population QALYs (1.5% discount)</td><td>34.5</td><td>-</td></tr> <tr> <td>Proportional shortfall (1.5% discount)</td><td>65.3%</td><td>1</td></tr> <tr> <td>Absolute shortfall (1.5% discount)</td><td>22.52</td><td>1.7</td></tr> <tr> <td>General population QALYs (3.5% discount)</td><td>22.52</td><td>-</td></tr> <tr> <td>Proportional shortfall (3.5% discount)</td><td>56.0%</td><td>1</td></tr> <tr> <td>Absolute shortfall (3.5% discount)</td><td>12.61</td><td>1.2</td></tr> </tbody> </table>	Severity Modifier	Value	Weight	General population QALYs (1.5% discount)	34.5	-	Proportional shortfall (1.5% discount)	65.3%	1	Absolute shortfall (1.5% discount)	22.52	1.7	General population QALYs (3.5% discount)	22.52	-	Proportional shortfall (3.5% discount)	56.0%	1	Absolute shortfall (3.5% discount)	12.61	1.2
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4	Economic model – updated base case incorporating the committees preferred assumptions Vertex has amended its original model structure and is providing the committee with a new version of the model where the committee's concerns are addressed and therefore uncertainty reduced. Furthermore, several of the committee's preferred assumptions are now reflected in an updated base case. Vertex appreciates the attempt made by the EAG to address the committee's concerns in the previous version of Vertex's model; however several inaccuracies have been found e.g. the EAG has inappropriately added a calculation of the costs of treatment withdrawal prior to exa-cel infusion and the prevalence of chronic complications. We therefore provide an updated model for decision-making, including the committee preferences that Vertex has accepted. We request that the model submitted with this response be used to run all scenarios in future. Vertex has provided an updated economic model incorporating an updated model structure and a selection of the committees' preferred assumptions. The following amendments and assumptions have been accepted and incorporated into the base case: • the company's updated model structure which addresses two important issues: ○ mortality in ACD point 3.6, whereby mortality is addressed by a standardized mortality rate (SMR), and, ○ link between VOCs and risk of developing SCD-related complication replaced by fixed risks/rates of complications derived from the literature • the company's preferred model input on standardised mortality ratio • model inputs on the risk of complications derived from the literature; different scenarios are provided: ○ data from Brousse et al. (2023) (9) severe population, ○ data from Udeze et al. (2023) (7) considered a more complete data set avoiding the need for strong assumptions to estimate cumulative incidence. • Exclusion of adverse events for exa-cel Economic model – corrections and comments Vertex has corrected an issue with the model's age- and sex-matched general population utility values. The error resulted in an inflation of utility values within the exa-cel and SoC cohorts, as noted by the EAG during ACM. The difference between utilities for patients with severe SCD and functionally cured from SCD was incorrectly subtracted from the general population utility values. Vertex has therefore corrected the age- and sex-matched utility adjustment in the model, using the multiplicative method. This therefore resolves the inflated utility value issue raised by the EAG during ACM. Vertex has also corrected the potential issue of double counting Acute Chest Syndrome (ACS) in the model. In point 3.11 of the ACD, the EAG noted that ACS is also included within the Vertex's definition of a VOC. To address this issue, Vertex have reweighted the rate of ACS reported in Udeze et al (2023) to account for the proportion of patients in CLIMB SCD-121 who experienced an ACD event that was then preceded by a VOC event. Note that this correction only applies when

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Udeze et al (2023) is used as the source for complications data. The rate of ACS is reweighted based on the following assumptions:

- 14 of the 43 subjects (32.6%) in CLIMB SCD-121 had an ACS event that was preceded by a VOC event.
- Based on this proportion, Vertex reweight the proportion of simulated patients who experience ACS per model cycle by the proportion of patients who experienced an ACS even that was not preceded by a VOC event (i.e., 67.4%) in CLIMB SCD-121.

We present this approach as a scenario in Table 11. Since we omit the proportion of patients who experienced an ACS preceded by a VOC event, this addresses the issue raised in point 3.11 of the ACD.

Vertex has also identified both major and minor issues with the latest amendments incorporated by the EAG in Vertex's original model and has thus spent significant resources reviewing and correcting such adaptations. Vertex would like to make clear that the EAG did not provide a change log of their initial adaptations. A change log was provided on request; however, Vertex found the change log lacked necessary detail to clearly document the adaptations implemented by the EAG. We have thus endeavoured to update our original model structure to capture flagged modelling issues, including the changes attempted by the EAG, to reflect Vertex's updated base case including committee's preferences.

As requested in the draft guidance document, we accept the use of the committee's preferred assumptions regarding modelling of comorbidities and mortality, also supported by the DSU, which addresses point 3.6 and 3.7 in the ACD. The updated base case at the end of this document has been run with an updated version of the company model with a selection of the committee's preferred assumptions. Vertex requests that this version of the model be used for any future analysis.

We have identified issues with the way the EAG has programmed their adjustments in their version of the updated model

While the EAG has added functionality to include their preferred scenarios, the overall programming used by the EAG limits the flexibility of the model and thus the ability of the user to explore different scenarios. Generally, the approach taken by the EAG to implement their preferred scenarios has made the model harder to investigate and review and added greater potential for unintentional user errors to occur.

Critically, the EAG has incorrectly calculated chronic complications

The EAG has applied incorrect calculations to chronic complications in the model. The approach taken by the EAG yields invalid results in the predicted prevalence of each chronic complication. Testing these calculations by means of standard internal and external validation exercises indicates a lack of validity in the estimation of chronic complications throughout the modelled time horizon.

The specific calculation issues with the EAG's approach, and the corrected calculations proposed by Vertex, are technically detailed in the Appendix. However, the issues with the EAG's approach to calculating chronic complications are apparent when considering the following:

- In Table 6 found in the *ID4016 exa-cel EAG TE additional works updated 30012024CM [CON]* document (44), the EAG state that "For chronic complications, cumulative lifetime incidence was calculated for Brousse over the life-years estimated for SOC in the model

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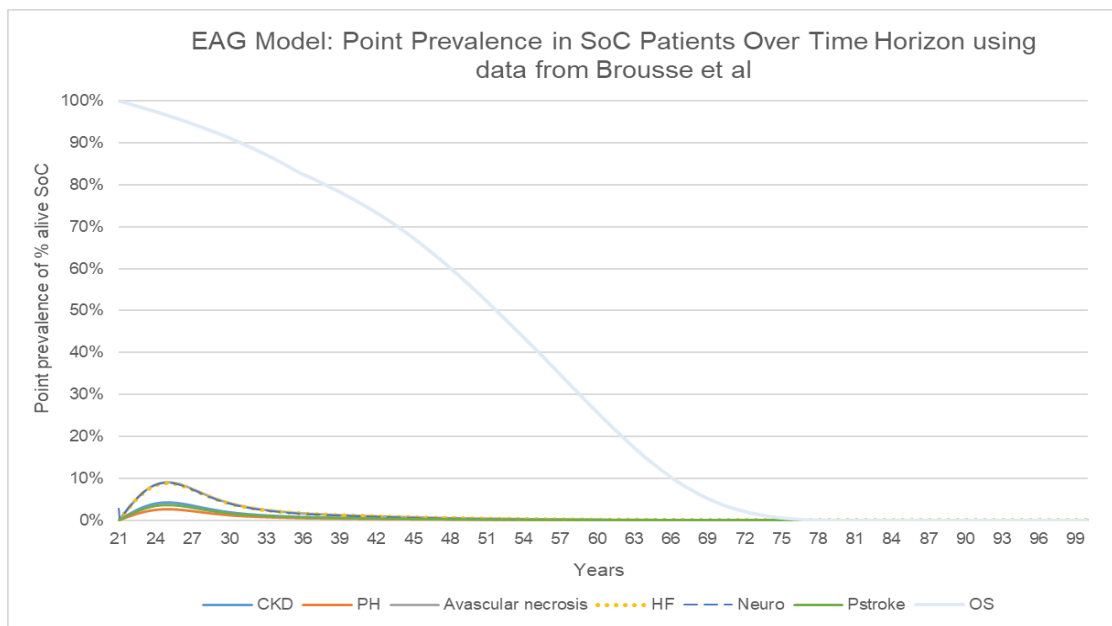
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(22.36) using probability from Brousse et al (median follow up of 7 years) converted to rate, scaled up to 22.36 years and reconverted to probability.”

The EAG has only provided a table with hard coded percentage values in their model, which it claims estimates the “cumulative lifetime incidence [i.e., prevalence]” of “chronic complications over the course of the model or equivalent.” To follow the logic of the EAG’s argument, this suggests that peak point prevalence in the modelled SoC population is expected at roughly 43.5 years of age (i.e., mean survival, calculated as baseline age plus the predicted mean additional life years of SoC patients, which is 22.36 based on the EAG’s statements). However, in the EAG’s model, peak point prevalence of chronic complications in the SoC cohort occurs at roughly 25-27 years of age (see Figure 3 – note the OS line in the graph is the overall survival of the SoC cohort over time). This contrasts with Brousse et al., who demonstrated that the rate of development of chronic complications continued to increase past age 40 (see Table 3 in Brousse et al.). The predicted peak point prevalence of chronic complications in the EAG’s model is thus clinically unrealistic. The peak prevalences are, furthermore, several orders of magnitude smaller than those observed in cohorts of severe SCD patients e.g. the prevalences at baseline recorded in Udeze et al., (2023) (7).

Figure 3: EAG model – predicted point prevalence of chronic comorbidities in the modelled SoC cohort over time



- The EAG does not appropriately incorporate baseline prevalence into their point prevalence calculations. This is especially noticeable when inspecting the modelled point prevalence of neurocognitive impairment over time (see dashed blue line in Figure 3). At model entry, prevalence sharply drops in neurocognitive impairment, indicating that baseline prevalence is not appropriately incorporated into the point prevalence calculation. This is similarly true for all other chronic complications in the model, whereby baseline prevalence is not correctly counted. Please also see Figure 7 in the Appendix, which provides a magnified visualisation of this issue.
- If you set the per cycle probability of developing chronic kidney disease (CKD) in the EAG’s model to 100%, the maximum point prevalence of CKD is 2802.9%, occurring in cycle 47 of

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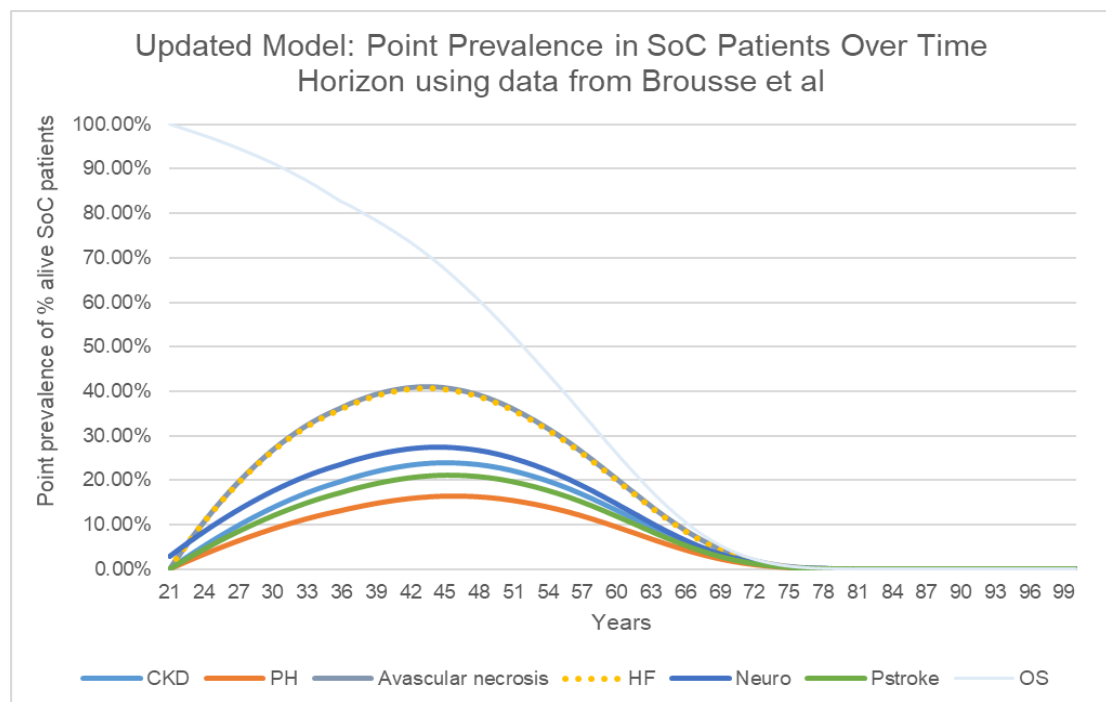
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the EAG's model. Whilst the sum of the point prevalence across all model cycles can exceed 100%, a cycle-specific point prevalence should never exceed 100%. For all other chronic complications altered by the EAG, the issue is similar.

Correction of this approach leads to more valid predictions that follow clinical reality

We have corrected the EAG's calculations in line with Equation 2 (see Appendix). These amended calculations lead to more realistic predictions. Predicted peak point prevalence in the updated Vertex model's SoC cohort occurs approximately between 42-45 years of age (see Figure 4 - note the OS line in the graph is the overall survival of the SoC cohort over time). This aligns more closely with the evidence presented in Brousse et al (9). Moreover, the predicted point prevalence of chronic complications generally follows the proportions that, according to the EAG, are to be expected at roughly the point of mean survival (i.e., expected additional LYs from model baseline) in the SoC arm. A tabulated comparison of these proportions, based on the arguments presented by the EAG in Table 6 of the *ID4016 exa-cel EAG TE additional works updated 30012024CM [CON]* document, is presented in Table 5.

Figure 4: Vertex model – predicted point prevalence of chronic comorbidities in the modelled SoC cohort over time



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Table 5: Expected prevalence after 22.36 years based on the Brousse et al (2023) severe population compared to the point prevalence predicted by the EAG and Vertex models in the SoC Cohort

Chronic complication	EAG's calculation for expected prevalence for severe patients after 22.36 years based on Brousse et al (Table 6 of EAG TE critique)	EAG model amendments predicted point prevalence after 22.36 years into model time horizon	Vertex model - as per Equation 2 - predicted point prevalence after 22.36 years into model time horizon
Chronic Kidney Disease	23%	0.38%	23.87%
Pulmonary Hypertension	15%	0.24%	16.16%
Avascular necrosis	42%	0.80%	40.93%
Heart Failure	41%	0.79%	40.66%
Neurocognitive impairment	N/A	0.79%	41.52%
Post-stroke	20%	0.32%	20.80%

The EAG's approach to calculating withdrawal prior to treatment with exa-cel is overly complex and double-counts the costs and outcomes of withdrawal prior to treatment with exa-cel

Vertex maintains its position [REDACTED] and, therefore, that the cost uplift applied by Vertex appropriately captures the expected risks of withdrawal within the UK target population. Nonetheless, Vertex recognises the committee's preferred assumption regarding this issue and has thus maintained model functionality to consider the additional costs and health outcomes of treatment withdrawal by means of a scenario. The scenario is implemented using the same approach used by the York EAG for the TDT model, with costs and outcomes weighted in a secondary table of results.

Vertex does however note concern with the EAG's approach to calculating the economic outcomes associated with patients who do not go on to receive exa-cel. The approach taken by the EAG seems to imply that patients only withdraw from the procedure for two reasons: inadequate apheresis or low manufacturing yield. The proportions of these patients are then used to inflate the costs of exa-cel and reduce its efficacy. Withdrawal prior to receiving exa-cel and exa-cel's actual efficacy ought to be modelled as separate issues. This is discussed in detail in Point 6 of this document. In addition to the fact that the methodology used by the EAG to estimate these proportions is highly ambiguous, Vertex considers the EAG's interpretation of the reasons for treatment withdrawal as most critical.

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	Of the 11 subjects who underwent apheresis but did not receive exa-cel infusion during the mobilisation period, the EAG's calculations imply that 6 of these patients did so due to low manufacturing yield. However, this is incorrect. The reasons for withdrawal of these 6 patients comprise various reasons: • [REDACTED] • [REDACTED] The EAG's calculations for withdrawal also imply that the other 5 patients did so due to apheresis failure. Again, the reasons are broad, and none are directly linked to apheresis failure: • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] Given the myriad causes for withdrawal of patients within CLIMB SCD-121, the approach taken by the EAG, to separate withdrawal patients into two distinct groups, relies on very strong assumptions. Vertex has therefore added an alternative approach to including the costs and outcomes of exa-cel patient withdrawal in the model. Please see the Appendix for further details on Vertex's approach to including costs and outcomes of treatment withdrawal. The EAG model errors identified by Vertex significantly bias against exa-cel and may lead to decision making not reflective of the true cost-effectiveness of exa-cel The errors and issues identified in the EAG's model amendments, particularly regarding treatment withdrawal and chronic complications, have a substantial impact on the ICER and significantly bias against exa-cel. For chronic complications alone, switching from using the EAG's method shown in Figure 3 to Vertex's method using Equation 2, which generates the point prevalences shown in Figure 4, reduces the committee's preferred ICER from [REDACTED] (roughly, a [REDACTED] decrease). Overall, Vertex raise significant concern with the EAG's approach to best practice modelling. Vertex would like to emphasise that the programming and some of the calculations used by the EAG are not in line with general good practices expected in health economic modelling. Both the issues with treatment withdrawal and chronic complications have significant impact on the cost-effectiveness of exa-cel. Moreover, using the EAG's calculations for chronic complications simply leads to flawed extrapolation. Again, we expand on this issue with greater technical detail in the Appendix. We therefore provide a corrected version of the model, based on the version submitted by Vertex at technical engagement as a starting point, incorporating the committee preferences which Vertex has chosen to accept (as summarised at the beginning of Point 4).
5	Uncaptured benefits SCD has a substantial impact on QoL, not just for patients but also for caregivers. SCD impacts caregivers' ability to maintain employment, and results in higher degrees of depression, anxiety and stress relative to those not caring for SCD patients. The committee

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	should take this into account when considering the most appropriate ICER threshold, beyond the flexibility in the threshold given for health inequalities. As described in Section 3.16 of the ACD, there are benefits to the treatment of exa-cel in SCD that are not captured in the economic modelling. The committee acknowledges some uncaptured benefits, such as the health inequalities that exist in SCD, but this has not been extended to the substantial burden SCD imposes on caregivers. These aspects contribute to the severity of SCD, and the potential benefit that exa-cel might bring in delivering a functional cure. SCD has a significant impact on caregivers' QoL and mental health, and treatment with exa-cel stands to alleviate these burdens for caregivers and family members. D'Amico Gordon <i>et al</i> (2024) surveyed caregivers of children with SCD in 5 US centres between 2014 – 2021 (45). Of the 244 caregivers in this study, 10.3% reported employment loss in the last 5 years due to having to attend the hospital, and 17.5% reported missing 10 or more days of work for the same reason. This study found that unemployment rates are much higher for families impacted by SCD than the general population, with rates of 20.7% and 4.7% respectively. The authors explained that SCD has many impacts that may make maintaining employment significantly challenging for caregivers, including the need for frequent appointments, home management of vaso-occlusive pain episodes, cognitive deficits, and chronic disability. Ebeid <i>et al</i> (2024) noted that parents of children with SCD had higher degrees of depression, anxiety, and stress and a significantly lower HRQoL compared to parents of healthy controls (46). This is further supported by Barcelos <i>et al</i> 2022, who observed a mean EQ-5D-5L score for caregivers in the UK was 0.62 and mean CarerQoL-7D score was 78 (47). A majority of caregivers reported mental health problems: 72% and 64% by EQ-5D-5L and CarerQoL-7D, respectively; 68% reported financial problems due to their caring responsibilities. The mean percentages of impairment due to caregiving (n=37) were absenteeism (22%), presenteeism (46%), overall work impairment (34%). Among all caregivers (N=69), the mean for activity impairment was 53% (24%). Mean missed work hours per year was 442 in the UK.
6	Accounting for patients who do not have exa-cel infusion in the model In the trial, and model, some patients undergo cell collection but do not go on to have exa-cel treatment. The reasons for this are related to the nature of SCD and systemic health inequalities experienced by patients. Equally, treatment effects for those patients that do not have exa-cel infusion should be removed from the exa-cel arm of the model, to ensure model results accurately represent the effect of treatment with exa-cel. A number of patients who underwent apheresis in CLIMB SCD-121 did not receive exa-cel treatment (~19%), and the committee expressed a preference that the costs and outcomes of these patients should be included in the exa-cel arm of the model. This essentially has the effect of capturing outcomes of patients who did not receive therapy, and will go on to be treated with SoC, and have poor outcomes, as though they received exa-cel, generating less QALYs overall for the exa-cel arm of the model. We strongly believe it is unreasonable for these patients to be modelled as having received exa-cel treatment, where no infusion was given. We acknowledge that in other appraisals for ATMPs where cell collection is involved, companies have accepted this way of modelling, however it is important that the committee reconsiders this approach due to some specifics of SCD.

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Modelling outcomes of patients who do not receive exa-cel infusion

The reasons that a patient may proceed to cell collection but not to exa-cel infusion are related to the nature of SCD rather than the treatment they received. Many were clinical trial related, and all are likely to be seen less outside of the clinical trial context. The proportion of patients not proceeding to treatment following their initial apheresis is higher in this patient population, compared to others, such as those patients undergoing CAR-T. This is partly due to the nature of their condition, as patients with SCD have challenges with collecting adequate stem cells during apheresis, and experience discrimination in the healthcare system. Depriving patients of treatment with exa-cel because of the characteristics of their disease would be adding to the already significant and systemic health inequalities experienced by this patient group (48).

Some of the reasons for withdrawal were clinical trial related due to the experimental nature of the treatment such as withdrawing consent, and this is unlikely to be the case now that exa-cel is no longer an investigational therapy and is approved by regulators. In CLIMB SCD-121, 6 patients discontinued due to inadequate cell collection following apheresis (not adverse event related) which is related to the nature of sickle-cell disease (29). Several SCD related problems make collecting adequate cells more challenging, due to factors including chronic haemolysis, inflammation and hydroxyurea use which is myelosuppressive and toxic to stem cells. In addition, granulocyte colony stimulating factor (G-CSF), the most commonly used mobilising agent can induce severe SCD complications and is therefore not used in SCD patients making cell-collection even more challenging (49).

It is therefore not equitable or reasonable to include the outcomes of the patients who do not receive exa-cel infusion in the exa-cel arm of the model, as this artificially dilutes the demonstrated efficacy of the therapy and may result in preventing approval of a much-needed therapy for this underserved population.

Modelling costs of patients who do not receive exa-cel infusion

Via the commercial discussions with NHS England and the treatment centres, [REDACTED] It would be unreasonable for the committee not to take a pragmatic approach to considering the exclusion of treatment effects for those patients that withdraw before infusion, thereby widening health inequity in this population.

The pre-treatment cost of patients who withdraw during pre-transplant is accounted for via a cost uplift in the model. Specifically, the pre-transplant costs of patients who withdraw are added to the pre-transplant costs in the first cycle of the model. This cost uplift adds an additional [REDACTED] to the pre-transplant costs in the exa-cel arm of the model.

We strongly believe that our proposed approach of removing the outcomes of patients who do not receive exa-cel infusion from the exa-cel arm of the model, as well as the steps we have taken to reduce financial risk for the NHS, should be considered and accepted by committee.

In addition, there is considerable uncertainty about whether the proportion of patients who have cell collection, but do not go on to exa-cel treatment would be the same in clinical practice as in CLIMB SCD-121 (29). Along with increasing knowledge and expertise in apheresis, and support that will be provided to centres the risk of withdrawal prior to receiving exa-cel will be reduced in clinical practice.

In recognition of this uncertainty, we present a scenario where [REDACTED] of patients withdraw during the mobilisation period (i.e. do not incur exa-cel treatment costs for patients who do not

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	receive infusion, but outcomes are included). This scenario accounts for the patients that do not go on to receive exa-cel due to inability to manufacture drug product. Our expectation is that in clinical practice, the other reasons for not receiving exa-cel listed in section 4 would not occur. This scenario is presented in Table 11.
7	Definition of baseline VOCs Vertex strongly believes that all VOCs that require healthcare attendance should be accounted for in the model. All VOCs are related to SCD complications, and result in a reduction in QoL. Further, issues with VOCs definitions in baseline vs follow up periods are alleviated by the new model structure. VOCs cause ischaemic tissue damage and inflammation, resulting in debilitating pain often requiring healthcare resource utilisation, and are directly linked to end-organ damage, direct healthcare costs and early mortality. There is no biological difference between a VOC requiring in-patient hospitalisation, and a VOC requiring attendance in a day unit or emergency department. The decision to admit to hospital will depend on local resources (e.g. whether a day unit is available), patient factors (social support, caregiver responsibilities), patient prior experience and patient and clinician preference. Therefore, the impact of VOCs on complications, mortality, quality of life and disease burden applies to all hospital attendances. VOCs requiring hospital attendance, not just those related to in-patient hospitalisation have an impact on quality of life, healthcare resource utilisation and long-term outcomes and should be included in the economic model. As described in our response to the non-reference discount rate issue, SCD has a substantial, and daily, impact on patients, with patient experts struggling to remember a day without pain. <u>Hospitalisation is related to multiple factors</u> Whether a patient is admitted to hospital is due to many factors, for example if day units are available patients will prefer to use these to avoid hospital in-patient stays and where specialist services are not available, patients may be admitted to hospital unnecessarily. The “No-One’s Listening” report highlighted that many patients avoid being admitted to hospital due to fear of substandard care, and prefer not to be admitted to hospital following attendance at an accident and emergency department (22). Further support for this comes from Drahos <i>et al</i> (2022), which found that amongst a cohort of 142 adults with SCD in the UK, France, and US, 68% of patients reported being treated unfairly while seeking care, typically due to race (67%) and/or requesting more pain medicine (65%) (27). <u>All VOCs are related to complications of SCD and mortality</u> As highlighted in a recent study by Brousse <i>et al</i> (2023) looking at the burden of sickle cell disease in a severe cohort of patients with a similar severity to those enrolled in CLIMB SCD-121, patients during follow-up had high rates of acute and chronic complications and had a median of 2 ambulatory medical visits per year and 2.9 in-patient hospitalisations per year (9). This study highlights that both hospitalisation and non-hospitalisation VOCs are similar in prevalence and contribute to the overall disease burden of patients with sickle-cell disease, and the associated reduction in life expectancy. <u>All VOCs are linked to reduced HRQoL</u> A recent global, longitudinal survey, focused specifically on the population with recurrent VOCs, including both in-patient hospitalisation and non-in-patient –hospital visits. The study defined SCD patients (as per the CLIMB SCD-121 study) with recurrent VOCs as having ≥2 VOCs/year, in each of

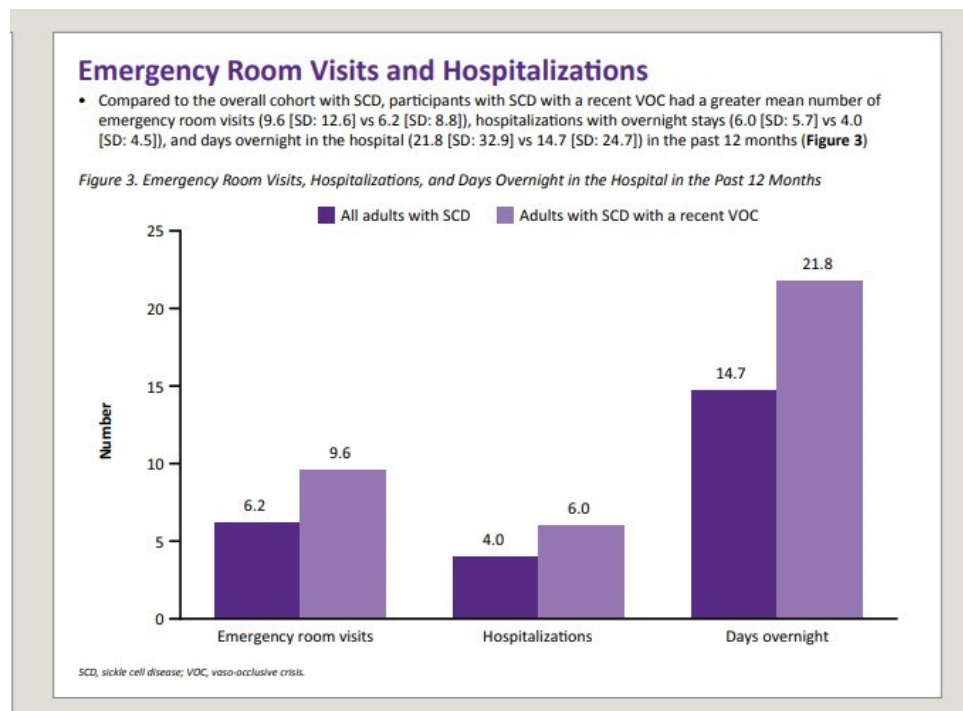
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the 2 years before study enrolment, that required interaction with a healthcare provider and administration of pain medication or an RBC transfusion. The survey showed the substantial humanistic burden of patients living with SCD, and the additional impairment posed by recurrent VOCs (21) (Figure 5).

Figure 5: Relationship between VOCs and requirement for hospitalisation



The SWAY study found that patients reporting a higher number of VOCs (irrespective of whether these required hospitalisation) in the 12 months prior to survey completion were significantly more likely to report a high impact of SCD on all aspects of daily life, schooling, and emotional wellbeing (4).

In summary patients with severe SCD suffer from VOCs, that often do not end up with in-patient hospitalisation, for a number of reasons including distrust of the healthcare system., All VOCs that require healthcare attendance impact a patient in terms of both QoL and disease-related complications and impose a significant disease burden. Therefore, all VOCs should be accounted for in the economic model.

The updated model estimates mortality and complications independent of VOC rate

The committee noted inconsistencies in the baseline definition of VOCs. Vertex believe that these issues are now addressed based on several changes in the model and from perusing the sources of the data used to estimate mortality and complications.

The discrepancy between the definition of the model baseline VOC and the calculation of mortality and complications is alleviated since mortality and complications are modelled independently of VOC rate in the updated model. Moreover, all data used to model mortality and complications aligns with the VOC definition applied in the model and CLIMB SCD-121.

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	Definition of VOCs used in CLIMB SCD-121 and data for mortality and complications used in the model generally align due to several reasons Since mortality and complications are now modelled independently of VOCs, the issue of inconstancy in the definition of VOCs for the data used in the model is negligible. Most data used to model mortality and complications are derived from unselected study populations. For mortality, Desai et al included patients with non-hospitalised and hospitalised VOCs (12). The majority of literature sources used to model complications, specifically Cahill et al (2019) (50), Shah et al (2019) (51), Shah et al (2024) (52), Singh et al (2016) (53), and Yeruva et al (2016) (54), did not have VOC-related inclusion criteria. Hence, the data from these studies are more representative of unselected, less severe populations than CLIMB SCD-121. Moreover, the study criteria of Udeze et al (2023) fully aligns with criteria of CLIMB SCD-121. These populations are thus highly comparable, and it is another reason why Vertex prefers using Udeze et al (2023) for complications input data. For Brousse et al (2023), these data are derived from the severe cohort. The VOC rates for non-hospitalised and hospitalised patients in Brousse et al (2023) are much lower than the rates reported in CLIMB SCD-121. For instance, Brousse et al report a rate of 1.67 per person year for hospitalised VOCs (compared to a rate of 2.6 per person year in CLIMB SCD-121). All these data therefore align with the general definition used in CLIMB SCD-121 and thus the model. In response to the EAG's suggestion that excluding non-hospitalised VOC reduced the need to model a relapse rate, we have already explained in Point 2 section 3 "<i>The benefits are likely to be sustained over a very long period</i>" that the non-hospitalised VOCs experienced by the patients post-exa-cel do not constitute a relapse, with underlying parameters such as HbF %, Hb concentration, and allelic editing remaining stable.
8	Modelling of SCD complications: choice of source While Vertex maintains the position that frequency of VOCs is a valid predictor of complications over time in severe SCD patients and therefore a hazard rate approach to model the risk of complications is appropriate, Vertex agrees to a new model structure whereby the risk of complications is derived from the literature e.g. from Brousse et al. Vertex presents two scenarios with data on complications derived from Brousse et al (as per committee's request) and data from Udeze et al. The latter provides a more complete source for the relevant population, based on UK data, and will therefore also be useful for the committee to consider. Vertex maintains its position that VOC frequency is a predictor of severe disease and risk of developing complications in SCD. In addition to the clinical evidence presented by Vertex throughout this submission substantiating this argument, Brousse et al. 2023 (9) carved out a more severe subgroup of patients based on the frequency of VOCs and the frequency of treatments for VOC (hydroxycarbamide prescriptions and/or blood transfusions). Brousse et al. demonstrates that the incidence of multiple comorbidities is higher in this severe cohort of SCD patients, supporting the argument that VOCs are a predictor of incidence of multiple comorbidities (9). Furthermore, when employing the Brousse publication comorbidity incidences, the EAG makes the strong assumption that all incidence rates were observed following 7 years of follow up, whereas this figure represents the median length of follow-up of patients within Brousse (interquartile range 4.2-7 years). In contrast, the Shah publication used by Vertex expresses complication rates as an incidence per 100 person-years (6), which requires no such strong assumption, having already been converted to a format suitable for implementation in an economic model by the authors.

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Finally, the EAG made adjustments to the patient denominators in Brousse to adjust for presence of patients who had received curative therapies. Again, this incorporates strong assumptions regarding the relative follow-up times of patients in the Brousse cohort who did versus did not receive curative treatment. The impact of these adjustments is unclear.

Despite these limitations, Vertex presents the committee's preferred approach as a co-base case, using Brousse, for calculating chronic complications in our updated. This is primarily because the rate of complications is derived from the more severe cohort in Brousse and thus should generate similar results to those when using VOCs as a predictor. However, Vertex present data on complications from Udeze et al (2023) as a preferred co-base case. These data provide an alternative and more complete source for the relevant population, based on UK data, and should therefore be considered by committee.

Vertex acknowledges the committee's preference to model complications unconditional on VOC rates

Notwithstanding the aforementioned reservations, Vertex understands that the committee would prefer to model complication rates independent of VOC frequency. Therefore, Vertex has adapted the version of the model submitted at technical engagement to calculate complication rates unconditional on VOC frequency. Vertex has implemented these changes using a different approach to the EAG, due to the calculation issues identified by Vertex in the model version shared by the EAG previously (discussed in detail in Point 4 of this response document and the Appendix). We have tabulated the point prevalence of chronic complications at 22.36 follow-up years based on the rates predicted by Brousse et al. compared to the EAG model and the updated Vertex model, as per Equation 2, in Table 5. We discuss the strengths of preferring Udeze et al (2023) and present a comparison of the expected chronic complications over time, between the updated Vertex model and the amended EAG model.

Vertex present Udeze et al (2023) as a preferred co-base case

As noted above, Vertex has added an additional co-base case as our preferred source for modelling complications, using complication data from Udeze et al (2023) (7). Vertex believes that this source is more robust than Brousse for several reasons. Firstly, Brousse et al. does not report data for six of the complications applied in the model. In contrast, Udeze et al (2023) report data for all complications applied in the model. Secondly, incidence of complications in Udeze et al. is reported as an incidence rate per 100 person-years, and it is thus not reliant on strong assumptions regarding duration of follow-up. However, this is required when using data from Brousse et al. because average duration of follow-up is not reported. Lastly, the definition and study criteria of a patient's VOC rate in Udeze et al (2023) aligns with CLIMB SCD-121, thus alleviating point 3.10 in ACD.

In Table 6 we compare the prevalence observed in patients from Udeze et al (2023) at baseline, indexed according to ages 12-35 and >36, with the predicted period prevalence of our updated model and the EAG model. The predicted period prevalence is calculated in each model as an average within two age groups. For the predicted period prevalence in ages 12-35, we take the average prevalence in the model from baseline age to age 35. For the predicted period prevalence in ages >36, we take the average prevalence in the model from ages >35 to age 86. We use a maximum age of 86 to align with the maximum age observed in the severe SCD cohort from Udeze et al (2023).

Vertex reiterates that, given the evidence presented in Table 6, the corrections, applied by Vertex in the updated model, lead to more valid predictions that follow clinical reality more closely.

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Table 6: External model validation of predicted model prevalence in SoC cohort compared to Udeze et al.

Chronic complication	Prevalence: Ages 12-35	Prevalence: Ages > 36
<i>Baseline prevalence based on Udeze et al</i>		
Chronic Kidney Disease	2.00%	7.63%
Pulmonary hypertension	2.62%	18.88%
Avascular necrosis	13.71%	33.33%
Heart Failure	Not available	9.64%
Neurocognitive impairment	1.69%	4.02%
Post Stroke	Not available	Not available
Retinopathy	8.17%	26.51%
Liver complications	5.08%	5.22%
<i>Predicted period prevalence based on updated Vertex Model</i>		
Chronic Kidney Disease	4.66%	5.76%
Pulmonary hypertension	7.79%	9.18%
Avascular necrosis	18.81%	18.61%
Heart Failure	6.67%	8.00%
Neurocognitive impairment	7.24%	6.58%
Post Stroke	2.04%	2.27%
Retinopathy	25.10%	17.22%
Liver complications	6.22%	7.50%
<i>Predicted period prevalence based on EAG Model amendments</i>		
Chronic Kidney Disease	1.01%	0.07%
Pulmonary hypertension	1.73%	0.11%

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	Avascular necrosis	4.59%	0.30%
	Heart Failure	5.01%	0.33%
	Neurocognitive impairment	4.63%	0.31%
	Post Stroke	0.42%	0.02%
	Retinopathy	19.07%*	37.90%*
	Liver complications	5.46%*	27.06%*
*In the EAG's model, please note that these chronic complications still use risk equations to estimate point prevalence.			
9	Utility of SoC patients at baseline and evolution over time As requested by the committee, Vertex provides a longitudinal view of how the net utility of SoC patients in the model changes over time, to ensure it is clear that patients experience a severe impact on their quality of life, especially as they grow older. Vertex has also implemented additional scenarios to evaluate the uncertainty related to baseline utility. We also include additional post-hoc analysis of the trial utility data, indicating significant ceiling effects in the baseline HRQoL trial data. At the point when patients receive exa-cel they will have relatively fewer complications; however, it is clear from the literature that without treatment, their QoL would continue to deteriorate as they grow older and accumulate further co-morbidities. The overwhelming body of evidence looking at all PROs from multiple studies in SCD including EQ-5D shows that SCD has a significant negative impact on quality of life. Therefore, the committee requested additional information on utility values over time in the SoC arm in the model. As patients in the SoC arm age in the model, they develop comorbidities which results in added disutility to the baseline SoC utility value. Vertex provides a longitudinal view of how the net utility of SoC patients evolves over time in Table 7. Although the baseline utility starts at 0.81 for the cohort of CLIMB SCD-121 patients (29), this decreases substantially over time because of the comorbidities incurred and the associated utility decrements. Vertex emphasises that the predicted utility values		

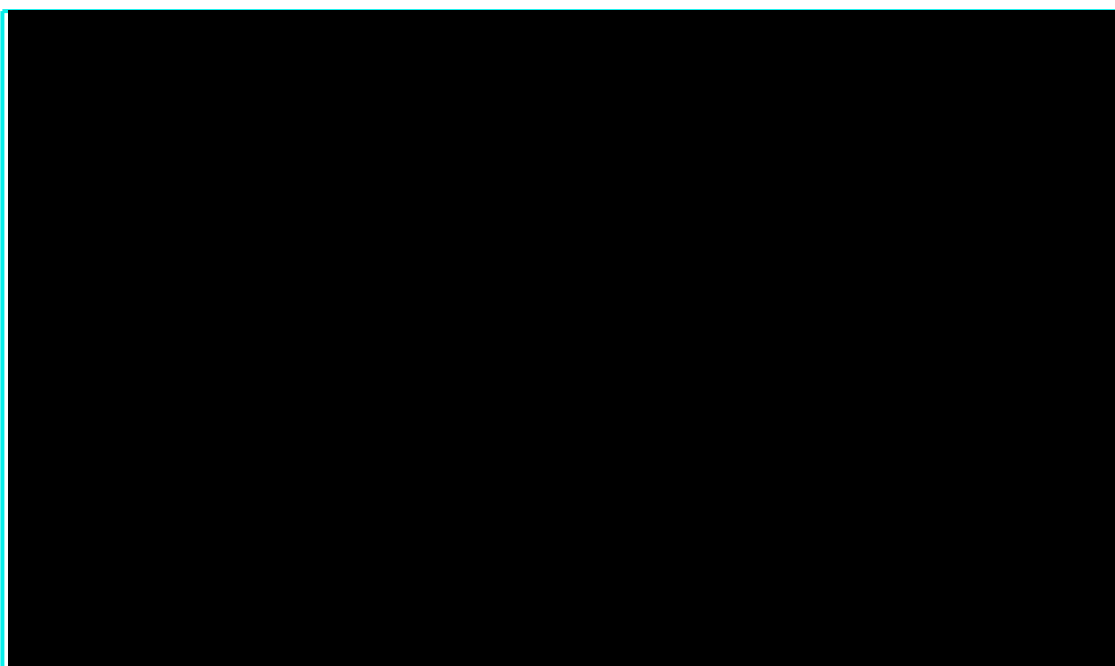
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are within the range of those reported in CLIMB SCD-121 when patients with a utility score of 1 are removed (see post-hoc subgroup analysis, Figure 6) (55).

Figure 6: Histogram of EQ-5D-5L UK Index Scores for patients with utility < 1 at baseline in CLIMB SCD-121 FAS (N=21)



As shown in Table 7 and Table 8, the predicted values closely align with the very low utility values observed in the post-hoc CLIMB SCD-121 utility analysis. In fact, when using a baseline utility value of 0.81, the predicted net utility at baseline is more closely aligned with the mean post-hoc subgroup baseline value when all disutilities are included compared to when acute complication disutilities are excluded (see 'Net health state utility' vs 'Net health state excl. acute disutilities' columns). Hence, there is a strong rationale for preferring a baseline value of 0.81. Likewise, the net utility predicted by the model between the ages of 21 and 35 comfortably lies within the realistic range of the values observed in the subgroup of patients aged ≥ 18 and ≤ 35 with a utility score of < 1 at baseline (Figure 6). As discussed in Point 2 of this document, the range of values observed in CLIMB SCD-121 are well supported by values documented in the literature. Please see a comparison of using an alternative baseline value of [redacted] in Table 8.

Table 7: Evolution of SoC SCD utility value in the economic model using data from Brousse et al. for complications

Age	Core health state utility including age decrement	All Comorbidity disutilities	Net health state utility	Chronic Comorbidity disutilities	Net health state utility excl. acute disutilities
21.2	0.81	-0.10	0.71	-0.02	0.79
30	0.80	-0.20	0.70	-0.13	0.67

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40	0.77	-0.29	0.48	-0.22	0.55
50	0.75	-0.38	0.37	-0.30	0.45
60	0.71	-0.45	0.26	-0.37	0.34
70	0.67	-0.53	0.14	-0.45	0.22

Table 8: Evolution of SoC SCD utility value in the economic model using data from Brousse et al. for complications but with a baseline utility value derived from the post-hoc subgroup analysis

Age	Core health state utility including age decrement	All Comorbidity disutilities	Net health state utility	Chronic Comorbidity disutilities	Net health state utility excl. acute disutilities
21.2	■	-0.10	■	-0.02	■
30	■	-0.20	■	-0.13	■
40	■	-0.30	■	-0.22	■
50	■	-0.38	■	-0.30	■
60	■	-0.45	■	-0.37	■
70	■	-0.53	■	-0.45	■

Since we incorporate data from Udeze et al (2023) for calculating complications as our preferred co-base case, we illustrate utility over time in the SoC cohort for this co-base case too (see Table 9). Please see a comparison of using an alternative baseline value of ■ when using data from Udeze et al (2023) in Table 10.

Table 9: Evolution of SoC SCD utility value in the economic model using data from Udeze et al (2023) for complications

Age	Core health state utility including age decrement	All Comorbidity disutilities	Net health state utility	Chronic Comorbidity disutilities	Net health state utility excl. acute disutilities
21.2	0.81	-0.13	0.68	-0.02	0.79
30	0.80	-0.19	0.60	-0.09	0.71
40	0.77	-0.26	0.51	-0.15	0.62

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	50	0.75	-0.32	0.43	-0.21	0.54																																										
	60	0.71	-0.37	0.34	-0.26	0.45																																										
	70	0.67	-0.43	0.24	-0.32	0.35																																										
Table 10: Evolution of SoC SCD utility value in the economic model using data from Udeze et al (2023) for complications but with a baseline utility value derived from the post-hoc subgroup analysis <table border="1"> <thead> <tr> <th>Age</th><th>Core health state utility including age decrement</th><th>All Comorbidity disutilities</th><th>Net health state utility</th><th>Chronic Comorbidity disutilities</th><th>Net health state utility excl. acute disutilities</th></tr> </thead> <tbody> <tr> <td>21.2</td><td>■</td><td>-0.13</td><td>■</td><td>-0.02</td><td>■</td></tr> <tr> <td>30</td><td>■</td><td>-0.19</td><td>■</td><td>-0.09</td><td>■</td></tr> <tr> <td>40</td><td>■</td><td>-0.26</td><td>■</td><td>-0.15</td><td>■</td></tr> <tr> <td>50</td><td>■</td><td>-0.32</td><td>■</td><td>-0.21</td><td>■</td></tr> <tr> <td>60</td><td>■</td><td>-0.37</td><td>■</td><td>-0.26</td><td>■</td></tr> <tr> <td>70</td><td>■</td><td>-0.43</td><td>■</td><td>-0.32</td><td>■</td></tr> </tbody> </table> To address the committee's uncertainty regarding the baseline utility scenario for severe SCD patients, Vertex have implemented additional scenarios To further aid the committee's assessment of the uncertainty in the baseline utility value, Vertex has implemented an alternative baseline utility scenario derived from the post-hoc utility analysis, which excludes patients with a baseline utility score of 1. When these patients are excluded, the cohort has an average baseline utility of ■. We tabulate the impact of this scenario in Table 11, utilising the post-hoc subgroup utility analysis baseline value of ■ and a utility gain value of ■ (see Point 10 of this document for further discussion).							Age	Core health state utility including age decrement	All Comorbidity disutilities	Net health state utility	Chronic Comorbidity disutilities	Net health state utility excl. acute disutilities	21.2	■	-0.13	■	-0.02	■	30	■	-0.19	■	-0.09	■	40	■	-0.26	■	-0.15	■	50	■	-0.32	■	-0.21	■	60	■	-0.37	■	-0.26	■	70	■	-0.43	■	-0.32	■
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70	■	-0.43	■	-0.32	■																																											
10	Choice of utility value following exa-cel treatment Vertex notes the committee's uncertainty with utility value following exa-cel treatment. Vertex believes that this value reflects the gain in QoL patients experience with functionally cured SCD patients. However, Vertex provides an alternative scenario value of 0.14, based on a post-hoc subgroup analysis (only includes patients with utility <1).																																															

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The committee has raised concerns about using the 0.11 mean change from baseline value and the resulting 0.92 utility value following exa-cel treatment in the model. The committee prefers using a health state utility value of 0.88 in the model for the exa-cel 'functionally cured' population.

The committee's preferred utility value following exa-cel treatment does not reflect the QoL gains associated with functional cure in severe SCD populations

As shown in Table 3, exa-cel resulted in improvements above the minimal clinically important difference, across all QoL measures, irrespective of whether these measured general QoL (EQ-5D), pain (NRS Pain Scale), or SCD-specific QoL (ASCQ-Me). The magnitude of post-treatment gains in QoL observed in the 24-month follow-up period for patients treated with exa-cel is supported by similar observations in several studies, presented in Jiao et al (2022) (56). For instance, in patients who received HSCT, Jiao et al. (2022) report significant gains in utility, especially when patients do not experience post-treatment related complications, such as graft failure or GVHD (56). O'Brien et al (2009) reports a baseline utility of 0.70 for severe SCD patients pre-HSCT (20). Post-HSCT, these patients without graft-failure report an average utility value of 0.95. Vertex would like to highlight that, similarly, no patients in CLIMB SCD-121 experienced graft failure or GVHD (29). Due to the evidence found in the supporting literature, and the utility gain of [REDACTED] reported in the post-hoc subgroup utility analysis, Vertex believe that using a utility gain value 0.11 is, in fact, conservative. However, because the committee has noted uncertainty in the model's baseline utility value for severe SCD patients (already addressed in Point 9) and the utility value following treatment with exa-cel, we provide additional scenarios to address these concerns.

Post-hoc analysis of trial utility data indicates a significant ceiling effect present in CLIMB SCD-121 baseline utility values

Post-hoc analysis of the utility data also shows that there are significant ceiling effects in the baseline utility values of several patients, with [REDACTED] of patients in the PES having EQ-5D scores greater than one at baseline. As explained in Point 2, we believe that this is because the EQ-5D fails to fully capture the QoL impact of SCD, as it is unrealistic for someone to be willing to trade off perfect health for a burdensome transplant with an experimental treatment.

To alleviate these ceiling effects, Vertex has conducted a post-hoc subgroup analysis of the CLIMB SCD-121 utility data (55), to derive an alternative utility gain value post-treatment with exa-cel. This analysis excludes patients with a utility score of 1 at baseline, aged ≥ 18 and ≤ 35 years at screening. A comparison of the base case and the post-hoc utility value scenario are shown in Table 9. Given the results of the post-hoc analysis, Vertex believes that using a utility gain of 0.11 post-treatment with exa-cel is, in fact, conservative. Again, Vertex strongly emphasise that the committee's preferred utility value following exa-cel treatment does not reflect the QoL gains associated with functional cure in severe SCD populations.

The post-hoc subgroup analysis shows a consistent gain of [REDACTED], at month 24 in the subgroup of patients who did not have a perfect utility score of 1 at baseline. This gain is largely consistent throughout the follow-up period. From baseline (n = 15), at month 12 (n = 15), patients reported an average utility gain of [REDACTED] without any patients lost to follow-up. Patients only ever experience a lower utility gain [REDACTED] at month 3 of follow-up. The utility gain reported at month 24 is also not affected by sample bias, since only 2 patients are lost to follow-up throughout the follow-up period. The scenario results, using the alternative post-hoc utility value of [REDACTED], are provided in Table 11.

Table 11: CLIMB SCD-121 utility gain over time

Source	Utility gain

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	Base case: CLIMB SCD-121	0.11 (24 months post-treatment with exa-cel)																																																	
	Scenario: CLIMB SCD-121 post-hoc	■ (24 months post-treatment with exa-cel)																																																	
11	Updated base case Table 12: Base case at 1.5% discount rate with severity modifier, using Vertex's accepted committee's preferred assumptions <table border="1"> <thead> <tr> <th>Base case</th><th>Incremental costs (£)</th><th>Incremental QALYs with 1.7 severity modifier</th><th>ICER with 1.7 severity modifier</th><th>Incremental QALYs with 1.2 severity modifier</th><th>ICER with 1.2 severity modifier</th></tr> </thead> <tbody> <tr> <td>Co-base case: Udeze et al</td><td>■</td><td>30.34</td><td>■</td><td>21.42</td><td>■</td></tr> <tr> <td>Co-base case: Brousse et al</td><td>■</td><td>30.96</td><td>■</td><td>21.86</td><td>■</td></tr> </tbody> </table> Table 13: Scenarios at 1.5% discount with severity modifier <table border="1"> <thead> <tr> <th>Scenarios</th><th>Incremental costs (£)</th><th>Incremental QALYs with 1.7 severity modifier</th><th>ICER with 1.7 severity modifier</th><th>Incremental QALYs with 1.2 severity modifier</th><th>ICER with 1.2 severity modifier</th></tr> </thead> <tbody> <tr> <td>Scenario: Udeze et al and reweighting ACS rate by % of patients who did not experience ACS preceded by VOC</td><td>■</td><td>30.00</td><td>■</td><td>21.18</td><td>■</td></tr> <tr> <td>Scenario: Udeze et al, including outcomes of ■ withdrawal (based on Vertex's approach)</td><td>■</td><td>28.25</td><td>■</td><td>19.94</td><td>■</td></tr> <tr> <td>Scenario: Udeze et al, post-hoc baseline utility (■) and utility gain value (■).</td><td>■</td><td>30.09</td><td>■</td><td>21.24</td><td>■</td></tr> <tr> <td>Scenario: Udeze et al, alternative utility gain based</td><td>■</td><td>32.03</td><td>■</td><td>22.61</td><td>■</td></tr> </tbody> </table>			Base case	Incremental costs (£)	Incremental QALYs with 1.7 severity modifier	ICER with 1.7 severity modifier	Incremental QALYs with 1.2 severity modifier	ICER with 1.2 severity modifier	Co-base case: Udeze et al	■	30.34	■	21.42	■	Co-base case: Brousse et al	■	30.96	■	21.86	■	Scenarios	Incremental costs (£)	Incremental QALYs with 1.7 severity modifier	ICER with 1.7 severity modifier	Incremental QALYs with 1.2 severity modifier	ICER with 1.2 severity modifier	Scenario: Udeze et al and reweighting ACS rate by % of patients who did not experience ACS preceded by VOC	■	30.00	■	21.18	■	Scenario: Udeze et al, including outcomes of ■ withdrawal (based on Vertex's approach)	■	28.25	■	19.94	■	Scenario: Udeze et al, post-hoc baseline utility (■) and utility gain value (■).	■	30.09	■	21.24	■	Scenario: Udeze et al, alternative utility gain based	■	32.03	■	22.61	■
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	on post-hoc analysis ()					

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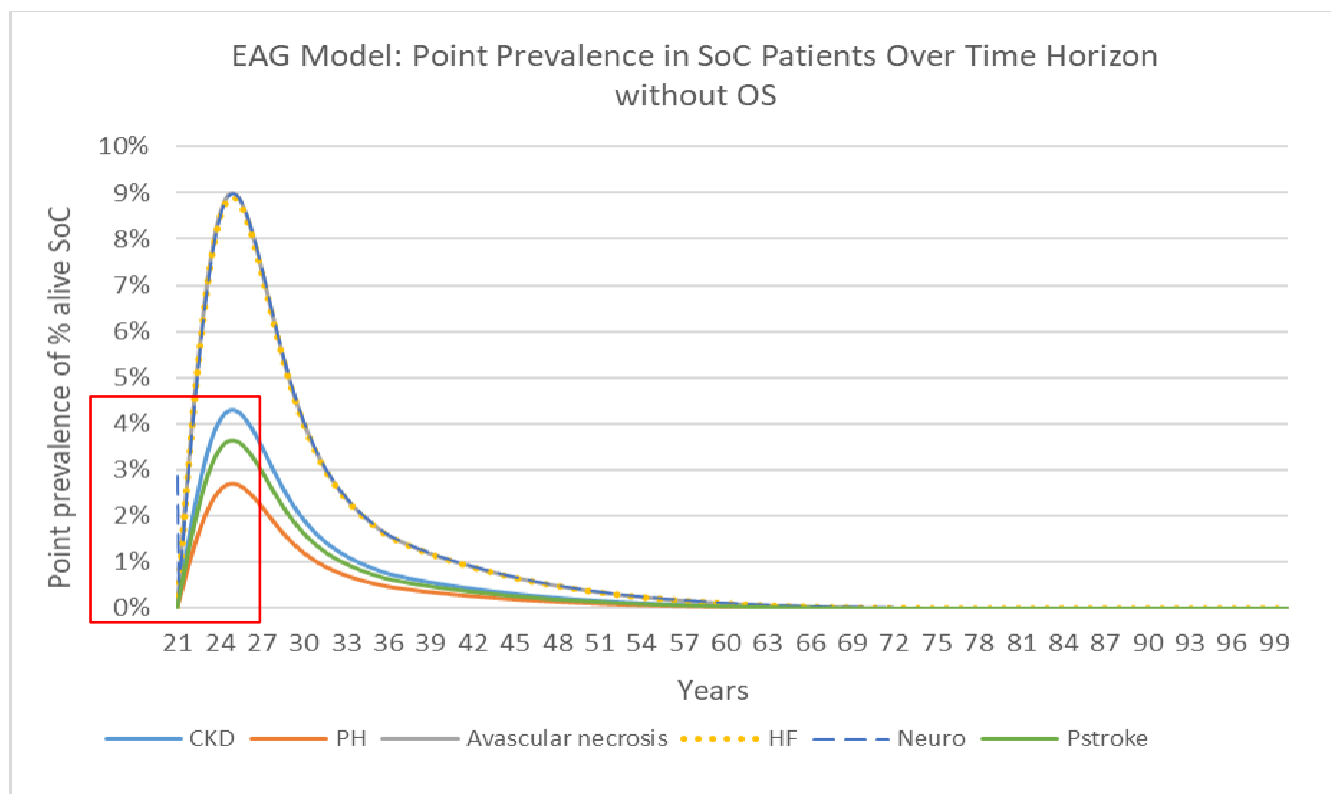
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Appendix

Figure 7 is a magnified visualisation of the EAG's model's predicted point prevalence over time, i.e., it is the proportion of simulated SoC patients who are alive and have chronic complications per cycle time. Note the baseline prevalence spike in neurocognitive impairment and immediate and significant drop in point prevalence, indicating that baseline prevalence and the point prevalence of the proportion of patients who are still at risk of developing the complication are not appropriately incorporated into the calculation.

Figure 7: EAG model – predicted point prevalence of chronic comorbidities in the modelled SoC cohort over time (OS excluded)



Although the EAG state in their critique of Vertex's Technical Engagement response document that the original model's "... rates of complications appear high, and substantially higher than those reported in the literature, despite variability...", this statement is unconvincing when reflecting on the results presented in Table 5 and Table 12 (below). The expected cumulative incidences of chronic complications for severe SCD patients are relatively high, even when these estimates are derived from the rates found in Brousse et al (2023) (which is the EAG's preferred source) (9). Therefore, to further expand on the issues found in the EAG's calculations for chronic complications, we perform supplementary external validation by comparing the expected lifetime prevalence of chronic complications of severe SCD patients based on the rates found in Brousse et al (2023) to the predicted total cumulative incidence of the EAG's and updated Vertex's models respectively.

To perform this comparison, we extrapolate the rates from Brousse et al (2023) over a 79-year horizon. We use the Brousse et al (2023) rates as calculated by the EAG. The 7-year rates were transformed to a year-period probability and then extrapolated using the standard equation $p_t = 1 - e^{-rt}$ where t is the modelled time horizon, i.e., 79 years. As per Equation 1, Vertex assumes that the EAG's incidence term is simply cycle incidence_t . This is a reasonable assumption since we are only removing the mortality adjustment from the EAG's equation in order to

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generate the total cumulative incidence unadjusted for mortality. In contrast, Vertex's incidence term, as per Equation 2, when unadjusted for mortality is $(1 - \text{prevalence}_{t-1}) \times \text{cycle incidence}_t$. The total cumulative incidence each model is compared with the expected lifetime prevalence predicted by the rates from Brousse et al (2023) in Table 12. We highlight that these predictions do not account for mortality, since extrapolating the fixed rates from Brousse et al is also unadjusted. To perform valid comparisons, we thus omit mortality adjustment. Hence, the cumulative incidence predictions provided in Table 12 should not be confused with the actual point prevalence (which is used to calculate the per cycle costs and health outcomes in these models) illustrated in Table 5 and Figure 3 and Figure 4.

Table 14: Expected and estimated cumulative incidence over the modelled time horizon comparing EAG versus Vertex's calculations with Brousse et al (2023)

Chronic complication	Expected prevalence based on rate based on Brousse et al (2023) over model time horizon	EAG model's total cumulative incidence over model time horizon	Vertex model's total cumulative incidence over model time horizon
Chronic Kidney Disease	76.60%	144.98%	76.56%
Pulmonary Hypertension	59.95%	91.37%	59.91%
Avascular necrosis	95.24%	303.75%	95.23%
Heart Failure	95.09%	300.60%	95.07%
Neurocognitive impairment	95.24%	303.45%	95.22%
Post-stroke	70.77%	122.78%	70.73%

Overall, the EAG's modelled cumulative incidence of chronic complications when unadjusted for mortality deviates significantly from the expected lifetime prevalence estimated from rates found in the Brousse et al (2023) (also unadjusted for mortality). The EAG's calculations are also clearly unreliable since total cumulative incidence can exceed 100%. Even when the EAG's approach is adjusted for mortality, the cumulative incidence for Avascular necrosis exceeds 100%. When assuming a fixed population (i.e., a population with a constant population size over time), it is intuitive to recognise that incidence of a chronic complication ought to tend towards 0 as the prevalence of the chronic complication tends to increase. In other words, if there is 100% prevalence of a chronic disease within a fixed population, there should be no new incidence once the point of 100% prevalence is reached. Hence, over time, total cumulative incidence should be bounded at a maximum of 100%.

The key issue with the EAG's calculations for chronic complications is that the interaction between incidence and point prevalence is not appropriately counted before being adjusted for mortality. The EAG's function used to calculate the proportion of alive SOC patients with chronic complications is shown in Equation 1.

Equation 1: EAG's function used to calculate point prevalence in alive SoC cohort

$$\begin{aligned} & \% \text{ patients alive with chronic complication at cycle } t \\ & = \text{prevalence}_{t-1} \times \% \text{ patients alive}_t + \% \text{ patients alive}_t \times \text{cycle incidence}_t \end{aligned}$$

The EAG's approach does not appropriately count the within cycle prevalence of each chronic complication before applying this to the alive SoC cohort. In addition to the fact that the EAG's approach double-counts mortality, the EAG's function also, critically, does not condition the incidence term on the proportion of patients who are still risk of developing the complication within each cycle. This therefore leads to the unbounded characteristics observed in

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the EAG's functions whereby both point prevalence per cycle and cumulative incidence can exceed 100% in the EAG's model.

The amended approach implemented by Vertex is calculated as shown in Equation 2.

Equation 2: Vertex's amended function used to calculate point prevalence in alive SoC cohort

$$\text{prevalence at cycle } t = (1 - \text{prevalence}_{t-1}) \times \text{cycle incidence}_t + \text{prevalence}_{t-1}$$
$$\therefore \% \text{ patients alive with chronic complication at cycle } t = \text{prevalence at cycle } t \times \% \text{ patients alive}_t$$

Using the approach illustrated in Equation 2, the function is able to separate the proportion of patients who are still at risk of developing the chronic complication from the proportion of patients who have already developed the chronic complication. The per cycle point prevalence is then applied to the proportion of patients who are alive in each model cycle, i.e., the per cycle point prevalence is adjusted for natural or primary disease mortality. This is a standard approach to modelling chronic complications assumed to not contribute to any excess mortality from secondary disease (thus aligning with the committee's preferred assumption, that complications do not directly contribute to the model's mortality).

Vertex has added an alternative approach to including the health outcomes and costs of treatment withdrawal

Vertex's scenario to include the health outcomes of treatment withdrawal is implemented via a simple decision tree. It uses the QALY outcomes of both SoC and exa-cel modelled cohorts and the costs pre-treatment red blood cell transfusions (RBCTs) and pre- and post-mobilisation.

To include the health outcomes of withdrawal, the total QALYs of the SoC cohort is weighted by the proportion of patients who withdrawal in the exa-cel cohort. Then, the total QALYs of the exa-cel arm are weighted by the proportion of patients who did not withdrawal. The sum of these weighted QALYs is then used as the total reweighted QALYs for all exa-cel patients. The sum of total costs of the SoC cohort, costs of pre-mobilisation, mobilisation, and pre-treatment RBCTs is weighted by the proportion of patients who withdrawal. The total costs of the exa-cel cohort are then reweighted by the proportion of patients who did not withdrawal. The sum of these two weighted costs is then used as the total reweighted costs for all exa-cel patients.

The model does have the functionality to also include the associated with exa-cel in addition to the costs of pre-mobilisation, mobilisation, and pre-treatment RBCTs, and the health outcomes of withdrawal. In this scenario, the decision tree is as described in the preceding paragraph, but also includes the cost of exa-cel in the total costs reweighting.

To calculate the costs of withdrawal including the cost of exa-cel, the sum of total costs of the SoC cohort, costs of pre-mobilisation, mobilisation, pre-treatment RBCTs, and the cost of exa-cel is weighted by the proportion of patients who withdrawal. The total costs of the exa-cel cohort are then weighted by the proportion of patients who did not withdrawal. The sum of these two weighted costs is then used as the total reweighted costs for all exa-cel patients. QALY outcomes are reweighted as described in the preceding paragraphs.

Vertex has also identified a minor input error in the latest EAG model version

Vertex identified an input error in the 'Cost inputs' sheet. Specifically, the plerixafor cost per unit was incorrectly changed to £4,881. The correct value, which was inputted in the technical engagement model version, is £4,880. Albeit a very small difference, this did have a minor effect on the ICER.

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Abbreviations

Abbreviation	Definition
ACD	Appraisal Consultation Document
ACM	Appraisal Committee Meeting
ACS	Acute chest syndrome
APPG	All Party Parliamentary Group
ASCQ-Me	Adult Sickle Cell Quality of Life Measurement Information System
ATMP	Advanced Therapy Medicinal Product
BMT	Bone marrow transplantation
CAR-T	Chimeric Antigen Receptor T-cell
CKD	Chronic kidney disease
DSU	Decision Support Unit
EAG	External Assessment Group
FACT	Functional Assessment of Cancer Therapy
FAS	Full Analysis Set
G-CSF	Granulocyte-colony stimulating factor
HbF	Fetal haemoglobin
HES	Hospital Episode Statistics
HPFH	Hereditary persistence of fetal haemoglobin
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HST	Highly Specialised Technology
ICER	Institute for Clinical and Economic Review
PES	Primary Efficacy Set
QALY	Quality-adjusted life year
QoL	Quality of life
RBCT	Red blood cell transfusion
SCD	Sickle cell disease
SmPC	Summary of Product Characteristics
SMR	Standardised Mortality Ratio
SoC	Standard of Care
STA	Single Technology Appraisal
SWAY	Sickle Cell World Assessment Survey
TCD	Transcranial doppler
TDT	Transfusion-Dependent Thalassemia
VOC	Vaso-occlusive crisis
VOE	Vaso-occlusive event

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Exagamglogene autotemcel for treating sickle cell disease [ID4016]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 11 April 2024. Please submit via NICE Docs.

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B.3.8 Managed access proposal – updated following ACM1

Vertex proposes that a managed access agreement within the Innovative Medicines Fund would be appropriate for exa-cel given the highly innovative nature of the therapy, its potential to address unmet need and significant clinical benefits (see sections see sections B.2.1, B.3.6 and B.3.12.1), and following the NICE committee's request for data collection.

The uncertainties described in Table 53 could be addressed through a period of managed access. At present, the main source of clinical evidence is the index CLIMB SCD-121 study in SCD patients; it is anticipated that supportive long-term data will primarily come from the corresponding long-term extension study for consenting patients treated with exa-cel (CLIMB-131), and a post-authorisation safety study (PASS) utilising the European Society for Blood and Marrow Transplantation (EBMT) registry. UK sites are included within the PASS protocol.

The post-committee meeting outputs and subsequent discussions with the NICE Managed Access team have recognised the evidence uncertainties already captured in our proposal that can be fully or partially resolved through managed access. Vertex has now updated the managed access proposal in order to address additional uncertainties highlighted by the committee; namely around treatment withdrawal pre-infusion, generalisability of the trial population age to the UK, health-related quality of life (HRQoL) and disease complications for current standard of care. Additionally, Vertex has also proposed data collection under a managed access agreement for the maximum 5 year period to ensure an optimally sized cohort with a total of 8-10 years' follow-up (from commencement of CLIMB-131), to provide robust assurances of treatment durability for healthcare providers and payers.

The non-reference discount rate is a major driver of cost-effectiveness, and for this to be accepted at the end of the MAA period durability of effect and ability to return patients to a near-normal health state would apply. Following the first committee meeting, clinical experts stated that if data were collected out to 3 years post-infusion showing sustained, increased levels of Hb, HbF and F-cells (demonstrating pancellular distribution of HbF),

then the risk of relapse would be negligible. Therefore, we propose this is the most important outcome to consider when ensuring future cost-effectiveness.

A summary of all stated uncertainties, with proposed data sources, is shown in Table 53.

Table 53: List of uncertainties and data that could be collected to resolve them

Clinical uncertainty	Outcome data	Data source
Durability of VOC-free status	Time period VOC-free following exa-cel infusion Time period free from inpatient hospitalisation for severe VOCs following exa-cel infusion	CLIMB SCD-121, PASS EBMT Registry, CLIMB-131
Sustained Hb and HbF levels	Haemoglobin concentration, grams per decilitre (g/dL) Haemoglobin fractionation measured to assess the relative proportion of Hb variants produced, including percent HbF Change from baseline in proportion of circulating F-cells (HbF distribution)	CLIMB SCD-121, PASS EBMT Registry, CLIMB-131
Sustained engraftment	Proportion of alleles with intended genetic modification present in peripheral blood and in the CD34+ cells of the bone marrow over time	CLIMB SCD-121, CLIMB-131
Safety of exa-cel	SAEs related to exa-cel, mortality and survival data (with primary and contributory cause of death)	CLIMB-131, PASS EBMT Registry
QoL*	Utility values for SCD patients	To include CLIMB SCD-121, CLIMB-131
Treatment withdrawals*	Number of patients withdrawing from the treatment process	Vertex Connects™
Standard of care*	Rates of complications, mortality	SLR/use of most relevant and up to date evidence at time of managed access finalisation (to be determined)

*Denotes new uncertainties raised by NICE following ACM1.

B.3.8.1. Proposed Data Sources to gather evidence for Managed Access Agreement

It is anticipated that the CLIMB SCD-121 and CLIMB-131 studies will fulfil most of the data gap requirements, with the latter as the main source of supportive long-term outcomes data, and further gaps to be filled with data from the PASS EBMT registry.

CLIMB-131

CLIMB-131 is an ongoing, multi-site, open-label, rollover study designed to evaluate the long-term safety and efficacy of exa-cel in patients who received exa-cel in a parent study (CLIMB SCD-121 for SCD) for a total follow-up of 15 years after exa-cel infusion. Consenting patients who completed or discontinued the parent study after exa-cel infusion were asked to participate. Applicable regulatory guidelines on follow-up of patients administered with gene therapy products (EMA/CHMP/GTWP/60436/2007 and FDA Guidance for Industry on Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events) were used to define the 15-year follow-up period.

Data from this trial will be reported periodically, as per timelines indicated in Table 54.

Table 54: CLIMB-131 Efficacy and Exploratory Endpoints and Analysis Methods (SCD only)

Endpoint	Method of Analysis
Secondary Efficacy Endpoints	
Hb concentration ^a : • Total Hb (in absolute value) • HbF (in absolute value and %)	<u>Main analysis</u> • Summarised as a continuous variable over time <u>Subgroup analyses^b</u> • Age at parent study screening ≥12 to <18 and ≥18 to ≤35 years of age) • Genotype (β^S/β^S and non-β^S/β^S) • Sex
Proportion of alleles with intended genetic modification present in ^a : • Peripheral blood • CD34⁺ cells of the bone marrow (parent study endpoint only; not followed in Study 131 for SCD patients)	<u>Main analysis</u> • Summarised as a continuous variable over time <u>Subgroup analyses^b</u> • Age at parent study screening ≥12 to <18 and ≥18 to ≤35 years of age) • Genotype (β^S/β^S and non-β^S/β^S)

	• Sex
Change from baseline in PROs ^a	<u>Main analysis</u> • Summarised as a continuous variable over time including dimensional score and total score (if applicable)
Proportion of patients who achieved VF12 ^{c,g}	<u>Main analysis</u> • 1-sided <i>P</i> value against a 50% response rate and 2-sided 95% exact Clopper-Pearson CI <u>Supportive Analysis</u> • Proportion of patients who remained VOC-free after achieving VF12 <u>Subgroup Analyses</u> • Age at parent study screening ≥12 to <18 and ≥18 to ≤35 years of age) • Genotype (β^S/β^S and non-β^S/β^S) • Sex • ≥3 VOCs/year for the prior 2 years at baseline
Proportion of patients who achieved HF12 ^{c,g}	<u>Main analysis</u> • 1-sided <i>P</i> value against a 50% response rate and 2-sided 95% exact Clopper-Pearson CI <u>Subgroup analyses</u> • Age at parent study screening ≥12 to <18 and ≥18 to ≤35 years of age) • Genotype (β^S/β^S and non-β^S/β^S) • Sex • ≥3 VOCs/year for the prior 2 years at baseline
For patients who achieved VF12 ^c • Severe VOC-free duration^g	<u>Main analysis</u> • Summarised as mean, SD, median, min, and max
For patients who did not achieve VF12 ^c : • Relative reduction from baseline in annualised rate of severe VOCs^h • Achieved at least 90%, 80%, 75%, and 50% reduction from baseline in annualised rate of severe VOCs^h	<u>Main analysis</u> • Descriptive summary from baseline starting from Month 12 after exa-cel infusion
For patients who did not achieve HF12 ^c : • Relative reduction from baseline in annualised rate of inpatient hospitalisations for severe VOCs • Relative reduction in annualised duration of inpatient hospitalisations for severe VOCs	<u>Main analysis</u> • Descriptive summary from baseline starting from Month 12 after exa-cel infusion
Proportion of patients with sustained HbF ≥20% for at least 3 months, 6 months, or 12 months ^{c, g}	<u>Main Analysis</u> • Point estimate and 2-sided 95% exact Clopper-Pearson CI

Change from baseline in haemolysis markers ^a : • Reticulocyte count (in absolute count and %) • Lactate dehydrogenase • Haptoglobin • Total and indirect bilirubin	<u>Main analysis</u> • Summarised as a continuous variable over time
Relative reduction from baseline in number of RBC units transfused for SCD-related indications ^c	<u>Main analysis</u> • Descriptive summary from baseline starting from Month 12 after exa-cel infusion
Change from baseline in SCD-specific and pain PROs ^a :	<u>Main Analysis</u> • Summarised as a continuous variable over time including domain score and total score (if applicable)
Exploratory Endpoints	
Hb fractions and change from baseline in proportion of circulating F-cells ^a	<u>Main analysis</u> • Summarised as a continuous variable over time <u>Subgroup analyses^b</u> • Age at parent study screening ≥12 to <18 and ≥18 to ≤35 years of age) • Genotype (β^S/β^S and non-β^S/β^S) • Sex
^a Analyses conducted in the PES, FAS, and patients in the FAS who were not yet eligible to be in the PES. ^b Analyses conducted in the FAS, only. ^c Analyses conducted in the PES, only. ^d [pertains to TDT only – no relevant footnotes for SCD] ^e [pertains to TDT only – no relevant footnotes for SCD] ^f [pertains to TDT only – no relevant footnotes for SCD] ^g The evaluation of the endpoint for a patient started 60 days after last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management. ^h Analyses were based on severe VOC events that met the protocol criteria for severe VOCs as adjudicated by an EAC.	

PASS utilising EBMT registry

The EBMT was established in the 1970s and is an established data source on allo-SCT or cellular infusion therapy procedures. The EBMT registry currently receives data from approximately 80% of European transplant centres and is the principal source of transplant data to conduct retrospective clinical studies, epidemiological trends, and feasibility studies to design prospective clinical studies, in the field of oncology. In more recent years, the EBMT registry has been qualified by the European Medical Agency (EMA) as a suitable platform for collection of data for post-authorisation studies (160).

The EBMT registry is the proposed data source in UK, France, Germany, and Italy for Vertex's regulatory mandated PASS in which exa-cel treated patients will be followed for a maximum period of 15 years. As part of the PASS, similar data will also be collected for patients in the United States via the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry. Vertex considers that the EBMT registry would be a relevant data source to gather evidence on effectiveness and safety of exa-cel in the real-world setting, given its primary data collection capabilities and availability of secondary data to support long-term follow-up studies. Study variables to be collected for the PASS are presented in Table 55. The PASS protocol synopsis has also been provided to NICE.

Table 55: Study variables from EBMT Registry (informing PASS)

Category	Overview of Variables
Primary Disease Diagnosis	• SCD diagnosis and genotype
Exposure	• HSCT date (as Day 0) • Autologous HSCT with exa-cel infusion • Allogeneic HSCT infusion
Safety Outcomes	• Neutrophil recovery • Platelet recovery • New malignancy, including haematologic • New or worsening haematologic disorder • Mortality, cause
Effectiveness Outcomes	• Primary disease severity measures* • Haemoglobin measures • Iron concentration measures • Disease-related end-organ damage / dysfunction • Iron overload management
Additional Key Variables	• Demographics • Health status • Mobilisation and conditioning regimen • Transplant-related complications • Disease-related therapies • Additional laboratory measures, including CBC • Pregnancy (with outcome)
CBC: Complete Blood Count; SCD: sickle cell disease; HSCT: haematopoietic stem cell transplantation *Includes red blood cell transfusions, vaso-occlusive crisis episodes (SCD only).	

Other potential sources

Data on treatment withdrawals pre-infusion will be available from Vertex Connects™, a secure order management portal used to facilitate steps throughout the exa-cel order management process for authorised treatment centre (ATC) staff. The system will track all the constituent actions required for each step of the order process following patient identification and evaluation: pre-mobilisation; mobilisation & collection of cells; drug product manufacturing and quality; conditioning, administration and engraftment. Anonymised metrics on pre-infusion patient withdrawals will be available via aggregate summary reports.

Vertex is currently exploring the feasibility of conducting a literature review to derive data inputs for current standard of care in SCD. Our main evidence submission presented data from an observational, retrospective database study we conducted to understand the clinical and economic burden of SCD in UK patients with characteristics similar to those eligible to receive exa-cel. The data collection period for this study could be extended to capture contemporary data on VOC burden, disease complication rates and mortality. Vertex can provide the study protocol to inform consideration of the feasibility of this approach.

B.3.8.2. Data Collection

Long-term data on the UK patients treated with exa-cel following MHRA approval will be collected by EBMT for the PASS. Data will be collected on SCD patients ≥ 12 years of age and treated with exa-cel at any of the ATCs in the UK. Vertex acknowledges that the number of exa-cel treated patients from the UK included in the PASS will depend on commercial uptake, and availability of patients' informed consent to share their data for research purposes. The PASS will enrol a minimum of 100 exa-cel SCD patients overall. All consenting global patients, taking into account sample size considerations, will be entered into the study for approximately the first 3 years post-approval and will be followed for 15 years. Long-term data on consenting exa-cel treated patients will also be collected

from CLIMB-131, a rollover follow-up extension of the pivotal trials in TDT and SCD patients.

Data on key outcomes, as well as important patient demographic and clinical characteristics, will be collected up to a maximum of five years or a period specified in the managed access agreement. EBMT will facilitate retrospective data collection for Vertex using standard existing registry forms such as Med-A and Med-B, and prospective data collection using a study-specific reporting form (Med-C) developed for the Vertex PASS in collaboration with EBMT investigators. Table 56 and Table 57 summarises the characteristics of these respective data sources.

Table 56: Overview of CLIMB-131

Study	A Long-term Follow-up Study of Subjects With β-thalassaemia or Sickle Cell Disease Treated with Autologous CRISPR-Cas9 Modified Hematopoietic Stem Cells (CLIMB-131)
Study design	Multi-site, open-label, rollover study
Population	Patients 12-35 years of age who received exa-cel in a parent study (CLIMB SCD-121)
Intervention(s)	Exa-cel
Comparator(s)	N/A
Outcomes	Total haemoglobin Total fetal haemoglobin (HbF) and % concentration Proportion of alleles with intended genetic modification present in peripheral blood and bone marrow CD34+ cells Absolute and relative reduction from baseline in volume/units/episodes of RBC transfusions - Change from baseline in proportion of circulating F-cells (HbF distribution) - Severe VOC events - Inpatient hospitalisations for severe VOCs - Haemolysis markers (reticulocytes/erythrocytes, lactate dehydrogenase, haptoglobin, and total and indirect bilirubin), SCD-specific and pain scale PROs Summary score for change from baseline in PROs
Indicate if study used in the NICE economic model	Yes, via parent study CLIMB SCD-121 (as described in section B.2)
Trial start date	September 2018
Data cut submitted to NICE	June 2023 (D120 data cut-off; database lock 16 April 2023)
Anticipated data cut after a period of managed access	Future data cuts to be confirmed and submitted as they become available.

Table 57: Overview of EBMT

Registry	European Society for Blood and Marrow Transplantation (EBMT)
Type of registry	Long term registry-based study of patients with beta-thalassaemia or SCD treated with exa-cel
Population	Patients with sickle cell disease, treated with exa-cel in participating centres reporting data to EBMT, will be eligible to

Registry	European Society for Blood and Marrow Transplantation (EBMT)
	enrol from the date of approval of exa-cel through to the end of the enrolment period (approximately 3 years)
Relevant data items collected	<u>RBC transfusion events pre- and post-transplant (to be defined as the receipt of RBC transfusions for the purpose of primary disease management, i.e. anaemia):</u> Number of RBC transfusions Number of units transfused Time from HSCT to most recent transfusion Number of severe VOC events pre- and post-transplant (including time from HSCT to most recent VOC event) Severe VOC events will include any/all of: acute pain events, acute chest syndrome events, priapism events, or splenic sequestration events. <u>Haemoglobin measures pre- and post-transplant:</u> Haemoglobin concentration (g/dL) pre- and post-transplant Haemoglobin fractionation pre- and post-transplant, including percent HbF Safety Outcomes: • Neutrophil recovery • Platelet recovery • New malignancy, including haematologic • New or worsening haematologic disorder Mortality, cause Effectiveness Outcomes Primary disease severity measures* • Haemoglobin measures • Iron concentration measures • Disease-related end-organ damage/dysfunction Iron overload management Additional Key Variables • Demographics • Health status • Disease-related therapy • Mobilisation and conditioning regimen • Transplant-related complications Disease-related therapy use Additional laboratory measures, including CBC

Registry	European Society for Blood and Marrow Transplantation (EBMT)
	Pregnancy (with outcome)
Data analysis	Vertex sponsored data that is collected and managed by EBMT will be analysed by registry statisticians per a statistical analysis plan developed by Vertex in collaboration with EBMT investigators. Data will be collected at pre-specified timepoints over the study duration: baseline, Day 100, Month 6, Year 1 and annually (Years 2-5). Results from all analyses will be shared by EBMT with Vertex as reports. Data on safety and effectiveness outcomes among exa-cel treated patients will be evaluated separately for TDT patients. Subgroup and sensitivity analyses will be performed on <i>a priori</i> identified characteristics, as appropriate. Ad hoc analyses may be conducted as per requirement.
Governance	Data collected by EBMT on exa-cel treated patients will be stored and maintained by the registry following internal protocols and processes. Currently, EBMT uses a web-based relational database management system called ProMISe as the platform to collect, store, conduct quality checks, and report on data collected by the standard registry forms. Prospective data collected using the study-specific reporting form will be stored in the EBMT system in a separate validated database. EBMT will be responsible for processing and storing the data according to the EU General Data Protection Regulation (GDPR) laws. Vertex will not have access to identifiable patient records but will be given access to data cuts by EBMT at pre-specified timepoints (annual progress reports after completion of the first 5 years of the study; interim analysis reports after enrolment completion [Year 3], minimum 5 years' follow up for all enrolled patients [Year 8], minimum 10 years' follow up for all patients [Year 13]). These data cuts will be stripped off any identifiable patient information and will be stored on a secure server. Additional details on governance and Vertex-wide use of data will be provided once a legal contract is signed.
Indicate if registry previously used within a NICE managed access	No

The data collection proposals for treatment withdrawals (Vertex Connects™) and standard of care, are presented in Table 58 and Table 59.

Table 58: Overview of Vertex Connects™

Database	Vertex Connects™
Description	Vertex Connects™ is a secure order management portal used to facilitate steps throughout the exa-cel order management process for ATC staff. The system will track all the constituent actions required for each step of the order process following patient identification and evaluation: pre-mobilisation; mobilisation & collection of cells; drug product manufacturing and quality; conditioning, administration and engraftment.
Data analysis	Anonymised, aggregate reports – generated by Vertex users only.
Governance	All portal users, whether sited at Vertex or at the ATCs, will only have permission to view and/or access the information necessary for their role.

Table 59: Proposed PICOTS framework for eliciting data on standard of care

Population	Patients aged 12 years or above with SCD
Intervention(s)	Hydroxycarbamide (hydroxyurea) +/- regular blood transfusions +/- concomitant iron chelating agents
Comparator(s)	Any
Outcomes	VOC events, haematological parameters, complication rates, utilities, mortality, average life expectancy
Timeframe	No limit
Study type	The following options will be considered: • SLR (to capture eligible research based on the criteria in this PICOTS framework) • Extension to current observational, retrospective database study of clinical and economic burden of SCD in the UK

Vertex anticipates that, based on expert opinion, a timeline of approximately 3 years' data collection following recommendation into the IMF would be sufficient to address uncertainties stated by NICE. Clinical experts, when consulted, have indicated that sustained increases in Hb, HbF and F-cells (demonstrating pancellular distribution of HbF) after 3 years of exa-cel treatment, with sustained engraftment plus improved iron status, will mean patients are likely to maintain a VOC-free status and, in turn, less likely to encounter further disease complications and subsequent organ damage. With mean duration of follow-up of 22.4 months as of June 2023 for patients who have already transitioned to the CLIMB-131 follow-up study, the proposed 3 years of data collection in the managed access agreement would include data for most patients in CLIMB SCD-121

beyond 5 years post exa-cel infusion, for a total of 8-10 years of follow-up in this group of patients.

Table 60 presents both Vertex and NHSE's estimates for patients in England that are predicted to have undergone therapy with exa-cel and engrafted over the initial five years.

Table 60: Forecast of Patients Commencing Engraftment

	Year 1	Year 2	Year 3	Year 4	Year 5
Vertex uptake estimates					
NHSE uptake estimates	0	28	58	73	78

Table 61 and Table 62 below presents an overall summary of the data uncertainties, proposed data sources, required length of data collection for resolution and availability of key data items throughout the managed access agreement period.

Table 61: Summary of data uncertainties, proposed data sources and length of data collection

Uncertainty	Proposed data collection source to resolve uncertainty	Length of data collection needed
Durability of the treatment effect of exa-cel (relapse rate)	CLIMB SCD-121, CLIMB-131	Up to 3.5 years
	PASS EBMT Registry	Up to 3 years
Rates of complications for exa-cel	CLIMB SCD-121, CLIMB-131	Up to 3.5 years
	PASS EBMT Registry	Up to 3 years
Whether people return to full health after exa-cel or whether complications persist	CLIMB-131	Up to 3.5 years
	PASS EBMT Registry	Up to 3 years
The number of exa-cel treatment withdrawals before the infusion is given	Vertex Connects™	Up to 3 years
Generalisability of trial population (age)	PASS EBMT Registry – age of post-authorisation patients at pre-mobilisation stage of exa-cel treatment process	Up to 3 years
Mortality and life expectancy for exa-cel	CLIMB SCD-121, CLIMB-131	Up to 3.5 years

	PASS EBMT Registry	Up to 3 years
SoC uncertainties: utility values, rates of complications, mortality and life expectancy	SLR/use of most relevant and up to date evidence at time of managed access finalisation (to be determined)	Up to 3 years

Table 62: Data Collection Summary

Total patients dosed at baseline = 46 (including 12 adolescents) Estimated sample size with ≥36 months follow-up for evaluation in managed access agreement = ■■■ (■■■ adolescents)									
Variable	Rationale	Baseline / Day 0	Day 100 / Month 3	Month 6	Year 1	Year 2	Year 3	Year 4	Data source
Age (at visit, transplant)	Generalisability to UK practice	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB-131, PASS EBMT Registry
Sex	Generalisability to UK practice	Yes	No	No	No	No	No	No	CLIMB-131, PASS EBMT Registry
SCD genotype	Generalisability to UK practice	Yes	No	No	No	No	No	No	CLIMB SCD-121, PASS EBMT Registry
Country of transplant	Generalisability to UK practice	Yes	No	No	No	No	No	No	PASS EBMT Registry
Mobilising and conditioning regimen	Generalisability to UK practice	Yes	No	No	No	No	No	No	CLIMB SCD-121, PASS EBMT Registry
Infused CD34+ Dose	Generalisability to UK practice	Yes	No	No	No	No	No	No	CLIMB SCD-121, PASS EBMT Registry
Neutrophil recovery	Return to health	No	Yes	Yes	No	No	No	No	CLIMB SCD-121, PASS EBMT Registry
VOC events	Sustained & durable efficacy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB SCD-121, CLIMB-131, PASS EBMT Registry
Reduction in annualised rate of severe of VOCs	Improvement in patient cohort where primary endpoint is not met	No	No	No	Yes	Yes	Yes	Yes	CLIMB SCD-121, CLIMB-131, PASS EBMT Registry
Total Hb and Hb fractionation measures	Sustained & durable efficacy, return to health	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB SCD-121, CLIMB-131, PASS EBMT Registry
HbF distribution	Sustained & durable efficacy, return to health	No	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB-131, PASS EBMT Registry

Blood allelic editing	Sustained & durable efficacy, return to health	No	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB-131, PASS EBMT Registry
EQ-5D-5L	Quality of life	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB-131
FACT-BMT	Quality of life	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB-131
ASCQ-Me	Quality of life	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB-131
Pain-related scales (NRS 11-point, Wong Baker FACES Pain Scale, FLACC Behavioral Pain Scale)	Quality of life	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB-131
Disease-related therapies	Return to health	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB-131, PASS EBMT Registry
Transplant-related complications	Long-term safety	No	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB-131, PASS EBMT Registry
SAEs related to exa-cel	Long-term safety	No	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB-131, PASS EBMT Registry
Treatment withdrawals	Number of pre-infusion withdrawals	Yes	No	No	No	No	No	No	Vertex Connects™
Mortality	Mortality & life expectancy	No	Yes	Yes	Yes	Yes	Yes	Yes	CLIMB-131, PASS EBMT Registry

B.3.8.3. Additional considerations that may impact feasibility of data collection

Informed consent – Lack of patient consent to give access to their data after treatment with exa-cel.

Follow up – Patients will be routinely followed up by the transplant centres (as part of the transplant clinic for year 1 and the long-term effects monitoring clinics thereafter). These clinics are resourced for data collection for EBMT and this will be part of their routine care. Patients will also be followed up by their haemoglobinopathy team with respect to long term sickle cell complications. Haemoglobinopathy patients represent a non-malignant population, and therefore may perceive less of a clinical imperative to adhere to follow-up visits when compared with patients with a malignant disease. It will be essential that patients are well informed about the need for long term follow-up to ensure they attend the long-term effects monitoring clinics at the transplant centre.

Socioeconomic status – Patients in England with SCD are disproportionately represented in ethnic minority groups and lower socioeconomic communities; thus, potential increased fluidity in population movement may also challenge adherence to follow-up.

In order to mitigate these considerations, Vertex will produce supportive educational materials for patients that fully detail the treatment process and explain the importance of compliance with data collection in the post-treatment period.

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Draft guidance comments form

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Anthony Nolan and The Sickle Cell Society	
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: - the name of the company - the amount - the purpose of funding including whether it related to a product mentioned in the stakeholder list - whether it is ongoing or has ceased.	Anthony Nolan has not received any funding from Vertex Pharmaceuticals Inc, nor any associated subsidiary entities. The Sickle Cell Society has received a total of £27,000 from Vertex Pharmaceuticals Inc between September 2022 and January 2024: £12,000 (Sept 22 to Sept 23) towards Secretariat Service for Sickle Cell & Thalassaemia All-Party Parliamentary Group (SCTAPPG) £15,000 towards Patient Education Day (01 Jul 2023).	
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None to disclose	
Name of commentator person completing form:	[REDACTED] and [REDACTED]	
Comment number	Comments Insert each comment in a new row.	

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Executive Summary Sickle cell has profound and life-limiting physical and emotional impacts on patients and their families. Severe sickle cell limits life expectancy and considerably impairs the life of people affected, as well as of their family members and carers. People with severe sickle cell experience numerous negative social, emotional and physical impacts causing poor quality of life, which is not fully reflected in conventional quality of life measurement tools. Exa-cel would meet the considerable unmet need for an additional therapy that can halt disease progression and provide patients with a vastly improved quality of life, as a functional long-term cure. Were exa-cel not to be made available it would disadvantage a community that has already endured decades of under-prioritisation in terms of the range and quality of services available to meet their needs. It would also disadvantage people with sickle cell who do not have a suitable stem cell donor and so cannot receive a stem cell transplant, and in particular adult patients for whom there are much more limited options for stem cell transplant. We urge the NICE committee to reconsider their draft decision and in particular we ask that the over 250 direct responses that we have received from patients, parents, family members, clinicians and others are closely considered as part of the committee's discussions around quality of life and severity of sickle cell, as they powerfully convey the clear and urgent need for additional and effective treatment options.
2	The impact of sickle cell on quality of life Anthony Nolan and the Sickle Cell Society are concerned by the NICE committee's comments with regards to the impact of sickle cell on Quality of Life (QoL). Whilst it would appear that the committee acknowledge the difficulty of using measurement tools such as EQ-5D to assess QoL in a condition such as sickle cell, and the extensive evidence of patient and clinical experts as to the profound and life-limiting physical and emotional impacts of severe sickle cell, the committee nonetheless conclude "<i>there was insufficient evidence to show that people would otherwise die or have a severely impaired life</i>". We find it highly concerning that the committee were unable to quantify the severity of sickle cell in their analysis. There are longstanding and well documented instances of people with sickle cell having their needs ignored and dismissed at an institutional level, with the "burden of proof" seeming to be higher in order for people from the sickle cell community to be taken seriously. While we believe that the committee has already been provided with ample evidence from the patient and clinical experts and literature as to the severe negative impact that sickle cell has on day to day quality of life on standard of care in the NHS, we have provided updated and additional evidence below. This information is drawn from direct conversations with sickle cell patients and family members, the over 250 responses we

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	received to this consultation, and from a survey jointly conducted by Anthony Nolan and the Sickle Cell Society from 13/12/2023 to 11/01/2024, during which we received 60 complete responses from patients and carers/family members. Key message: Sickle cell is a lifelong and progressive condition. It is therefore very difficult to objectively measure QoL and compare it to healthy individuals. Sickle cell patients should not be penalised for this. • 85% of people responding to our survey were either diagnosed through newborn screening, or in early childhood. • People living with severe sickle cell have never had what would be considered by most a “normal” life, having only known what it is like to live with regular pain crises, having to manage their illness as best they can with very limited treatment options at every stage of life. • We welcome the committee’s willingness to further consider the limitations of the EQ-5D score in this context. Key message: People with sickle cell who would be eligible for exa-cel have a severely impacted life. We believe the criteria for the non-reference case discount rate has been met. • 82% of people responding to our survey said that sickle cell has either a negative impact or very negative impact on their quality of life. Sickle cell has a negative or very negative impact on their emotional health and wellbeing (79%), work and education (76%), and family and social life (70%). • Nearly half (46%) of people who responded to our survey had experienced over 8 crises in the last two years, and a further 36% had experienced 2-7 crises in the last two years. This is despite the vast majority being on a current standard of care treatment (67% on hydroxyurea, 52% on blood transfusions, 30% on “other” treatments). • Crises are debilitating and disruptive, often requiring emergency inpatient treatment that interferes with daily life – in the last two years, a third of respondents had received emergency care 4 or more times due to a sickle cell crisis, an additional third of respondents had received emergency care at least 2 or 3 times. • In their own words, this is how living with sickle cell has impacted people’s lives: <u>Impact on family and social life</u> <i>“The impact is wide ranging. As a result of SCD, I have kidney failure and am a transplant patient. I am now unable to work due to ill health. I have frequent breathlessness and fatigue periods and limited mobility and stamina. My whole family has to bear my limitations in mind which causes them worry and anxiety whenever I am unwell.”</i>

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	<i>"I worry about the overall effectiveness of the current treatment. Although it may help slightly, the reality is that my son continues to have sickle cell complications. The condition also impacts his ability to take part in regular activities with his friends such as football and swimming which can leave him feeling left out. This has the ability to impact his mental health which is worrying for me as his mother. The other side to consider is his education due to volume of school missed due to sickle cell complications."</i> <u>Education and employment</u> <i>"My Sickle Cell disease has left me not able to do the things which I want to do, I could not finish my college because I was always in and out of hospital all the time, 50% in college and 50% in the hospital."</i> <i>"I find it hard to keep hold of a job due to the fact that my employers are less supportive and show less empathy. I have been laid off work twice due to my health and it is extremely frustrating, emotionally exhausting."</i> <i>"It has been very stressful because I can't work due to the severity of my sickle cell anaemia."</i> <i>"It affected every aspect of my life including independence, family, work (dismissal as not able to make extra reasonable adjustments to work from home), social life (unpredictable nature of sickle cell) and emotional wellbeing (regular appointments with the clinical psychologist)."</i> <i>"Can't work. Been sacked 3 times due to health. No energy, managing pain all the time. Living very isolated. Opposite of best life."</i> <i>"I have had to give up work. Chronic pain physical and emotional impact. Need support Sometimes cannot physically emotionally get out of bed. Flat adaptations. Isolation. Lack of understanding or support from family and friends It's a very hard lonely journey. Hard to maintain or have an intimate relationship."</i> <i>"The side effects I had was the 6 weekly transfusions. This really affected my normal living and even had an impact on work and being able to manage and workaround it. For example, I couldn't plan things around the weekend of my transfusion as o know I would be exhausted and wasn't sure if it would lead to hospitalisation."</i> <u>Mental health</u> <i>"Sickle cell anaemia has made my life a living hell, right through my childhood I have suffered from severe painful crisis that affected my years of getting an education, it has made me disable[d] I now have a bad limp when walking (both my hips are damaged plus my shoulder). Am always in pain most times and am unable to work, or even enjoy my life with friends and family my social life is non-existent due to having developed the fear of falling, Agoraphobia, I can't go out by myself, I need somebody to always be beside me, if not I cannot go out by myself. It saddens me that all my mates, friends from school and family members are all doing well in life and all achieving their goals and dreams and I am stuck in a corner stagnant with nothing, but a heart full of sadness, and wishing and praying to one day wake up from this terrible nightmare of a life."</i>

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	<i>"I had to switch careers completely because a crisis left me unable to do my job. I do not partake in a lot of social activities that would trigger a crisis. I am often very depressed and feel like doing nothing. I am in my 20s and still live at home because between sickle cell and cost of living it is not possible to live independently. I miss at a minimum 50 days of work a year between crisis episodes and hospital appointments."</i> <i>"The fact that taking medication is part of your daily life, it's in your subconscious like a shadow."</i> <i>"It affects my daily living. It has started to affect my mental health. My outlook of life is getting more negative."</i> <i>"I would describe the impact of Sickle Cell demoralising. My social and emotional wellbeing as a result of the condition is compromised."</i> <i>"I am usually an extrovert until two years ago that I had a severe acute chest which has now affected my independence, social life and emotional wellbeing."</i> Physical health <i>"It can be challenging at times [to do a] simple everyday task when in pain."</i> <i>"Since I was a teenager, this condition has changed my life. At some point I believed or wanted to assume that my condition would not affect me, but she was always there to remind me; No matter how much I try to live like others or like a healthy person, it has been affecting my organs, completely changing my life by reaching the point of not being able to work and sometimes not even do my personal things."</i> <i>"It affects my body so much. Find it hard to complete tasks on some days. Because I had a TIA it has affected my brain and see how much of a struggle it is for me to study. It affects a lot of my day to day. A lot of chronic pain. Effects on my lungs and veins."</i> <i>"Being on hydroxycarbamide gave my son a lot of side effects - continuous stomach pain."</i> <i>"Susceptibility to infections, nausea, blackening of gums. I worry about the impact of hydroxyurea on her future fertility."</i> <i>"The Pregabalin makes me drowsy and sleepy, the Sevredol helps my pain a bit, but it makes me too tired to do house chores."</i> <i>"Had reactions from blood exchange and hydroxycarbamide has messed up my blood cells before."</i> <i>"Frequent mouth ulcers and changes in severity of them when the dosage goes up. Also, the dosage has had to be stopped due to low retics count and then monitored closely (twice monthly bloods)."</i>

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	<i>"When you have a crisis pain relief is delayed, they try and give you paracetamol when you need morphine."</i> <i>"My 7-year-old daughter is currently on hydroxycarbamide and 4 weekly blood transfusions and still has sickle cell pain crisis. This is all the treatment available for her. So, she lives with the pain and risk of further complications."</i> Impact on parents, carers and siblings <i>"I am constantly anxious, worrying, the trying to prevent a crisis from occurring. You at work and are called your kid is sick, it has started. Poor sickness record, trying to catch up with school and work. My fear I will get the sack at every job. Got the sack from the housing association where you even expect support. Constantly thinking of renewing the meds with the doctors every 4 weeks, absolute horror."</i> <i>"It is a very unpredictable condition as it can impact on my child's health spontaneously which has impact on family life and plans."</i> <i>"It's discerning when you have to be faced with how much others just don't care, and how mean and insensitive even doctors can be."</i> <i>"It's difficult to convey as this is an invisible condition. Little awareness. Often, we are misbelieved."</i> <i>"It can be very overwhelming at times and unpredictable."</i> <i>"The cost of medication and unavailability of the medications. Time consuming too."</i> <i>"It is emotionally and mentally exhausting."</i> <i>"Very stressful and challenging."</i> <i>"It makes me have more empathy and care for people with disease and illness going through pain."</i> <i>"Extremely tasking physically and emotionally."</i> <i>"Caring for someone with sickle cell disease is very scary and very difficult."</i> <i>"Can be difficult and a strain on my physical and mental health."</i> <i>"Traumatic for all involved. Day to day life is a challenge, with schools and hospitals. We are far from normal family life. This is an emotional drain."</i> <i>"Your whole life is shaped around sickle cell. You try your best to prevent extreme pain and severe complications. My 6-year-old has necrosis of the hip a complication of sickle cell and often crawls to get around. It's a horrific condition, every day is a battle to prevent pain and as some of the triggers are things we have little control over, it's very difficult."</i>

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	<i>"Its heart reaching to see the volume of pain they are in and knowing there isn't anything you can do to help them! Its heart wrenching seeing the emotional toll it has on my son!"</i> <i>"There isn't much support for carers of those with sickle cell anaemia. So, you are left to deal with a lot of the mental stress on your own. It can be draining."</i>
3	The impact of exa-cel on restoring patients to full or near-full health We are concerned that the committee does not appear to be considering the benefits of exa-cel to patients within the context of the available treatments. Patients with severe sickle cell can already access haematopoietic stem cell transplant (HSCT) on the NHS, and HSCT is transformational for the quality of life and wellbeing of patients in whom it is successful. HSCT has been available for a number of years on the NHS and in our view the efficacy of HSCT for sickle cell should support the likely effect of exa-cel given the close similarities between the two treatments. Exa-cel can offer this transformational benefit to patients who do not have a suitable stem cell donor, and it should be noted that the majority of adults with sickle cell in the UK do not have a fully-HLA matched sibling donor (the only donor type accepted for HSCT under current NHS commissioning criteria). In addition, exa-cel has the benefit of avoiding the risk of graft-vs-host disease (GvHD). We welcome the willingness of the committee to consider further data collection to evidence the efficacy of exa-cel in restoring patients to full or near-full health and hope that all parties will collaborate to ensure access for patients whilst this additional data is being collected.
4	The duration of benefit to patients from treatment with exa-cel As above we welcome the willingness of the committee to consider further data collection to evidence the long-term durability of exa-cel and hope that all parties will collaborate to ensure access for patients whilst this additional data is being collected.
5	Health inequalities We acknowledge the committee's willingness to accommodate extra uncertainty and to raise the ICER threshold as reasonable adjustments for this appraisal. However, we disagree with the conclusion that the committee's recommendations <i>"do not have a different impact on people protected by the equality legislation than on the wider population"</i>. Sickle cell predominantly affects people with African/African Caribbean/Black ethnicity, and it was made clear in the 2022 'No-One's Listening' report that there is low awareness of sickle cell among healthcare professionals and clear examples of inadequate training and insufficient investment in sickle cell care. There were frequent reports of negative attitudes towards sickle cell patients and a weight of the evidence suggested that such attitudes are often underpinned by racism. With this as the background to the experience

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	of those living with the condition, the draft decision not to recommend exa-cel is clearly a disadvantage to this group. The draft recommendation also disadvantages people with sickle cell who do not have a suitable stem cell donor and so cannot receive HSCT. Furthermore, it disadvantages adults with sickle cell. Current NHS commissioning criteria allows children to receive HSCT for sickle using any available donor including matched unrelated donors. In contrast adults can only receive HSCT from a fully matched sibling donor. The majority of adults with sickle cell in the UK do not have a fully matched sibling donor available. Exa-cel is an important treatment option for these patients.
6	Public consultation responses Anthony Nolan and the Sickle Cell Society have jointly put out a call to the wider sickle cell community to respond to this NICE consultation. Due to the need to register on the NICE website, some public commentators have chosen to share their responses directly with us for inclusion in our submission. We received over 250 responses directly, and have compiled the detailed submissions in separate comments below. It is important to remember that these responses came from a community who experience chronic tiredness, regular pain and often face challenges in getting through daily tasks. For this reason, it is understandable that some wished to do as much as they were able and showed their support for the approval of exa-cel, or expressed their appeal to the committee, through just one or two lines of text. We welcome the message this sends about the overwhelming and urgent need, in the community, for new safe and effective alternative approved treatments for sickle cell disorder. While it is important that we acknowledge all commentators and the efforts they placed in responding to this consultation, we are only able to include in this comments form those who offered some detail in response to the points requested. In addition to those included, there were an additional 77 short responses which simply asked for exa-cel to be made available. The majority have been anonymised, but we have included names and job titles from individuals who have explicitly given us their permission to share these details.
6.01	As chair of the Sickle Cell All-Party Parliamentary Group (APPG) for nearly 2 years, I frequently interact with people with sickle cell. Sickle Cell is a hidden and severely painful condition. It has a negative impact on a person's quality of life. Whenever the APPG meets every 3 months without fail we constantly hear harrowing truths from patients' life experiences. Therefore, considering the severity of sickle cell on day-to-day life, the worsening impact that sickle cell has over time and what this means for life expectancy, it is vital that NICE acknowledges the benefits of new gene therapy treatments and what this will mean for

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	people with Sickle Cell and their families. It will allow this marginalised group of patients, from mainly diverse backgrounds, to have the chance to live a normal life. Yours sincerely, Janet Daby MP Chair of the Sickle Cell All-Party Parliamentary Group
6.02	I am writing as I fully support Exa-cel being available for Sickle Cell for the following reasons: • The negative impact that severe sickle cell has on the day-to-day life of people living with the condition. • The worsening impact that sickle cell has over time. • The impact of sickle cell on life expectancy and the risk of mortality. I hope the NICE reconsider their decision and allow the gene therapy Exa-cel to be used for those suffering and take away their misery. Baroness Floella Benjamin, OM DBE DL
6.03	I would like to express my deep concern of the negative general, and mental health impacts the NICE decision will have, NOT to recommend the new gene therapy, exa-cel, for the treatment of severe sickle cell disease. Sickle cell disease causes severe pain and other life-threatening health complications such as major infections, acute chest syndrome and stroke. The experienced pain of a sickle cell crisis can occur anywhere in the body, but most often in the chest, arms, and legs. The interruption in blood flow may also cause tissue death. Acute chest syndrome occurs when sickling of the red cells happens in the chest and can be life-threatening. A sickle cell crisis occurs suddenly when under stress from infection, fever, and dehydration. The spleen can also become enlarged and painful from the increase in blood volume. After repeated episodes, the spleen becomes scarred, and permanently damaged. A sudden and severe stroke is another complication for sickle cell patients because the misshaped red cells (sickle shaped cells) can block the major blood vessels that supply the brain with oxygen. Too many interruptions in the flow of blood and oxygen to the brain can result in severe brain damage. Even jaundice is a factor for sickle cell patients and is a common sign and symptom of the disease. Sickle cells do not live as long as normal red blood cells and, therefore, they are dying faster than the liver can filter them out. Lastly, I would like to point out Priapism, which is a painful obstruction of the blood vessels in the penis by sickle cells. Any of the major organs are affected by sickle cell disease. The liver, heart, kidneys, gallbladder, eyes, bones, and joints, can suffer from the abnormal function of the sickle cells and the inability to flow through the blood vessels correctly, and may include the following problems : Increased infections, leg ulcers, bone damage, early gallstones, kidney damage, eye damage, multiple organ failure,

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	Just fifty percent of patients with sickle cell disease survive beyond their fifth decade. A large proportion of those who die have no obvious chronic organ failure but died during an acute episode of pain, chest syndrome, or stroke. For the above reasons and many more, I am expressing my views that the NICE decision to say 'NO' to the new gene editing therapy for sickle cell patients should be overturned. Beverley De-Gale OBE AB+ ACLT Co-Founder, and Director of Operations
6.04	I am writing on behalf of the All-Party Parliamentary Group for Ethnicity Transplantation and Transfusion to submit our response to the consultation on the draft recommendation concerning exa-cel gene therapy for the treatment of severe sickle cell disease. Many of the Groups stakeholders and supporters are sickle cell patients. The Group recognises the critical role of NICE in ensuring that treatments recommended for use within the NHS are both effective and provide value for money and we appreciate the complexity and the rigorous evaluation processes involved in such decisions. However, we are concerned about the preliminary decision not to recommend exa-cel for NHS use, given its potential as a transformative treatment for individuals suffering from severe sickle cell disease. Sickle cell disease significantly impacts the quality of life of those affected, with severe cases frequently experiencing excruciating pain, debilitating fatigue, and increased susceptibility to infections and organ damage. The introduction of exa-cel as a treatment option represents a significant advancement in potentially offering a curative solution to individuals who have lived with the condition's severe implications on their daily lives. For many patients with severe sickle cell disease, the lack of a suitable stem cell donor limits their treatment options. Exa-cel presents an innovative alternative that could circumvent this limitation, offering hope to those who currently have few, if any, options for a cure. While we understand the concerns regarding the cost-effectiveness of exa-cel, we urge NICE to consider the long-term benefits of providing a cure for sickle cell disease. These benefits include the potential reduction in hospital admissions, the need for ongoing treatments, and the overall improvement in patients' life expectancy and quality of life. Additionally, offering a cure can have profound implications for mental health, employment opportunities, and the ability to lead a normal, productive life. In light of these points, we respectfully request that NICE reconsider its draft recommendation on exa-cel. We believe it is essential to factor in the broader implications of this treatment, not only in terms of direct healthcare costs but also in its potential to significantly improve the lives of those affected by severe sickle cell disease. We are committed to engaging with NICE, healthcare professionals, and patient advocacy groups to ensure that the voices and needs of sickle cell patients are adequately represented and considered in this crucial decision-making process.

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	Thank you for your consideration of our response. Yours sincerely, Yaser Martini Team Margot
6.05	The cure to Sickle Cell Disease (SCD) should not be up for consideration because of the following reasons I present: As someone who has two sisters that live with sickle cell disease. My sisters are and have been on a monthly cell exchange for over 5 years now. I have seen the life they have been subjected to due to this chronic condition and it is far from a normal life. It is hardly a happy life, and the idea of a cure is something that we couldn't have imagined. The risks of living with SCD include, but are not limited to stroke, vision problems, delayed growth, infection risk, acute chest syndrome, organ damage etc. These are very serious complications. Having SCD is like a death sentence because it comes with daily excruciating bone pain which can occur in any part of the body. Pain so severe that hospitalization is required urgently. The daily experience of extreme fatigue that no-one talks about. Multiple monthly admissions. This is the life that people living with SCD silently live. Not to consider the impact of and the effect it has on individuals' physical abilities, exacerbating financial difficulties, the employment challenges faced due to living with SCD, the burden on family members. These matters should not be taken lightly. The psychological impact of living with SCD cannot be understated, individuals living with SCD experience chronic anxiety, secondary depression, and stress due to ongoing health complications in their daily life. The lives of individuals living with SCD dramatically changes by approving exa-cel treatment. The burden it has on the family unit and on healthcare is also dramatically lifted as time and resources are saved just by putting a stop to this chronic condition. I want to also note that some people living with this condition appear to have multimorbidity which puts them in a more compromising situation. I urge the exa-cel consultation committee to seriously re-think this decision and the significant impact it will have on the quality-of-life for individuals living with this chronic condition. I thank you for your favourable consideration in this matter and I trust that the right decision will be made in favour of life, and to secure the future of those suffering with Sickle Cell Disease. Sovereign I. Secondus

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	Ph.D. Candidate Faculty of Medicine & Health Sciences Researcher in Sickle Cell Disease and Motherhood University of Nottingham
6.06	Quality of Life is a subjective measure, a concept which aims to capture the well-being of an individual or a population. According to the World Health Organization QoL is explained as a subjective evaluation of one's perception of their reality relative to their goals as observed through the lens of their culture and value systems. Common facets of QoL include; personal health, education status, work environment, social status, wealth, relationships, freedom, autonomy in decision making, a sense of security and safety. Sickle Cell Anaemia affects all the facets listed above, however for intended purposes, I will attempt to focus on 'personal health' by answering: a) How challenging it is to live with Sickle Cell? b) And why a therapy and potential cure is needed? How challenging is it to live with a condition causing life-long anaemia and pain, a long-term condition, a so-called hidden disability which meets the definition of disability under the Equality Act 2010, and is suffered by approximately 15,000 people in Britain, however, is barely treated as a disability by institutions of Education, Employment and Social Welfare. Where do I begin? As a person living with severe Sickle Cell for 45 years I can attest that the condition has had a huge negative impact and continues to impact every facet of my life, my family and those within my sphere. • I have to take several medicines every day to function and keep as fit as possible. • I am not provided any financial support or benefits by the UK Government, to pay for these daily medicines and supplements I require to survive • My life expectancy is shorter than the national average. • I have had several life-threatening moments as a result of Sickle Cell. My most significant experience of the condition was in 2018, I suffered a Stroke, Pulmonary Embolism & Delayed Haemolytic Transfusion Reaction, which led to 10 days in ICU, 30 days in hospital, 6 months in physiotherapy, over 12 months in therapy and 9 months not working. I felt weak all the time. This was the lowest point in my life. This impacted my freedom and independence, my ability to work and to have a steady source of income, my career trajectory, my ability to contribute towards society. The cost of managing Sickle Cell on the NHS does not appear to be quantified. Why is qualitative data not being sourced or not accessible to quantify the cost of treating Sickle Cell versus curing Sickle Cell? The bottom line comes down to cost and financing new treatments. And whether NICE believes Sickle Cell Anaemia is relevant and negatively impacts the wider population. Hence a sustainable therapy or cure, already approved by

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	the US FDA, could possibly be more cost-effective on the NHS and enable me and people like me to live a fuller, healthier, longer life. Why is a therapy and potential cure is needed? As a Sickle Cell Patient who experienced Alloimmunisation in 2018 post a Blood Exchange (the formation of antibodies to red cell antigens). Alloimmunisation can lead to delayed haemolytic transfusion reactions that render me 'un-transfusable'. Some context for you – the mortality rate of acute haemolytic transfusion reactions can reach 44% and it accounts for 20% of all transfusion-related mortalities (www.escholarship.org 2018, Authors Purcell, Michael, San Miguel, Christopher) Hence it is of great importance to me to have access to a therapy or cure, as I have been rendered un-transfusable, which is the regular go-to treatment for a majority of Sickle Cell Patients. What do I do the next time I am in a serious medical emergency? Cross my fingers and hope for the best! Kind regards, Ms. Lanre Ogundimu Sickle Cell Society UK, Trustee
6.07	To whom it may concern at the National Institute for Health and Care Excellence (NICE), As an active advocate of 28 years standing for raising awareness about Blood Disorders and Blood Cancer, including the only known cure for Sickle Cell Disease being a Stem Cell transplant, I am personally and professionally highly disappointed at the draft decision of the National Institute for Health and Care Excellence (NICE) to NOT fund via the NHS the clinically trialled and potential groundbreaking CRISPR gene therapy, called Exa-cel (brand name Casvegy). I am also a member of the African and Caribbean community, and I am genuinely concerned that if this draft decision is NOT overturned it will leave generations of present day and future severe Sickle Cell patients (who are eligible for a transplant but do not have a suitable matching stem cell donor), with no potential beacon of hope of an effective cure. This decision is a devastating blow to our community, which has long faced significant health inequalities (because of lack of access to pain relief, blood transfusions, and stem cell donors, etc.) especially when it comes to Sickle Cell Disease which is a genetic blood disease that predominantly affects individuals of African and Caribbean descent. In the UK, it is estimated that 1 in every 2,000 babies born are affected by Sickle Cell Disease making it the most common inherited condition in the UK and the numbers are steadily rising, with the majority being of Black African or Black Caribbean heritage. This chronic condition causes severe/immense pain, organ damage, stroke(s), and a significantly reduced life expectancy. The experienced pain of a Sickle Cell crisis can occur anywhere in the body, and the interruption in the blood flow (caused by the misshaped sickling of the red cells) may also cause tissue death. Shockingly, the average life expectancy for someone with Sickle Cell Disease in the UK is just 40-60 years, compared to the national average of 81 years.

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	The impact of Sickle Cell Disease on the Black community is absolutely staggering. In England, Black people are over 80 times more likely to have Sickle Cell Disease compared to White people. Furthermore, the mortality rate for Sickle Cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with Sickle Cell Disease dying before the age of 18. In my capacity as the Co-Founder and Chief Executive of the ACLT (African Caribbean Leukaemia Trust) and Chair of the NBTA (National BAME Transplant Alliance), I communicate with many Sickle Cell patients who struggle physically and mentally on a day-to-day basis living with the fear of an unplanned Sickle Crisis which occurs suddenly when under stress from infection, fever, and dehydration and can result in severe brain damage or a potential fatal outcome. The above statistics and narrative highlight the urgent need for effective treatments like the CRISPR gene editing therapy called Exa-cel (brand name Casvegy) to be made available to the Sickle Cell patients who can receive a stem cell transplant but have no matching donor and who predominantly are from the Black community. The NICE decision sadly mirrors the daily health inequalities faced by the African and Caribbean communities in the UK, which are well-documented such as Black people being more likely to experience poverty, discrimination, and barriers to accessing quality & healthcare across many well documented disorders. Sickle Cell Disease has been prominent in the UK for approx. a century and heavily concentrated since the arrival of the Windrush Generation. However, there has historically been (and continues today) highly unacceptable variation in healthcare service provision and lowering in standards of care towards these patients especially in light of the severe NHS funding costs in recent years. The standard and access of treatment options are extremely limited for Sickle Cell patients in comparison to other inherited conditions such as Cystic Fibrosis. The above facts are backed up by a report by the NHS Race and Health Observatory that found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts. Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including Sickle Cell Disease. This new CRISPR gene therapy offers a revolutionary approach to treating Sickle Cell Disease by addressing the root cause of the condition. By modifying the patient's own stem cells to produce healthy foetal red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with Sickle Cell Disease. The recent US trials of Exa-cel (brand name Casvegy) show that over 94% of patients have not had a Sickle Cell crisis within 12 months shows the true efficacy of this CRISPR gene edit therapy. This innovative treatment can greatly improve the quality of life for those affected and reduce the financial burden on the National Health Service system in the long run, due to lower primary care costs (hospital admissions, blood transfusions, blood exchanges, pain relief, etc.) in comparison to other health disorders which have far fewer affected patients. It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to Sickle Cell patients in the UK, particularly those from the African and

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	Caribbean community who are disproportionately affected by this condition. Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future. Moreover, the decision to stop the availability of gene editing therapy for Sickle Cell patients sends a troubling message about the priorities of our healthcare system. It suggests that these lives do not matter and the well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be. This is unacceptable and goes against the principles of equality and fairness that should underpin our society. By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long. In closing, I sincerely hope and implore NICE to reconsider and reverse its decision towards making gene therapy for Sickle Cell Disease more widely accessible as part of the urgent need to prioritise the health and well-being of many UK patients. The 17,000 Sickle Cell patients and the Black community in the UK deserves the same opportunities for improved health outcomes as any other group of patients. Ultimately for the above reasons, my view is that the NICE decision to say 'NO' to the new gene editing therapy for Sickle Cell patients should be overturned.
6.08	I write in my capacity as a Paediatrician with experience in West Africa and the United Kingdom, where I looked after children with sickle cell disease. I currently work in the middle East, at a hospital providing Bone Marrow Transplant for children, including for sickle cell disease. In the 34 years of my practice, I have come to value the many positive developments in the care of patients with sickle cell disease. Notable amongst these has been the introduction of Exa-cel gene therapy. I wish to strongly discourage the NICE consultative group from recommending the removal of Exa-cel from NHS funding for this vulnerable group of patients. We continue to make advances in treatment for numerous conditions, all of which are very deserving and sickle cell disease must not be left out or allowed to fall behind in access to high quality care.
6.09	Sickle cell is a life-changing and life-limiting diagnosis, especially for patients who have the severe variety. The gene therapy offers absolute cure and over all savings as it reduces inpatient stays, need for frequent transfusions, and prevention of progression of complications needing further treatments e.g. dialysis, renal transplant etc.
6.10	Dear The National Institute for Health and Care Excellence (NICE), I understand that a draft decision has been made <u>not</u> to recommend exa-cel for NHS funding.

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	I write to you as a mother, a sickle cell patient, a sister, daughter, aunty, friend, a sickle cell advocate and recently published author, who desperately asks for the reconsideration of this decision. The latter two titles have come with a self-proclaimed huge responsibility and determination to raise awareness, for this life threatening and altering condition that I continue- as well as many others- to suffer with on a daily basis. As a sickle cell sufferer with the SC type, it's commonly thought to be 'less severe or considered 'milder' than those suffering with sickle cell SS. I can personally assure you that there is nothing 'mild' about my condition. The amount of pain and suffering this condition brings is indescribable. In fact my condition deteriorated so bad post pregnancy, I developed a widespread 'bone death' condition called avascular necrosis. Which meant I required bilateral double hip replacements a year after my son was delivered by emergency c-section, which was considered to be bought on by a sickle cell crisis. My son was also born with abnormalities, which then meant he had his own additional care needs - a ventilated tracheostomy. Becoming a first time mum and then developing a degenerative bone death condition met with the most excruciating vilest pain, is an experience that no person should ever have to be faced with at all, especially soon after entering motherhood. On top of enduring this nightmare with my poorly baby in tow, I wasn't believed by the health care system when I noticed soon after the right hip replacement was carried out, that it was done incorrectly. Subsequently, I was left for four years and three months to suffer until it was finally revised. Before this eventually happened, my quality of life was so poor, I literally felt suicidal had it not been for my son I would have surely went through with ending it all as the pain was truly unbearable. Either that or I even envisioned cutting my leg off to excuse me from the pain! Nothing I did or took helped ease the pain. I'd routinely dose my hip and leg in deep heat, take several baths as and when I could, sleep with hot water bottles in between my legs at night (which affected my skin). Sleep with various pillows. I could barely walk. I suffered immensely. Before I had each side of my hip replaced, I'd go either temporarily blind in the opposite eye and/or experience floaters with shadows. I struggled to care for my son, couldn't walk let alone run after him. I couldn't sit crossed legs and join in the stay and play groups I still was determined to take him to so he didn't miss out. As well as both sides of my hips being affected, I also have the same condition bilaterally in my shoulders. I am currently awaiting shoulder replacements. The pain is awful. Even something as simple as putting the seat belt on in the car is a painful experience, never mind 'simply' lifting my arm. Sickle cell suffers are living in agony in silence, we are not believed, our pain is often disregarded, or often assumed to be drug seekers even when we do try and seek some relief for the pain. It was really disheartening to learn about the treatment currently not being made available on the NHS, as this would have been literally life saving for people like me who are suffering with this dreadful condition. Sickle cell anaemia is the fastest growing genetic condition in England, we deserve to have the opportunity of a decent quality of life - just

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	like other conditions, whereby there are many treatments available (all discovered many years after sickle cell was first discovered in 1910). I ask you please to reconsider the decision? We as a community, and as a country that is nationally affected with those affected rising, we need some hope that there are better and pain-free days ahead of us.
6.11	Dear NICE, My mummy is very strong, but she shouldn't have to go through all this pain. Please help her live without pain anymore! Thank you. (Aged 8)
6.12	To National Institute for Health and Care Excellence, Sickle cell not only affects the individual, it also affects the whole family. I have had to watch for years my brother and sister battle this illness. In and out of hospitals, crisis after crisis, trigger after trigger. I've wanted to take their pain away, but I can't. The levels of pain I've seen them both separately and together going through is unreal. It seems to worsen over time! My sister's just got overall worse in so many different areas! Even last year, as well as everything else she's had to have done, I witnessed her suffering from a blood clot on her lung! It's unbelievably the way it progressively deteriorates. However, I'm optimistic about the possibility of this new treatment. I think many would greatly benefit from this treatment being introduced. It's well overdue. I urge you to strongly reconsider for all sickle cell patients.
6.13	To whom it may concern: The significant impacts of severe sickle cell on your daily life vary: Fatigue: This is a very common issue that people with severe sickle cell suffer from, it hurts your daily lifestyle, which limits the amount of activities you can do daily. Severe pain (Crisis): This is a pain episode that patients with severe sickle cell conditions, it affects your bones, and joints which causes damage to your joints and can cause weakness in your body. Sickle cell worsens over time, the older you become the more challenging it becomes to manage the condition, and you become at risk of major organ failure, it can be fatal because it is a hidden condition that is not easy to detect when there is a problem. It puts patients at high risk which means that we have to receive rigorous treatments and check-ups, which can take a toll on our bodies and make us extremely irritated and agitated.

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	During the colder seasons of the year, sickle cell patients are more susceptible to colds and infections which can deteriorate over time and if care is not taken can become fatal. Life expectancy for sickle cell patients decrease over time, is due to the type of rigorous treatments we receive which can have adverse effects on our body system, when we have pain crisis this can also lead to serious complications which can become life-threatening and lead to death. Due to complications that patients with sickle cell have most times it affects too late before a solution can be found and they die. And it's devastating to see that this condition isn't taken as seriously as other conditions neither are the patients being attended to with the immediate urgency that is required when they go into hospitals, is it until the mortality rate starts getting higher that this condition will be taken seriously. Having sickle cell puts you at risk every single day of your life because the smallest infections or disease could mean the end of your life. I as a sickle cell patient would like a fighting chance to have a better life by receiving treatments that can make that possible, so if you decide not to put the Exa-cel (CRISPR) on the NHS then we have no chance of having a better life which means that we have no chance of surviving and we may all die, please do not gamble with the lives of innocent people who want a shot at living a fulfilled life because you want to weigh out the cost of the treatment versus the quality. When I read the first decision that NICE made I was angry and disappointed because it felt like the only chance I had of getting better was taken away from me and other sickle cell patients will feel that way to because this may be the only one chance we get and yet you want to deprive us from it and that is not right and there is no justification for that. I hope you reconsider your decision because so many sickle cell patients including myself are counting on this.
6.14	As a mother whose child battles severe sickle cell disease every day, I am writing to you with a plea from the depths of my heart. I need you to understand the pain, the anguish, and the relentless suffering that my child endures, and why funding for Exa-cel (CRISPR) treatment is not just a luxury but a lifeline. Watching my child suffer is a pain like no other. From the moment they were born, I knew life wouldn't be easy for them. But nothing could have prepared me for the sheer magnitude of their suffering – the endless nights spent writhing in agony, the tears shed in silence, the dreams shattered before they even had a chance to take flight. Sickle cell doesn't just affect my child physically; it takes a toll on their spirit, their innocence, their very essence. I watch as they struggle to keep up with their peers, to find joy in the little things, to simply be a child. It breaks my heart to see them robbed of their childhood, their laughter muted by the weight of their pain. And as if the pain weren't enough, there's the constant fear – fear of the next crisis, the next hospitalisation, the next brush with death. It's a fear that grips me tight, refusing to let

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	go, no matter how hard I try to push it away. I live in a perpetual state of anxiety, always on edge, always waiting for the other shoe to drop. I've lost count of the number of times I've held my child's hand as they underwent yet another surgery – lines inserted, lines removed, organs removed – each one a stark reminder of the fragility of their existence. And through it all, I've had to be strong, to put on a brave face, to be their rock when all I wanted to do was crumble. And then there's COVID-19. Like so many others, my child's health was put at risk, their fragile body unable to withstand the onslaught of the virus. It was a nightmare come to life, a battle for survival that we were ill-prepared to fight but even more so as sickle cell already made her more vulnerable. She didn't just get covid 19 and fight it off like many her age, she got pneumonia and had to fight for her life. Your decision not to fund Exa-cel (CRISPR) treatment on the NHS leaves me feeling helpless, desperate, abandoned. It's not just about my child's future; it's about their very survival. I need you to see beyond the numbers, beyond the bureaucracy, beyond the red tape. I need you to see my child – their pain, their suffering, their unwavering spirit in the face of adversity. Please, I'm begging you, don't let us down. Listen to our cries, our pleas, our prayers. Give my child and countless others like them the chance to live a life free from pain, free from fear, free from sickness. With a mother's love and desperation.
6.15	I understand that the National Institute for Health and Care Excellence (NICE) made a decision NOT to recommend NHS funding for Exa-cel (CRISPR), a new gene editing therapy for sickle cell. I find this hugely disappointing given the number of sickle cell sufferers and the fact that for the longest time their needs have not been addressed. Other medical conditions which affect significantly fewer people do not seem to have treatments that could make such a difference held back or restricted. I along with many others urge that the decision not to recommend be reconsidered and revoked.
6.16	I am 44 years old. I have been living with sickle cell disease all my life. This is a condition I would not wish on my worst enemy. It is very painful and debilitating. It is a scandal in this country that more isn't done to support and help people with this condition instead they are made to feel like drug addicts and criminals. Treatment for sickle cell disease is life long and painful. The drugs and medications used are akin to those who have cancer. However, patients experience very different treatments from doctors and clinicians under the NHS.

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	Even when a cure could be possible in terms of bone marrow and stem cells not enough research is being done. In fact, it's the opposite research is being stopped. I find it disgraceful. Do people with sickle cell disease not work and contribute to the NHS? Then why can't they be treated the same way and supported to manage and cure their health condition?
6.17	• The significant negative impact of severe sickle cell on daily life. • Sickle cell worsens over time. • The effects of sickle cell on life expectancy and mortality risk. The above are points which I wish to highlight as the mother of a child with sickle cell. It has meant that my son was often absent from school, only attending three days a week at best, and me having to employ someone to stay at home with him so that I could go to work to look after the financial needs of my family. Huge heating costs, private transport costs to and from school due to his inability to stand in the cold at bus stops have been a constant drain. In turn the school absences have negatively impacted my son's educational achievements and ability to interact and socialise and consequently his career prospects. Frequent sickle cell crises requiring time off work; not being able to sit in a workplace environment without additional heating and not being able to choose jobs requiring standing, outdoor work or much walking has been severely impactful. Further, sickle cell crises weaken the organs over time and has significant effects on life expectancy and mortality risks. Funding needs to be focused on this neglected area and I would urge you to include it and re-dress this perceived neglect and imbalance.
6.18	I'm emailing to voice my concern at NICE's decision to decline the new gene altering therapy which could help so many sickle cell patients. I urge NICE to reconsider, funding CRISPR through the NHS would help so many people in need. I have witnessed first-hand the day-to-day impact Sickle Cell has on lives and how debilitating and painful it can be. How exhausting it is to get blood transfusions. As a nation we should be helping people with sickle cell lead normal, pain-free lives. CRISPR is the first step towards finding a cure for sickle cell, and is a little glimmer of hope for those with a disease that only worsens over time and decreases life expectancy. Please, I urge NICE to reconsider and grasp the severity of what they are blocking. Sickle cell is a very serious, life-threatening disease - it's our moral obligation to help people who need it and not let money stand in the way.
6.19	As a member of the African and Caribbean community, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom.

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	This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease. Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent. In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage. This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years. The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people. Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18. These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community. The health inequalities faced by the African and Caribbean community in the UK are well-documented. Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare. A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts. Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease. Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition. By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease. This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run. It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition. Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future. Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system. It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be. This is unacceptable and goes against the principles of equality and fairness that should underpin our society. I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible. The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group. By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long.

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	Thank you for your attention to this critical matter. I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.
6.20	More awareness is required especially in a multicultural society that is ever growing. Subsequently more funding where required.
6.21	I would like to voice my strong opposition to the plans to stop the provision of new gene therapy to help the suffering of sickle cell patients. My 26yr old daughter has been living with sickle cell anaemia her whole life and the detriment to her quality of life cannot be underestimated. • She has to deal with so many issues we take for granted on a daily basis, including regular crises, constant tiredness, period pains, and of course the fear of the unknown for her future. • The deterioration of her organs over time including her liver, and eyes. • Of course, her life expectancy is so much less compared to other young adults her age, having already been through so many severe crises where I felt she wouldn't survive. Please do all you can to ensure the gene editing treatment can be made available to sickle cell patients.
6.22	As we navigate through the critical phase of advocating for Exa-cel (CRISPR) therapy for sickle cell disease, I want to express my deepest appreciation for your unwavering commitment to this cause. Your dedication to amplifying the voices of those affected by sickle cell is commendable, and together, we can make a tangible difference in shaping the future of treatment accessibility. 1. The Significant Negative Impact of Severe Sickle Cell on Daily Life: It's imperative to underscore the profound challenges that individuals with severe sickle cell face in their daily lives. From debilitating pain crises to limitations in physical activities and social interactions, the impact is multifaceted and deeply disruptive. By conveying these lived experiences, we can provide crucial insights into the urgent need for effective treatment options. 2. How Sickle Cell Worsens Over Time: Sickle cell disease is characterized by its progressive nature, with symptoms often worsening over time. Chronic pain, organ damage, and increased susceptibility to infections are just a few examples of how the condition can deteriorate as patients age. Emphasizing this progression underscores the necessity for proactive intervention to mitigate its detrimental effects on patient well-being. 3. The Effects of Sickle Cell on Life Expectancy and Mortality Risk: One of the most sobering aspects of sickle cell disease is its impact on life expectancy and mortality risk. Studies have shown that individuals with sickle cell disease have a significantly reduced life expectancy compared to the general population, with complications such as stroke and organ failure contributing to increased mortality rates.

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	This stark reality underscores the critical importance of access to innovative therapies like Exa-cel in improving patient outcomes and extending life expectancy. Please can you consider continuing or reducing the funding instead of ceasing it. Please. Thank you once again for your steadfast dedication to this vital cause. Together, we can drive meaningful change and pave the way for a brighter future for sickle cell patients in the UK.
6.23	I wanted to contact you in regard to the recent denial of sickle cell gene therapy and the impact this has not only on my 12-year-old son, but members of my family who suffer with sickle cell and the impact this has on us as a family and carers. Last year we lost my aunt from this terrible illness and my family spend a large part of their lives in hospital or unwell, my son included. He has sickle beta thalassemia and whilst this is considered the milder form, it is not without its challenges. His missed time in education, his fears around doing too much sport and missing out crucial bonding with his friends and even down to travelling and crisis that regularly means he is unwell on holiday. Every person deserves to have the same opportunity in life and those affected by sickle cell deserve to have the recognition and the right to fair treatment and care as one of the most common blood disorders in the UK. It's sad that this crosses my mind, but I often wonder if this illness affected white people, would there be more money spent in this area? I like to think this wouldn't be the case, but it's sad to feel like that in 2024 but systemic racism is still very much alive, so you do wonder. There are many talent individuals that with healthy, full lives will contribute to the next generation of our world who, with a real chance, could go on to make a huge positive impact on our country and world. Please reconsider this decision. I look forward to hearing from you.
6.24	The impact assessment of not funding gene editing therapy for sickle cell sufferers should take into account the inherit inequalities in health for black and minority ethnic communities. Most importantly the cost and impact on the whole family when a sickle cell sufferer is in crisis is significant. The limitations on economic activity, life experience and life expectancy for the sufferers and the families. How will we understand the full potential of this treatment without the treatment being funded. It is important that you are able to show that the human suffering outweighs the financial cost.

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6.25	Give the future of the Sickle Cell Warriors the help they truly need. With your expertise and the pharmaceutical assistance, you are giving HOPE, REASSURANCE & a FUTURE for SICKLERS. PLEASE don't stop the Exa-cel on the NHS as this significant consequence to SICKLERS is a wholehearted NEGATIVE one and the fact that the disease worsens over time plus the life expectancy and mortality risk is in your hands. Please take into consideration the above heartfelt email. WE need you, please make a positive decision.
6.26	I wish to state my concern why NICE should reconsider CRISPR. 1. Severe sickle cell disease can profoundly affect daily life, causing chronic pain, fatigue, organ damage, and limitations in physical activities and social interactions. 2. Sickle cell disease tends to worsen over time, with recurring pain crises, increased risk of infections, progressive organ damage, and potential complications such as stroke or acute chest syndrome. 3. Sickle cell disease significantly reduces life expectancy and increases mortality risk, particularly due to complications like organ failure, infections, and stroke, highlighting the need for comprehensive management and care throughout the lifespan. These factors underscore why sickle cell disease is a critical public health concern that requires urgent attention and comprehensive interventions to improve patient outcomes, alleviate suffering, and reduce the socioeconomic burden on affected individuals and healthcare systems.
6.27	• The negative impact that severe sickle cell has on the day-to-day life of people living with the condition is extremely profound. The pain is relentless and excruciating. • The worsening impact that sickle cell has over time includes missing out on school with the resulting debilitating psychological and vocational impacts. • The impact of sickle cell on life expectancy and the risk of mortality can have a significant negative impact on the sufferers. Approval of this gene therapy by NICE will be highly significant at treating the sufferers both physically- at eliminating the horrendous symptoms - and also psychologically. I hope NICE will reconsider their recommendations and grant the required approval for the benefits of sickle cell disease sufferers.
6.28	Sickle cell disease is a very severe, incurable, genetic condition with damaging organ damage and pain with cost implications to the NHS greater than thalassaemia untreated. Gene-editing provides a curative approach, which should get even cheaper in time, with further iterations of the technology, therefore bringing about cost-benefit to the NHS and lifesaving changes for the individuals who prior had sickle cell disease.
6.29	•The negative impact that severe sickle cell has on the day-to-day life of the condition: Sickle Cell Disease (HbSS) is an inherited disorder present from birth. The sickle

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	haemoglobin becomes rigid and sticks together causing the long premature breakdown of the red blood cells resulting in low blood count (haemolytic anaemia) and 2) vaso-occlusion which is the sticking of red blood cells in small blood cells resulting in downstream lack of oxygen to the tissues and therefore damage to the organs affected. Information around sickle cell has not fully been grasped therefore information needed to help the patients are suppressed. For instance, the severity of our blood cells imploding rapidly in our bodies and releasing haem (can be seen as poison in the blood stream) which has severe impact on our day to day lives. Sickle cell severely impacts our activities of daily living. Such as cooking, cleaning, remembering to take medication, laundry, shopping, managing our personal finances, communication and taking transport. Because patients have learnt to cope with their daily lives because of the lack of education and knowledge surrounding the illness due systemic racism, we've adapted to being unsupported. Not only is the physical impact of sickle cell crushing, the emotional and mental challenges are worse. The emotional and mental impact of sickle cell is what is medically ignored the most because of lack of funding that goes into adequate teaching and global recognition. Therefore, this means the day-to-day challenges of sickle patients is intensified because the challenges are ignored and suppressed by the medical industry. Sickle cell patients are relied on to teach, be volunteers for the medical industry while also being gaslighted about the condition. This means sickle cell patients are most likely to be discriminated against. •The worsening impact that sickle cell has over time: The mental and emotional turmoil developed over time by realising that we are scape goats in the medical industry and no one truly cares despite the performative activism we are constantly exposed to. The damage to our organs from being exposed constantly to a sickle cell crisis that is severely under managed by health professionals we are meant to trust and be grateful for. Sickle cell patients are constantly abused and discriminated against which leads to severe emotional damage that can lead to severe depression or worse, suicide. The worse impact is realising nobody is really coming to help or save us and the performative help is nothing but politics. The fact that pharmaceutical companies are willing to invest millions in research for medication but not thousands for proper training and education speaks volumes to the sickle cell community. Sickle cell receives low and unfair equity as opposed to cystic fibrosis that receives up to 9 times more funding and education. The exposure to racism and discrimination is directly linked to poor health management as you realise, we are the sole authors of our care and health. •The impact of sickle cell on life expectancy and risk of mortality: The risk of mortality is extremely high in the sickle cell community because of the exposure to systemic racism, discrimination and ignorance. Because of the lack of equity and funding that goes into sickle cell patients, we are more exposed to premature deaths when we visit Accident & Emergency department. The lack of resources and education given at university stage for medical students perpetuates the ignorance shown in hospital. Our life expectancy has direct links to being exposed to sickle cell abuse and poor treatment. If that is combined with inadequate funding, that then becomes the perfect cocktail for a shortened life expectancy and a high rate of mortality.

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6.30	Please reconsider the decision not to approve gene therapy for people with sickle cell disease. We lost a beautiful son who worked hard and graduated from [X] University despite his medical condition he worked so hard as an international recruiter for a giant petroleum company. He passed away at the age of 33 due to his sickle cell condition. His loss is long suffering for us, his parents and also for his siblings. With gene therapy, [son] may have had the chance to become a father, an uncle and good role model for other people. Therefore, I beseech you to take my story into considering along with many families who have experienced the pain and suffering due to this debilitating genetic condition. Thank you.
6.31	I have a daughter with Sickle Cell Anaemia SS. My daughter has suffered tremendously all her life with hundreds of admissions to several hospitals. The worst was when she was ventilated in [X] hospital PICU and required several blood exchange transfusions due to sepsis. I thought at that time that I was going to lose her. But due to the hard work of NHS staff she managed to pull through. She stayed in hospital for months and had to go through rehabilitation. My daughter goes through several painful crises which are so painful, and she is mostly unable to mobilize. Her quality of life is affected and as a young lady of 21 years old and a 3rd year student at [X] University, these crises are affecting her psychologically. She usually cries when she can't do things with her friends when she gets a crisis suddenly when they had planned something. This therapy would benefit her both physically and emotionally. Funding is desperately needed to benefit Sickle Cell patients and make awareness much public in the UK. Thanks in advance for your consideration of my email.
6.32	I wanted to share my concerns and disappointment at the lack of funding for CRISPR because of the March decision by NICE. I support the effort in persuading them to consider this decision, as this is a major break through which will allow the 17,000 suffers to live better quality lives and reduce the pain of this condition. I don't want to feel that the country of my birth is ignoring this condition because it affects only a relatively small number of people. It is only an accident of birth that I, nor other family members do not suffer with this condition.

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	As part of the efforts of the NHS to provide fairer treatment and outcomes for Black and Brown patients, funding treatment for this condition which only affects Black and Brown patients is a fundamental step towards this.
6.33	As the parent of two adult sickle cell parents, I write in support of the campaign to make Exa-cel treatment available on the NHS. The negative impact of sickle cell on the daily life of my children started from the moment my daughter was diagnosed with the condition at 17 months of age. Twice daily prophylactic penicillin was prescribed to prevent infection. Her brother was born two months later and was prescribed penicillin within a week of birth. Initially both were protected from pain by their foetal haemoglobin but as this receded, symptoms started to appear. My son was the first one to show obvious symptoms; as a toddler he endured painful swelling of his hands and toes. He gnawed at the plaster on the walls of our house. During his primary school years crises manifested as priapism and, on one occasion after going swimming, blindness. He also suffered severe headaches that could only be quelled by being taken for a long drive until he fell asleep. Even though we described these headaches to his consultant they were not taken seriously until one happened during a consultation. This led to a brain scan that showed reduced flow to his brain and multiple ischemic infarcts; six weekly top up blood transfusions were prescribed. These helped, he had fewer headaches, could go swimming and, even on cold days, was able to play outside. He stopped gnawing at the walls. However, the transfusions led to iron overload which causes organ damage. In order to reduce the iron levels, he was prescribed an iron chelation therapy comprising a needle and tube set that was applied overnight three times a week. Occasionally, if the treatment was not complete, he wore the contraption to school. He continued to have headaches, but they were less severe. [...] In secondary school he continued to suffer headaches, the school made a huge effort to support him. In his early teenage years, he underwent surgery to provide oxygen to his brain by bypassing the restricted artery. By then he was on eight weekly exchange blood transfusions. He did well enough in his GCSE to pass 8 exams and was about to take his 'A' levels when he was involved in a life changing accident. At the present time he has 24 hour support to help him undergo his blood tests and transfusions, to take his daily medications, to attend hospital for organ scans, to stay warm and to dress appropriately. My daughter was an anomaly, she kept her foetal haemoglobin for longer but still suffered crises that led to hospital admissions with morphine as pain relief. By the time she was five she was determined not to go to hospital so would try to manage her pain at home. During her school years she had three major crises, one of which occurred after taking part in a school athletics session. She was so determined to be "normal" she kept running and, because she manifested as "normal" her teachers did not advise her to stop. During one crisis she asked me if she was going to die. While still at primary school she too was found to have brain infarcts and a more restricted blood flow than her brother but had not suffered headaches. Six weekly top up transfusions were prescribed which led to iron overload which led to iron chelation three nights a week.

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	While in secondary school she was moved on to exchange transfusions; she still needed iron chelation, but this had now changed to a chalky tablet which was more convenient, but she found the texture hard to tolerate so would not take it as prescribed. She is 33 years old now and despite being on exchange transfusions for approximately twenty years is still dealing with the consequences of the top up transfusion iron overload. At nineteen she started university [...] she completed Year One but during the first term of year two her gall bladder was removed; another sickle cell complication. When she returned to university, the course had changed, she was required to do Year One again. However, she was ill which led to absences but had completed many of the modules in the first year of her time at university. They decided that she should repeat Year One for a third time and would make no concession to her condition. At this point she decided to leave with a student debt of £40,000 and no degree. After having taken a part-time three-year [x] course at which she was top in her class twice, she was employed by a local company for approximately four weeks. The company had a big show to prepare for, my daughter had a crisis during which she was hospitalised, the company did not believe her, she presented as “normal”, she was sacked. At present she is a full-time mother to two children. During the pregnancies, she had to be injected daily by her husband or a family member. Both births were induced early and were by caesarean. She had to stop iron chelation while breast feeding so is not able to breast feed for as long as she would like. Both my daughter and son have suffered organ and brain damage. They are at high risk of stroke and have been on transfusions for at least twenty-five years. They have regular scans on their hearts, brain, liver, kidneys, eyes and undergo hearing tests. This damage can be slowed by the transfusions and by medication but is ongoing. It will shorten their lives. Sickle Cell Anaemia has negatively affected all aspects of my children’s lives. They have suffered severe pain, physical limitations, social isolation, stigmatisation in education and lack of employability. As they do not have a matched sibling donor, the Exa-cel treatment is their only chance to arrest the increasing toll being placed on their bodies.
6.34	I have Sickle Cell disease and my whole life has greatly been impacted by this inherited disease. Firstly, I had lost 3 siblings to Sickle cell crisis. I personally have had 3 strokes, I have regular painful episodes, and very low Immunity. I am very susceptible to infections and fatigue. Due to Sickle Cell, I have developed other life-threatening problems such as retinopathy, Sickle cell neuropathy, asthma, spleen removal, chronic kidney disease, etc. I am not

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	able to work or socialise. My emotional psychological and mental health is greatly affected. Sickle cell affects my life and those of my family, friends and community. I spend so much time in and out of hospital that my life revolves around that. My family are anxious all the time whenever I show any sign of any painful episode. Ever since I had the understanding about my condition, I have been praying for a cure. Now that prayer has been answered. It would be a shame if this life changing treatment and possible cure is not made available for us to benefit from it on the NHS. The need and urgent desperate urgency for the adoption of the life changing gene-therapy for thousands of people affected by this dreadful disease cannot be over-emphasized. The lives of thousands of people living with Sickle Cell and their family and loved ones will be positively improved and changed. Adopting Exa-cel (CASGEVY) gene-therapy to be made available on the NHS would give me and thousand others a new lease of life. Thank you.
6.35	I support the new sickle cell treatment. People are in desperate need of the gene therapy. Allow this treatment to save lives.
6.36	Please overturn this decision. Sickle cell is devastating and impacts everyone in the family and is debilitating to the sufferer. Often when they go for treatment they are treated horribly and discriminated against sometimes treated like criminal's time wasters and junkies.
6.37	Dear Whomever It May Concern, I am writing to express my strong support for the inclusion of gene therapy for sickle cell disease within the NHS coverage. As a person living with severe sickle cell, I want to shed light on the daily challenges and worsening conditions that affect individuals like myself. Living with severe sickle cell disease presents a myriad of obstacles that affect every aspect of daily life. From excruciating pain during crises to the constant fear of complications, the burden is relentless. Simple tasks become daunting challenges, and the unpredictability of the disease casts a shadow over future plans and aspirations. Moreover, as we age, the impact of sickle cell only intensifies. The cumulative effects of recurrent crises, organ damage, and other complications take a toll on our health and quality of life. Each passing year brings new challenges and limitations, further exacerbating the already difficult circumstances we face. The prospect of gene therapy offers a glimmer of hope for the sickle cell community. It represents a breakthrough in treatment that has the potential to alleviate suffering,

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	improve outcomes, and enhance quality of life for individuals with this debilitating condition. Access to this innovative therapy through the NHS would not only provide relief to current patients but also offer a lifeline to future generations affected by sickle cell. In light of the profound impact that sickle cell has on individuals and families, I urge you to consider the urgent need for accessible gene therapy within the NHS. By prioritizing the inclusion of this treatment option, we can offer hope, dignity, and a brighter future to those living with sickle cell disease. Thank you for your attention to this critical matter. I trust that you will give due consideration to the voices of those directly affected by sickle cell as you deliberate on this important decision.
6.38	Don't stop the gene therapy, which will be lifeline for sickle cell carriers primarily for the black and Asian communities. Sickle cell as an illness doesn't have a great awareness/profile. We do need this therapy in light of equality and fairness for these suffers and their families.
6.39	I am writing regarding the recent draft consultation by NICE (National Institute for Health and Care Excellence), who have decided not approved Gene Therapy treatment for Sickle Cell Anaemia patients. My experience with Sickle Cell has at sometimes been so excruciating, that I have prayed to die many times, while going through a sickle cell painful crises. It is a pain that is indescribable and that you would not wish on anyone else. As a teenager I was given a life expectancy of 17 years old, it is devastating to be told you want live a long life, because of an inherited blood disorder. At age 26 years old I had a Cholecystectomy to remove my gall bladder, which was damaged due to sickle cell. I was told that I was very young to be having surgery for this. The unpredictability of this disorder means that I can be fine one minute and the next I am screaming out in pain and have to be rushed into hospital. It can affect any part of my body, but as I got older I started to have many Acute Chest Syndrome (ACS), which would mean that I am hospitalise for at least three times a month. I now have lung disease and I'm constantly short of breath, due to the damage over the years that sickle cell has done to my organs. I feel fortunate that I have not had a stroke or a heart attack yet, which I know many patients with SC have had. It is no exaggeration to say that I wake up every day in pain, and I go to sleep in pain, I have never known a pain-free life. I do not rely on strong analgesic medication. As you know SC is an inherited disorder, which effects nearly 18,000 people in the UK. We have not had many treatments for this disorder, as far as I am aware there are only

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	two drugs that are currently used to treat patients with SC, and one of them was only approved in 2022 after 20 years of absolute nothing. I feel that Gene Therapy would not only enhance our lives, but it would also save the resources on the NHS, which is already stretched. I also believe that Gene Therapy is one of the most successful treatments for sickle cell today, and we should be given that option on the NHS, not just for us but for future generations to come. All we want is a better quality of life, a pain free life, a long and healthy life. This community has been overlooked for far too long and we deserve the same respect as those with other severe health conditions. I would like to urge you to reconsider your discission to withdraw the funding of Exa-cel gene therapy as a treatment for sickle cell patients on the NHS.
6.40	People with sickle cell disease experience severe pain. They are limited in activities they can do and could shut themselves from what is happening around them. They suffer emotional distress which could affect their mental health. When in crisis, their absence from work as adults and from school as children affect self-esteem. Families of sickle cell patients are also affected emotionally as they look on helplessly when their loved ones suffer excruciating pain. Living constantly in an environment with a feeling of helplessness and the inherent stress with it could lead to family breakdown.
6.41	I have sickle cell Anaemia. I want to oppose the motion to stop Gene therapy for qualify sickle cell patient. I believe it will improve quality of life for younger generation of sickle cell sufferers. They don't need to live a life of pain that I have to endure, and they can have better treatment outcome. Gene Therapy should be continued for sickle cell patients, this move will make care provision fair to people affected by sickle cells disease. Thanks
6.42	Dear NICE, I am writing to you to express my deep concern and disappointment regarding your recent decision to potentially stop the availability of gene therapy for sickle cell patients here in the UK.

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	I carry the sickle cell trait and have sadly lost friends prematurely because of the disease. I am in the process of writing a book for children and young people to raise awareness about the devastating chronic condition because many of our children are suffering and isolated because of it. Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent. It causes immense pain, organ damage, and a significantly reduced life expectancy. Some children and young people do not reach their full potential at school because of the condition and may struggle to make friends. In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage. Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare and the impact of sickle cell disease on our community is staggering. A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts. Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of eighteen. These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community. Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition. By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease. This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run. The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group. Accordingly, I urge NICE to reverse its decision and work towards making gene therapy more widely accessible and available to sickle cell patients in the UK. I thank you in anticipation of your assistance. Yours sincerely,
6.43	Dear NICE, As an employee in a job role that supports the African and Caribbean community, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom. This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease.

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	Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent. In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage. This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years. The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people. Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18. These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community. The health inequalities faced by the African and Caribbean community in the UK are well-documented. Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare. A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts. Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease. Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition. By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease. This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run. It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition. Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future.

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	Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system. It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be. This is unacceptable and goes against the principles of equality and fairness that should underpin our society. I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible. The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group. By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long. Thank you for your attention to this critical matter. I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease. Yours sincerely,
6.44	I have recently heard that you will no longer be funding the Gene therapy, treatment that so many patients are relying on. I have a number of family members who so heavily rely on this treatment and it has made a remarkable impact on their everyday life. It will be such a shame if you stop this treatment as it will have massive implications for people living with sickle cell. I strongly urge you to reconsider and will be happy to be kept informed of where this all goes. Thank you.
6.45	I have a relative that is suffering from sickle cell and is in need of constant medical treatment and relies on the NHS for their care. It is vital that this treatment of Gene therapy is supported under the NHS.
6.46	I am a 44 year old sickle cell anaemia patient. I have 2 children and have struggled with the effects of having sickle cell since birth. When I was 2 years old, I ended up in hospital with pneumonia and then was diagnosed with sickle cell. From then on, my life has always been a struggle with constant sickle pains and reoccurring infections due to my weak immune system. Over the years I have had a number of medical issues which I have had to attend hospital for and be off from work. Some of those conditions have included further incidents of pneumonia, chest infections, sickle crisis, necrosis of both hips, Reynolds, Sjogren's syndrome and arthritis.

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	Having this type of gene therapy when I was younger would have been a great help to myself and my family. It could have avoided all the pain and suffering that I experience daily and the elevated the stress and hardship that my mother had to go through raising both myself and my sister who also had sickle cell. Our family lost my sister in 1995 due to her enlarged spleen a result of having sickle cell, she died in hospital after the hospital insisted my sister was fine and my mum could take her home. If only we had this therapy and some care when we were younger then maybe my sister would be here today. I think you need to care enough about us sicklers the way that other medical conditions are cared about and stop neglecting us and leaving us to fend for ourselves. It is not fair to treat us like this, we matter too. The amount of funds that is needed to help us patients in and out of hospital and with us not being able to hold a job the way we would love to would reduce if we were not constantly ill. There are thousands of patients in the UK alone that have the condition but surely at least helping the younger ones now to have a full pain free life for the future is what is most important. Please consider us as human beings and not just as another statistic or funding cuts.
6.47	I hope this email finds you well. I am writing to you on behalf of not only my family but also countless others who have been deeply affected by sickle cell disease. As an organization committed to supporting individuals with sickle cell, I know the Sickle Cell Society understands the gravity of the challenges faced by those living with this condition. Sickle cell disease has been decapitating for those who suffer from it, including several members of my own family. Their lives have been marked by constant struggles, spending the majority of their time in and out of hospitals. Witnessing their battles firsthand, I can attest to the immense toll it takes on their physical and emotional well-being. It impedes their ability to live a full and fulfilling life, holding them back from reaching their true potential. It is imperative that funding for Gene therapy - curing sickle cell patients is implemented without delay. The current lack of resources and attention dedicated to finding a cure is not only unjust but also exacerbates the suffering of those already marginalized by their health condition. What's more, the disproportionate impact of sickle cell on ethnic minorities highlights the systemic inequities within our healthcare system. To neglect funding for such a critical cause further underscores the ongoing disregard for the well-being of ethnic minority communities. Therefore, I want to show my support to advocate vigorously for the allocation of adequate funding to the NHS for the research and development of the effective treatment and, ultimately, a cure for sickle cell disease. Every individual battling this condition deserves the chance to lead a life free from the shackles of pain and limitations. Thank you for your attention and continued efforts in supporting those affected by sickle cell disease.
6.48	Dear NICE Committee,

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	I'm reaching out to you because I need you to understand what it's like to live with severe sickle cell disease every single day. I'm not alone – there are many of us, and we need your help. You're deciding whether to fund Exa-cel (CRISPR) treatment, and I want you to know why it's so crucial. Imagine waking to sleep fine and waking up in agony, as if your bones are being crushed in a vice. That's what it's like for me and many others with sickle cell. It's not just the pain; it's the feeling of being trapped in your own body, unable to escape the torment. Sickle cell doesn't play fair – it gets worse over time. It's like a relentless storm that never lets up, slowly wearing you down until you feel like you can't go on. And it's not just the physical toll; it's the toll it takes on your spirit, your hopes, your dreams. I sometimes feel like I want to give up just for the pain to end. My mental health is affected the longer it goes on. Living with sickle cell means living with constant fear. Fear of the next crisis, the next complication, the next time your body betrays you. It's a fear that never leaves you, no matter how hard you try to push it away. I've had several surgeries– from putting in lines to taking them out to having my gall bladder removed. Each one leaves its mark, a reminder of everything this disease has taken from me. As a child I had a silent stroke, so I spent my Saturdays in hospitals having blood transfusions instead of attending my classmates birthday parties. And then there was COVID-19. I just turned 21 so I was in my last year of school when covid hit. While others my age might have shrugged it off, for me, it was a nightmare. I ended up with pneumonia, gasping for breath and wondering if this was the end. Sickle cell made me more vulnerable, more susceptible to the worst that this virus had to offer. Your decision not to fund Exa-cel (CRISPR) treatment on the NHS leaves me feeling stuck, abandoned, forgotten. It's not just about access to a treatment – it's about access to hope, to a future where I'm not constantly battling against my own body. Please, I'm begging you, don't let us down. Listen to our voices, our cries for help. We need you to stand up for us, to fight for us, to give us a chance at a better life. With hope and desperation.
6.49	This is to voice my concern and objection to the removal of gene therapy treatment for sickle cell patients. This is just another discriminatory attempt to deny ethnic minorities of treatment that is life changing. If this was a Caucasian disease like cystic fibrosis would it be removed as a treatment? Obviously not.
6.50	Dear NICE,

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Consultation on the draft guidance document – deadline for comments 5pm on 11 April 2024. Please submit via NICE Docs.

	I am writing to as a member of the African and Caribbean community. More importantly, I am writing as a parent of a SCD patient. I want to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom. This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease. Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent. In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage. This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years. The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people. Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18. These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community. The health inequalities faced by the African and Caribbean community in the UK are well-documented. Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare. A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts. Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease. Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition. By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease.

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	This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run. It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition. Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future. Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system. It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be. This is unacceptable and goes against the principles of equality and fairness that should underpin our society. I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible. The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group. By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long. Thank you for your attention to this critical matter. I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.
6.51	I am personally aware of many people who are suffers of Sickle cell and is very interested to know that the Gene therapy would be considered for helping them and other generation.
	This is to express my strong objections to reported plan to remove gene therapy treatment option for people suffering sickle cell disease, on NHS. Please let's know of any other helpful support we may be able give.
6.52	<i>Matters arising in the Decision on the Exa-cel Gene Therapy</i> When SCD is severe, its impact falls heavily on the individual, their family and friends, the health system and society in general.

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	The fruits of any drug therapy that has the potential to significantly alleviate the symptoms of SCD will be reaped bountifully directly or indirectly by everyone concerned. People with SCD should be helped by all means available to medical science to live complications-free; and living long and healthy, to contribute their quota to society. I strongly encourage NICE to recommend Exa-cel (Casgevy) for NHS funding for the benefit of the SCD community. Though still in its infancy, results from experimental gene therapy for SCD shows great promise. People with SCD - and their loved ones - should not have to face a life of uncertainty, or the fear of worsening symptoms as they grow older. Thanks for urgent action on the above.
6.53	Dear Sir/Madam I am sending this email to request that people with Sickle cell should be given treatment that they deserve.
6.54	Years ago, I was on a Access to Nursing course and when asked to do a large health project viewed to highlight Sickle Cell being a Black man and this ailment being an ailment that effects mainly Black people. I never saw the pains of sickle cell growing up, although one of my sister's carry the sickle cell trait from my father. So, it is only by the grace of God that my mother did not carry the trait as some of us children might have suffered the pains of sickle cell. But whilst doing this project I was made aware that a family friends' son had sickle cell. I went to see him to gain more knowledge on this illness and cannot put into words how this ailment has destroyed his life, his happiness, and the control of him going forward in life. If gene therapy could have altered this suffering it could have given a lifeline to a child who was very outgoing and happy go lucky when young from dying inside due to being ravaged by the pain and disruption of sickle cell in his life robbing him of so much opportunity due to continually feeling so poorly. Jobs effected, relationships effected, and the fear of procreating being stamped on him for fear of not being able to play his part in bringing up a new life and more the fear of passing on this life sentence of sickle cell. Whatever might help free sufferers of sickle cell from this suffering and torment in tomorrow's world from today needs to be fought for If gene therapy can aid to make the sickle cell gene dormant to relieve a life of pain and suffering then let's all raise our voices and open up our pocket books to make it happen.
6.55	Dear NICE, As a member of the African and Caribbean community, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom.

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	This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease. Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent. In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage. This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years. The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people. Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18. These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community. The health inequalities faced by the African and Caribbean community in the UK are well-documented. Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare. A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts. Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease. Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition. By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease. This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run. It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition.

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	Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future. Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system. It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be. This is unacceptable and goes against the principles of equality and fairness that should underpin our society. I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible. The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group. By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long. Thank you for your attention to this critical matter. I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.
6.56	Dear NHS and Other Health & Social Care Institutes, It has come to mine and the attention of the world that the Gene Therapy treatment that keeps about 20,000 sickle cell patients from a life time of pain is about to be closed without a wider consultation with those who benefit from the Gene Therapy treatment and those who potentially will benefit from it. Please without further ado keep the treatment going for it benefits everyone to keep going. It benefits the government in terms incomes and in terms of working age population increase instead of decrease.
6.57	I heard about plans by the government of the United Kingdom to remove Gene Therapy as a treatment option for Sickle Cell Disease. I join millions of others around the world to object to the plan. Gene Therapy is the only treatment that gives a person living with Sickle Cell the chance to escape from a life time of pains and sickness thus significantly improving their quality of life. I am see first hand the effects of this disease on the lives of people especially people of colour young and old. I have lost two dear friends to Sickle Cell disease crisis, and just

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	this week, another friend's daughter battled for her life for the second time in as many weeks because of this debilitating disease. I am a carrier of the Sickle Cell Gene (AS) and I have a daughter who suffers from the disease (SS). Ending, the only known hope for long term relief is many taking steps back. In fact, governments should double their efforts to grow access to this treatment and lower the cost of treatment in the UK and other nations around the world. Thanks for advocating for people living with Sickle Cell disease. We all should join in improving their chances of experiencing higher quality life.
6.58	As a mother of a two-year-old living with Sickle Cell, I am deeply disheartened by the apparent lack of understanding from NICE regarding the profound challenges faced by those born with this condition. My son was born just weeks after 'Crisanlizumab' was greenlit for NHS use. By 10 months old, he had already undergone three blood transfusions and was placed on hydroxycarbamide to manage his condition. Both sufferers and healthcare professionals assured me that the landscape was changing, offering hope for a more manageable life. Gene therapy is now here as a potential cure. Yet, in just two short years, it's become painfully clear that progress has not matched expectations. While progress is being made in other countries, the availability of treatments for the Sickle Cell community in the UK seems to be falling behind. Despite the availability of treatments and potential cures, there's a glaring disparity in access and understanding, even within our own healthcare system. The fact that treatments exist to alleviate pain and prolong life isn't reason enough for approval here, despite their adoption in other countries. The NHS should set the gold standard for care, yet reports like 'No One's Listening' and tragic cases like Evan Nathan Smith's death underscore the urgent need for a re-evaluation of our stance on making these curative methods accessible. I urge you to reconsider your position and make these curative methods available to those who desperately need them. Additionally, measures should be taken to streamline access to existing treatments for those fortunate enough to have HLA-matched donors. I am more than willing to provide further insights if needed.
6.59	I am the parent of 3 children with SC disease age's ranging from 13 to 35 years old. Over the years I have seen treatments changing or my youngest child being offered medication which my older kids was not offered or was not available at the time. However still experiencing crisis that can damage organs in their bodies. I believe the new treatment of Gene therapy can change all their lives. Giving them an equal opportunity to live a life without suffering. I would like all children with this Sickle Cell to be considered for this treatment.
6.60	Please, I am pleading that you should not remove gene therapy as a treatment option for Sickle cell patients. We all unique in our own little way, and everyone deserve to live

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	dignity life free from pain and anguish. Even if it is only one life being save with this treatment is definitely worth keeping the treatment option. Thanks for your empathy and understanding.
6.61	In response to the consultation on the above, I am writing to state my objection to removing Gene Therapy as a treatment option for Sickle Cell.
6.62	I am 38 years old, soon to be 39 in a month's time. Living with sickle cell has been an ongoing battle, a relentless struggle that has left me emotionally and physically drained. I have lost count of the times I have been hospitalized, fighting for my life. I experienced a TIA, a terrifying event that I can't even pinpoint. My lungs bear the scars of numerous chest infections, my immune system weakened and fragile. At just 38 years old, my bones resemble those of an 80-year-old, and I rely on medication to strengthen them, to prevent them from crumbling beneath me. The six-weekly blood exchange transfusions are a lifeline, a desperate attempt to manage my sickle cell, yet even with this treatment, I find myself back in the hospital time and time again. My heart bears the burden of this disease, with an ejection fraction in the left ventricle that constantly threatens my well-being. Gallbladder issues plague me, causing constant stomach problems that leave me in constant fear. My veins are a graveyard, a reminder of the many battles I have fought, the portacath a painful reminder of the blood clots that tried to claim me. With sickle cell retinopathy, lesions in my brain, and avascular necrosis in my ankles and knees, the effects of this disease are evident in every part of my body. I am currently grappling with spine issues, a new battle that my doctors are trying to understand. The pain, the fatigue, the weakness, the never-ending cycle of suffering that is my reality - it never stops, yet somehow, I have learned to endure it, to push through the agony and find a sliver of hope. The prospect of Exa-cel gives me hope, a glimmer of light in the darkness of my condition. To deny us this possibility would be a cruel injustice, robbing us of the chance for a better tomorrow, a life free from the constant torment of pain and suffering. With every day that I am able to leave the hospital, I am grateful, knowing that it could be my last. The spectre of a shortened life expectancy looms over me, a grim reminder of the fragility of my existence. I implore you to reconsider, to see the humanity in my words, in my plea for Exa-cel. This could be the lifeline we have been waiting for, the beacon of hope that has the power to transform our lives. Please, do not turn your back on us, on those who have endured so much and continue to fight each day for a chance at a better, healthier future. Let us have Exa-cel, let us have the hope we so desperately need and deserve.
6.63	I am writing this after hearing the news about the second consultation that would be going on concerning the approval for use of gene editing therapy for Sickle Cell anaemia treatment by NHS; as someone who grew up with my sibling suffering from sickle cells who spent most of the time in the hospital watching him in unexplainable pain.

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	I was thrilled to hear that the treatment was approved for use by UK government. My sibling needs this treatment; he grew unable to do the things other people of their age could, and I am always fearful whenever he is rushed to the hospital when going through a Sickle Cell Crisis. They are human beings too, no matter what it takes. This treatment was made to help them. I can tell you that no one wants to be in pain. Please (NICE) help them to live a pain free life like others, because they deserve the right to live a healthy life too and approve the treatment for NHS use.
6.64	Good day , I heard about the news of non-approval of gene editing therapy for treatment of sickle cell patients for NHS, this is heart breaking as I have had to live with my older brother who was born with sickle cell anaemia, he has lived a very troubled life having to go to hospital almost every month, days with sleepless nights going to crisis and pains , having this gene therapy will help my brother as he would finally live the life he has always wanted with good health and I'm sure many other people living with this illness will never forget it if this goes on , please consider this people as they are human beings and they also deserve the chance to live with a clean state of health.
6.65	To whom it may concern, I understand that Gene Therapy is being withdrawn as a treatment for Sickle Cell Anaemia, a condition that largely effects the African, Caribbean Community. As is usually the case, things that ensure the life, health and survival of the aforementioned community are barely considered in daily discourse let alone prioritised. I implore you, as a member of the effected community to furnish me with whatever tools are available aside from this letter of appeal. So, I can do my bit to bring this issue into greater public view. It is the least I can do. Yours With Hope.
6.66	My Nephew has sickle cell so I understand the importance this drug and how this can help other others suffering from sickle cell.
6.67	I am 35 years old with HbSC. Sickle Cell has hindered my life; I spent a lot of my childhood in hospital wards due to painful crises that could not be managed at home. It hindered my mother's ability to work having two children with sickle cell who were always sick. I missed school a lot and when I did attend school I couldn't play outside with the other children or fully participate in PE due to the risk of having a crisis. I started puberty late which caused me distress in my teens. University was a stressful time and again I could not reach my full potential because of the amount of school that I missed. My work life has been hindered as I now have AVN in my shoulder and retinopathy in both of my eyes restricting my vision especially when looking at a computer screen. I had

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	my dream job working overseas in different countries but the anxiety and worry about getting sick and being away from home left me in the emergency departments on many occasions from having panic attacks just because I fear having a crisis. This anxiety has deeply restricted my life and I have to live a routine life to reduce the number of crisis and always ensure I can get adequate treatment should I get sick, or my eyes suddenly flare up. I also have kidney issues and I am sure many more issues to come. My biggest worry is the anxiety the condition gives and restricts me and it's all reasonable anxiety because I can be having the best time of my life and then get sick. This is what Sickle Cell is. My earnings potential is restricted because I cannot subject myself to a high-pressured job and also because my body could not tolerate a more difficult degree and career path. If gene therapy was available to me or my younger siblings, it would be we could live limitless lives like others in society and would no longer suffer. I attend many outpatient appointments each year because of how sickle cell is damaging my organs (eyes, kidney, heart, lungs, osteo). A cure would also save the NHS money and save me further disability discrimination.
6.67	I am sickle cell patient and I want to plead that the gene therapy should not be cancel because it will benefit the future generations. As we know gene therapy help sickle cell patients by introducing healthy genes into their cells to replace the defective gene responsible for causing sickle cell disease. This could help to reduce or eliminate the symptoms of the disease, increase the production of healthy red blood cells, and improve patient outcomes overall.
6.68	Dear NICE Committee, I am writing to express my deep concern about the draft recommendation not to recommend the new gene therapy, exa-cel, for the treatment of severe sickle cell disease. As a carer of a child suffering from sickle cell, I witness the firsthand excruciating pain and trauma that people who suffers from sickle cell endure, both mentally and physically. Sickle cell has a devastating impact on the day-to-day life of patients, causing immense suffering and damaging their organs. The constant hospital admissions and treatments not only take a toll on their well-being but also place a significant financial burden on the NHS. Furthermore, I want to draw your attention to the "No One's Listening" report, which highlights the systemic racism and discrimination faced by sickle cell patients, particularly those from communities of colour. It is unacceptable that individuals are being denied access to potentially life-saving treatments due to racial disparities in healthcare. Investing in innovative treatments like exa-cel is crucial not only for improving the quality of life for sickle cell patients but also for reducing the burden on the healthcare system. By providing effective treatments, we can minimize hospital admissions and regular clinic visits, ultimately saving resources and improving patient outcomes. I urge the NICE Committee to reconsider its decision and prioritize the needs of sickle cell

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	patients. It is essential that the committee listens to the voices of those directly affected by this condition and takes steps to address the systemic issues that contribute to disparities in healthcare access and treatment options. Thank you for considering my perspective and for your attention to this important matter.
6.69	I have heard that there is consultation that Gene Therapy is likely to be discontinued. Please can we find a way to rescind this decision. I am a carrier of the trait as is my son. Until there is a cure and I am thankful that I do not have the disease but others are not as fortunate. They need this treatment. Thank you.
6.70	Exa-cel treatment for sickle cell. The burden of severe sickle cell disease on individuals' day-to-day lives is immense. Constant pain, fatigue, organ damage, and limitations on daily activities create a relentless struggle for those affected. As time progresses, the condition tends to worsen, leading to cumulative organ damage and a decline in overall health. This not only diminishes the quality of life but also significantly impacts life expectancy, with individuals facing a heightened risk of mortality from complications such as acute chest syndrome and severe infections. In light of these challenges, the introduction of new treatments like exa-cel holds immense promise in alleviating suffering, improving quality of life, and potentially extending survival for those battling this debilitating disease. Therefore, it's imperative for NICE to reconsider making exa-cel available on the NHS, as it has the potential to make a profound difference in the lives of individuals living with severe sickle cell disease, offering hope where there was once only despair.
6.71	Dear NICE Committee, I am writing to you as a concerned mother of two children who are living with severe sickle cell disease. Upon hearing the draft recommendation not to recommend the new gene therapy, exa-cel, for the treatment of severe sickle cell, I felt compelled to share our family's story and urge you to reconsider this decision. My children both suffer from excruciating pain and trauma due to their sickle cell condition. The impact on their day-to-day lives is profound, with frequent hospitalisations, missed school days, and limitations on their activities. Witnessing their suffering, both mentally and physically, breaks my heart as a mother, knowing that their organs are being damaged, and their childhood experiences are marred by pain. The systemic racism and discrimination faced by sickle cell patients, as highlighted in the "No One's Listening" report, further exacerbate the challenges my children and others like them face in accessing timely and appropriate care. It is crucial that NICE recognizes the disproportionate impact of sickle cell on communities of colour and takes steps to address these disparities in healthcare access and treatment options.

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	Furthermore, I want to emphasise the significant cost burden that severe sickle cell places on the NHS. With each hospital admission and emergency room visit, resources are strained, and the long-term implications on healthcare expenditure are substantial. By investing in innovative treatments like exa-cel, the NHS has the opportunity to not only improve the quality of life for sickle cell patients but also to realise cost savings in the long run through reduced hospital admissions and regular clinic visits. I urge the NICE Committee to reconsider its decision and to prioritise the needs of individuals like my children who are living with severe sickle cell disease. Access to exa-cel could offer them hope for a better future, free from the constant pain and trauma they endure. Thank you for your attention to this matter, and I hope that you will take our voices into account as you make your final decision.
6.72	I would like to state my objection to the withdrawal of Gene Therapy. If this is something to help those with Sickle Cell, then let it continue. Furthermore, as someone with the Sickle Cell trait it is very important to know these things are available.
6.73	The negative impact that severe sickle cell has on the day-to-day life of people living with the condition. Sickle Cell Disorder (SCD) is a chronic debilitating condition where new treatments and research are necessary in order to find a way to stop the suffering people with SCD experience throughout their life- span. The results of my study on the Employment Experiences of Black Women with Sickle Cell Disorder (SCD) found several alarming results that negatively impacted the life of individuals with SCD. Ten black women living in England were interviewed about their employment experiences. The interviews were digitally recorded and transcribed then analysed using an Interpretive Phenomenology Analysis method that interpreted and analysed their narratives. The results identified 5 themes. The data from the themes included some of the following negative aspects the women shared below. SCD impacted their productivity at work and limited their work and employment opportunity, the majority experienced lack of support at work and frequently experienced exhaustion and tiredness on regular basis. The majority were negatively affected by stress and anxiety at work and by lack of knowledge and understanding from employers. A participant reported ‘, I was ill constantly. Constantly in body pain, constantly having mini crises at home’. Others had similar experiences. <i>‘The negatives um, obviously living with sickle cell it’s tiring. The job’s demanding. Er, which then obviously had a knock-on effect on my health. So, I was in hospital more, I was having more crisis than usual. Or I was just getting sick, like chest infections or with my sickle cell’.</i>

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	The study also found participants described being dismissed or not getting a job because they had SCD and there were 'limits to what they can do'. They had intermittent sickness absenteeism jeopardising their jobs. At the same time, they pushed themselves to go to work even when they were ill and in pain. They were treated unfairly and faced discrimination. SCD affected participants in work and employment in many both little and significant ways. Despite some positive experiences, most of the women indicated that employment was a challenge to acquire and maintain. The narrative themes revealed profound insights into the black women's experiences. Together these results would seem to suggest that participants were able to enjoy employment when supported to do so. However, there were considerable challenges for many of the women. The research gives a more in-depth understanding of black women's employment experiences living with SCD. The worsening impact that sickle cell has over time. As a professional now retired and currently carrying out research, I have in my career worked with and have family members and clients living with SCD and have seen the devastation SCD caused in their daily life. I have experience of individuals with SCD having life changing health issues. Examples include having strokes from childhood to adulthood, blindness, organ damage, overtime shortening their life span, continuous chronic pain, - infection and many more debilitating conditions such as pulmonary hypertension - and damage to vital organs – subsequently having a lower life expectancy. Gene therapy has the potential to improve the lives of people like my participants and the millions of others affected by SCD worldwide.
6.74	My late partner died from Sickle cell in 2013 at the age of 32, leaving behind a son, who is now 12 years old. He had a number of health complications due to sickle cell but a blood transfusion he received as a child, subsequently damaged his liver (Cirrhosis). I lost count of the number of times I would have to leave work in the middle of the day, rush home or to the hospital because he was having a crisis and was home alone with our baby. He never thought he would be able to have children, when in reality he was never able to live life as a dad and watch his son grow. Not only did he have to deal with the severe pain living with sickle cell causes but he had to deal with paramedics or NHS staff who did not know anything about sickle cell, thus not knowing how to care for him, and not listen to him advocate for himself, usually because of their own racial bias. This is something he had to battle with all his short-lived life. But this is continuing to happen today in 2024. Having learnt about Gene Therapy and the possibility of it stopping the sickling of cells, I believe if this treatment were made available to those who suffer with sickle cell, it would cut down the number of hospital visits and stays for sickle cell patients, thus providing a better quality of life and free up beds inside of NHS hospitals.

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	Do not allow another child to grow up without their parent, or a family lose someone dear to them when there is a cure to prevent this.
6.75	As a member of the African and Caribbean community, I would like to add my voice to the many expressing our concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom. As other life-threatening conditions get more support, it is sad to see a condition that predominantly affects the black population again being sidelined. We are happy to put the work in if you could share with us what we need to do to keep this important therapy available.
6.76	Dear NICE, As a parent of a child with sickle cell and a member of the African and Caribbean community, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom. Paediatrician, Lead Clinician
6.77	Dear NICE Team, As a father of sickle cell patient, we were glad when we heard about UK approval of gene editing therapy for treatment of sickle cell patients without bone marrow donor match, late last year 2023, it was a relief and the best news I have ever heard in my life. But we are now very very sad to hear that the treatment was not approve for NHS use by NICE. Sickle cell disease is a terrible experience any parent will not want for his child or any loved ones in life. My son lives an unexplainable painful life almost every day. Excruciating pain, he says it's as if more than one thousand ants are biting his bones from inside at the same time. The pains are from chest pain to Tommy, waist, legs. For him there's nothing like future plan with his condition. He is at A & E almost every time, because the sickle cell crisis is unpredictable, it does happen anytime at any place. For him, there is nothing like social life, he misses lectures almost 40% every month due to sickle crisis. Because he doesn't sleep in the night, we the parents don't sleep, we all cry with him. He asks us questions every time, that, why is he living in this type of permanent pain, is this the way he will continue. THE EXPERIENCE IS MORE THAN TERRIBLE. We want to strongly appeal to NICE to reconsider their earlier decision and approve the treatment for NHS use, because the sickle cell patients too deserve the right and chance to live a healthy LIFE like everyone.
6.78	Please do not stop Gene therapy for sickle cell patients. This treatment is a lifeline to thousands who are living with this debilitating, sometimes life limiting disease.

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

Draft guidance comments form

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	Thanks, and God bless.
6.79	I am sending this heartfelt plea to the Sickle Cell Society to state my objection to removing Gene Therapy as a treatment option for Sickle Cell Disease. Thank you.
6.80	Dear Sir\Madam, I'm protesting against plan to more or less close treatment that relieves our children pain of sickle cell. It's unfair to expand treatment of HIV/AIDS caused by pleasures of sinful acts than d life of innocent babies who did not ask for it and may never live to enjoy life. Please be good Samaritans to these children and God will double your blessings.
6.81	I would like to add my voice to say how crucially important the Exa-cel gene therapy (CASGEVY) is for people living with sickle cell. I have witnessed first-hand, the extremely severe pain experienced by family members with the disease and with friends absent from school for long periods. Again, one of my relatives was a beneficiary of this therapy and has seen a dramatic improvement in his quality of life. This therapy has been like a long-awaited miracle giving young people and children with sickle cell a chance at a life without pain. I plead for the funding of this therapy and that it should be made available to all young people with sickle cell in the UK.
6.82	I am writing to lend my voice to the call to NICE to rescind their decision re banning the Casgevy Gene Therapy. This i believe is due to the non-awareness of the degree of suffering and distress people living with the condition go through. This is in addition to the loss of income survivors and carers experience as well as carers' distress. This intervention will not only go a long way in improving the quality of life of people living with the condition, it will also support their mental health and that of their family. It will reduce the morbidity and mortality and improve the wealth of persons and community. Thank you.
6.83	I would like to ask Exa-cel to kindly consider saving the lives of people suffering from sickle cell. We have families and are suffering from the results of sickle cell disorder. I feel we should not be denied to have the transplant which has a high chance of treating this condition. I have Sickle cell SS and have been contributing and working and have worked with people adults and young people doing social work. I have managed to touch people's lives and offer help where I can. An opportunity to a successful transplant will mean more lives being saved, families suffering less and a lot of contribution helping other people through working in the community and finally we (people) living with sickle cell getting the opportunity to live a normal life.

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	Please kindly consider our situations, families, and life to have access to having a transplant.
6.84	I write to register my vehement objection to removing Gene Therapy Treatment option for sufferers of sickle cell anaemia disease. I am a sufferer of this disease and already [X] years on the [X]. I have lived a lifetime of pain and will not benefit from it but please LET ALL LITTLE CHILDREN out there wherever they may be, be spared this lifetime of pain. Give them the OPTION to live well. Let Gene Therapy treatment option for sickle cell stay.
6.85	I hereby forward my objection to the removal of gene therapy for sickle cell disease for the following reasons. Cystic Fibrosis which mainly affects Caucasians and there are about 10,500 patients has 60 Specialist Centres, fully stocked with Physio, Social Care etc. A ratio of 1 Specialist Nurse to 75 patients and 511 APPROVED treatment options. Sickle Cell has 10 Specialist Centres for about 17,500 patients, little wider medial or social back up. 1 Specialist Nurse to about 400 patients and 4 APPROVED treatment options. It might not be consciously done but the optics do not look good. And don't get me wrong, I understand that the ship has sailed, and I won't be one of the ones who benefit from this treatment option. I am too old. But there is a child struggling to come into this world and lots more who are present on this earthly domain who can and will benefit. Please give them an opportunity to miss a lifetime of pain.
6.86	Good morning, I hope this email finds you well. I am a charity worker based in [X]. Upon hearing about consultations to remove gene therapy as a lifesaving option for sickle cell sufferers (they are suffering), I write to you to state the importance of what could potentially save my 9 year old nephews life. We in the Afro-Caribbean community already feel that we're often neglected/less important medically, I can tell this would literally make us feel even worse. Sickle Cell disease is a predominantly BLACK PERSONS DISEASE, which, a lot of black families have to unfortunately, lookout for when thinking about starting a family, which is traumatic enough. Then the woman falls pregnant, and she now has to stress and wonder what she's going to do if her unborn child is tested, and the test runs positive for Sickle Cell. If she or her partner have already seen the firsthand experience of the suffering, this could then lead to the soon-to-be parents making the hard decision to abort their baby. I know firsthand from my sister how that can affect you mentally, especially in her case were she already has one child with sickle cell and then to find that another is on the way with it...

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	NO WORDS! The trickle effect it has on our extended family was hard. I would not wish it on anybody. I ask you all to think deeply of all the families that would be affected by this decision if it was to go ahead. I thank you for taking the time to read my plea to you all.
6.87	Please reconsider your decision on the exa-cel gene therapy for NHS funding. Sickle Cell impacts not only the suffers but their families, employment, communities, and society as a whole. This therapy has the potential to release months of NHS resources from GP appointments for general ill health to apheresis blood exchange sessions allowing specialist to further progress understanding of this disease. Being able to offer such therapies under the world leading MHRA would allow the UK to maintain its position as leaders in the field, supporting not only the progress the CRISPR gene technology provides but giving hope to families impacted by this debilitating disease. Please permit exa-cel gene therapy for NHS funding. Thank you in advance.
6.88	I would want to express firmly my objection to the suspension of gene therapy for the treatment of sickle cell disease. It is now the sole treatment that provides patients with a fighting chance and hope for their families. Stopping it would be extremely unfair and would create the incorrect image of a sickness hierarchy. This shouldn't happen. Thank you for your great work.
6.89	I am writing to make clear my family's objection to Gene Therapy withdrawal. There is a huge discrepancy in the way in which we treat ethnic minorities and the plights that face them. It is important that this option is not withdrawn, as it will be inhumane and hugely detrimental to the well-being of those that are sufferers of this disease. I am asking that you would please do the right thing in this instant and stop the move to withdraw the said. Many thanks.
6.90	I write to oppose and object the removal of Gene Therapy from treatment of Sickle Cell.

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	As it is the funding and treatment is currently underfunded and inadequate. I sincerely hope my objection is taken into consideration.
6.91	I am writing to object to the removal of Gene Therapy as a treatment option for Sickle Cell disease. Please this is a method that eradicates pain for SC patients; stopping it will be devastating for them. Thank you.
6.92	Please keep this treatment option available to support young sickle cell patients to enjoy a pain-free life.
6.93	Please, can gene therapy be available as a major treatment for sickle cell. Please do not discontinue this life saving treatment. We should rather seek more funding for this laudable lifesaving treatment for sickle cell patients. Thanks for your anticipated cooperation.
6.94	Beyond the sickle crisis, more facts are emerging on the draconian disease sequelae & complications including irreversible Sensorineural hearing loss! Hence, no amount of investment is too much to aim at eradicating HbSS.
6.95	As a parent of sickle cell patient, we were glad when we heard about UK approval of gene editing therapy for sickle cell patients without bone marrow donor match late last year, it was a relief and best news I have ever heard in my life. We are now sad to hear that the treatment was not approve for NHS use. Sickle cell disease is a terrible experience any parent will not want for his child or any love ones in life. My children lives an unexplainable painful life every almost day. Excruciating pain, from chest pain to Tommy, waist, legs. They are at A & E almost every time. For them there is nothing like social life, they misses lectures almost 40% every month due to sickle crisis. Because of sleeplessness in the night, we the parents don't sleep, we all cry with them and they ask us questions every time; "why living in this type of permanent pain, is this the way we will continue?" We want to strongly appeal to NICE to reconsider the decision and approve the treatment, because these sickle cell patients too deserve the right and chance to live a healthy life. Thank you so much for your kindness and help.
6.96	I am suffering with pains which the doctors don't understand because they never had a patient like myself at [X] Hospital living this long with all this health issues. One of the main problems is suffering with pain. At home the only treatment I have is medication. Whilst in hospital there is oxygen which helps with my pain greatly pain relief by injections which helps with the pain. At home I think on many occasions I am going to die sometimes I have taken extra medication when I shouldn't I????

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	I keeps on forgetting I am not young anymore. I suffer with chronic pain daily and sometimes that flares up and I have to come in for pain relief and the opioids gets it under controlled. There isn't a non-opioids medication out there yet to treat the flare up of chronic flare ups yet????? myself and others are being used as guinea pigs. Please remember when we are been used and it is not working it affects us by pain. The pain gets me down very depressed I hate going out because I have a happy go lucky personality everyone thinks I am fine, but I am not only the closest people and family around me are aware of my situation. I am an inpatient at [x] Hospital at the moment so pls forgive my grammar. Why some doctors are better than others are because they listen to the patient, so the patient gets the right treatment the patient is happy and gets well faster and gets discharged quicker from hospital. The after care is just important. That hasn't been sorted out yet. The next important thing pls get health professionals who wants to work with patients with sickle cell not those who just want to be paid.
6.97	As a sickle cell warrior, I'd like to voice my concerns about the decision by NICE I have lived with this debilitating condition my whole life with one excuse after another as to why nothing can be done about it. Finally, when a real option is on the horizon for the next generation to be cured from this chronic illness it is once again being denied to us, why? Please use my voice and this email to let NICE know that I do not agree with their proposal.
6.98	I write this as the parent of a child that was able to undergo a bone marrow transplant via donation of marrow from his older brother. We are forever grateful to the NHS as this would not have been possible without their assistance. My son is one of the lucky ones and during his stay at the [X] hospital in [X] a few children lost their lives as they were not as fortunate to have a sibling that would've been a close match for the transplant (so had to gamble with their parent's bone marrow which unfortunately didn't work). This unfortunate outcome might've been avoided with the use of gene therapy and this is why we urge NICE to do the right thing here. Thank you.
6.99	Thousands of lives can be transformed and it would be an humanitarian injustice if this treatment option is removed.
6.100	I write regarding the proposal to remove Gene therapy as an option for the treatment of Sickle Cell Anaemia. Sickle Cell is a disease that affects a large number of the black community, and we deserve every chance available to live a normal and healthy life. I am opposed to this treatment being removed and would like to know why this is being proposed.

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6.101	I hereby state my objection to removing Gene Therapy as a treatment option for Sickle Cell. Sickle Cell a condition that affects mainly black has only 10 Specialist Centres for about 17,500 patients, little wider medial or social back up. 1 Specialist Nurse to about 400 patients and 4 APPROVED treatment options. Compared to Cystic Fibrosis which mainly affects Caucasians and there are about 10,500 patients has 60 Specialist Centres, fully stocked with Physio, Social Care etc. A ratio of 1 Specialist Nurse to 75 patients and 511 APPROVED treatment options. One of the most successful methods of treating Sickle Cell is Gene Therapy and you are currently thinking of withdrawing it as an option. With this treatment children born with Sickle Cell have a fighting chance to avoid a life of pain. A Ray of Hope is being given to our succeeding race. The National Institute for Health and Care Excellence should stop the consultation to stop offering this treatment for Sickle Cell. We know it is a very expensive treatment, but it is one treatment that eradicates a lifetime of pain. Please don't stop offering this treatment.
6.102	I was extremely excited when I found out there will be gene therapy for sickle cell patients in the UK. It reminded me of my housemate in university who was in so much pain every time she was in SC crisis! I am very sorry this joy is to be short lived. NICE has opened a consultation to consider withdrawal of the only hope SC sufferers have to definite cure and remission of their symptoms. There are over 17500 of such patients and are they not entitled to same care as other suffering patients in the UK I ask NICE to please think of the pain and great impact these symptoms have on the SC patient's quality of life and extend this therapy to all patients that need it. Thank you.
6.103	Please take this letter as a statement of my objection to removing Gene Therapy as a treatment option for Sickle Cell. Thousands of lives can be transformed, and it would be an humanitarian injustice if this treatment option is removed.
6.104	To Whomever This May Concern, I understand that there is a proposal in place to remove the Gene Therapy Treatment which is used for Sickle Cell sufferers. I would like to express my deepest concern in regard to this and plead that this does not take place. Sickle Cell affects black peoples more than any other race and I can't help but think that if this was not the case then this would not even be considered as an option.

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	Please think about the severe pain and life long impact of this disease on individuals and families. Please give those who are eligible for this treatment a chance at having a normal life free from pain. Please do not stop this treatment it's important. Thank you for reading my email.
6.105	I write to plead with you not to stop Gene Therapy as a treatment for Sickle Cell Anaemia. I have a sister who lives each day with this dreadful and I see the terrible pain and suffering she goes through, but I know also that Gene therapy has vastly improved the lives of others will continue to do so. As such, I implore you to reconsider and to please keep the option of Gene Therapy open and available to all SS sufferers. Thank you very much.
6.106	Please kindly don't take away the Gene therapy, this treatment helps/saves people with Sickle cells disease from a lot of pain.
6.107	Please find below my views and submission to help NICE consider how challenging it is to live with sickle cell, and how the Exa-cell gene therapy, and potential functional cure is needed. The most common symptoms of sickle cell anaemia is pain. These are mostly vaso-occlusive pain crises some of which can be acute or chronic and have a great impact on the day to day life of people like myself who live with the condition. Some of these include problems in emotional and physical wellbeing, challenges in relationships and disruption in school and work. These pain crises can be so severe and also be experienced several times in a year which result in frequent hospitalizations that disrupt the normal life of sufferers and deteriorate our quality of life. These pain crises also cause anaemia and fatigue, as well as sleep difficulties all of which make normal everyday living very difficult and stressful. The worsening impact that sickle cell has over time, is that it can lead to severe health complications including stroke, acute chest syndrome (a condition that lowers the level of oxygen in the blood), organ damage, other disabilities, and in some cases premature death. The lack of oxygen-rich blood can also damage bones, eyes, nerves and other organs, including the kidneys, liver and spleen, which can be fatal. According to reports, it has been found that Sickle cell sufferers have a life expectancy which is more than 2 decades shorter than the general population and the complications of the condition still significantly increase the risk of premature mortality. I hope NICE will consider the points I have raised before coming to a final decision.

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6.108	I am writing to add my voice to support the many who face the prospect of untold pain and disruption by the proposed removal of gene therapy as a treatment option for sickle cell. Please do not let this happen.
6.109	Please don't remove Gene therapy from the treatment list of SCD. Ridding a single life from Crisis and pain cannot be overstated. Life free of pain is priceless.
6.110	I am writing to show my objection to the removal of Gene Therapy as a treatment option for sickle cell disease. Considering the pain, it causes for those who have it and little or no funding in this area of medicine especially as it affects people of ethnic descent, it is only fair you retain the treatment. Thank you in anticipation!
6.111	I would like to state my objection to the removal of gene therapy treatment as an option to people with sickle cell disease. If this treatment can alleviate the pain of people with this condition, I believe it should be made available.
6.112	I am writing to state my objection to removing Gene Therapy as an option for the treatment of sickle cell. I understand it may be deemed expensive, but will eradicate a lifetime of pain. With so few approved treatment options for this condition. Sickle cell patients deserve a chance.
6.113	Please take this email as my objection to removing Gene Therapy as a treatment option for Sickle Cell. One of the most successful methods of treating Sickle Cell is Gene Therapy. With this treatment children born with Sickle Cell have a fighting chance to avoid a life of pain. The National Institute for Health and Care Excellence have opened consultation to stop offering this treatment for Sickle Cell. I get it, it is a very expensive treatment, but it is one treatment that eradicates a lifetime of pain. Cystic Fibrosis affects about 10,500 patients has 60 Specialist Centres, fully stocked with Physio, Social Care etc. A ratio of 1 Specialist Nurse to 75 patients and 511 APPROVED treatment options. Sickle Cell has 10 Specialist Centres for about 17,500 patients, little wider medial or social back up. 1 Specialist Nurse to about 400 patients and 4 APPROVED treatment options.

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6.114	From my understanding, one of the most successful methods of treating Sickle Cell is Gene Therapy, this treatment allows children born with Sickle Cell to have a fighting chance to avoid a life of pain, essentially a ray of hope. I understand that it's a very expensive treatment, but it is one has the best capacity to eradicate a lifetime of pain from the lives of sufferers. I know that as a sufferer myself that ship has sailed and I won't be one of the ones who benefit from this treatment option as I am too old, but there is a child struggling to come into this world and lots more who are present on this earthly domain who can and will benefit. Please give them an opportunity to miss a life time of pain and continued misery. Please do not take that chance away from them so that they too can have a life worth living. Thank you.
6.115	Please help me. I am a mother of sickle cell patient please do not withdraw gene therapy from sickle cell patient.
6.116	Appealing that gene therapy should not be discontinued for sickle cell patients. Though expensive, what can be expense in the face of a lifetime of crises and misery? Worldwide appeal for funding and research should be intensified. Thanks for providing a listening ear.
6.117	It will be a great thing to have treatment for sickle cell and thing to do for us the carrier because sickle cell is nothing to write home about, the pain is not what I will even wish for my worst enemy, the crisis, so please if there's any treatment to assist us with kindly go ahead with it please....God bless you all and thanks for the privilege for letting my voice to be heard.
6.118	As a lifelong sufferer of sickle cell disease, I have endured tremendous trauma and challenges due to this chronic blood disorder. When I heard the news about a possible cure, I was overjoyed, though unsurprised to learn it was withdrawn. Given the exorbitant cost, I knew access would be limited for the sickle cell community, who already face appalling struggles for basic care. We are in an endless battle just to get the normal support needed to manage this condition. Any progress comes only after needless patient deaths or disgusting mistreatment. Though mentally and physically exhausting, I will continue advocating until I no longer can. Diagnosed at age 3, I recently celebrated my 60th birthday, grateful for the gift of life and treatments that helped me reach this milestone. It has been an immense struggle, and while this treatment would not benefit me after the ravages of sickle cell, it could help younger sufferers before their bones and organs are damaged. In my 60 years with this condition, I endured recurrent, severe pain crises that disrupted my education and filled my childhood with hospitalizations. I also suffered pneumonia, spleen and gallbladder removal, avascular necrosis in both hips requiring full left hip replacement, kidney papillary necrosis and kidney stones, atrial fibrillation, and hypertension. If as a young child Exa-Cel (Casgevy) Gene therapy was available to me, it would have been a dream come true for my parents, family, and the entire Sickle Cell community. Sickle Cell Disease has been a lifelong struggle filled with debilitating pain, endless

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	hospital visits, and the fear that any illness could be life-threatening. The complications and traumas that come with this condition have robbed me of living a normal, carefree childhood that so many take for granted. My parents would have wept tears of joy knowing I could be cured and spared from a life of suffering. The daily agony of watching their child endure extreme bouts of pain with little they could do to help has been heart-breaking for them. My family would have celebrated knowing I could finally have the energy to play outside with my siblings and cousins without risking a painful crisis. The Sickle Cell community would have rejoiced, as this therapy would provide real hope that the next generation may be able to live full, healthy lives unencumbered by this terrible disease. Exa-Cel represents a chance at a pain-free life that Sickle Cell patients like myself can hardly dare to dream of. It offers the possibility of living unchained from the gruelling treatment regimens, isolation, and physical limitations that have defined our existence. Please give us this chance to be normal, to thrive without the shadow of suffering looming over us. We desperately need this hope if not for myself but for the future generation who are suffering and enduring an endless life of pain. Please do not take this hope away
6.119	I will like to express my unreserved objections to the proposed removal of Gene Therapy as a treatment option for sickle cell. This is already a painful and debilitating condition without the stress of limiting treatment options available. I hope this proposal will be reconsidered in the interest of individuals and families affected by sickle cell. Thank you.
6.120	I just read gene therapy is to stop? Kindly reconsider as this would expose children with sickle cell anaemia to a lifetime of pain. My humble appeal please.
6.121	Please take this email as my objection to removing gene therapy from the NHS treatment. With this treatment children born with Sickle Cell have a fighting chance to avoid a life of pain. A Ray of Hope is being given to our succeeding race.
6.122	I am writing to object to any removal of Gene Therapy for Sickle Cell Therapy. In fact, more investment is needed to fund this, more nurses and centres. Thank you.
6.123	By all means I encourage further observations into the nature of this treatment and its potential side effects, but this could be revolutionary. Considering that this disease affects

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	majority those of Caribbean and African heritage, this treatment definitely requires more support so that those, already underrepresented, can live the life they deserve.
6.124	I was diagnosed with Sickle Cell Disorder at the age of 3yrs. In the 70s there was limited information and treatment and 40 years on still not that many treatments. Sickle Cell has affected my day to day that I am envious of those who can live a normal life. I wake up each day in pain from waist down to my feet, both sides and my shoulders. Before I can do anything to alleviate the pain, I need to eat something lite to line my stomach as I was diagnosed with protein urea. I start off with either slow release 10mg morphine or 1 naproxen along with omeprazole, depending on how severe the pain is. Then I mix my laxative in water as morphine makes me constipated. I have trigger fingers, asthma, osteoarthritis and arthritis so unable to do stairs and use a cane. During COVID-19, I was diagnosed with DCIS Breast Cancer. Due to complications, I am also struggling with neuralgia and scar tissue as I was burnt during radiotherapy. The past three years I have to rely even more on family to cook, clean, help with hygiene, cut up my food and shop. All my life I had had to rely on family for support, but unfortunately, it also means I have to wait till they come to me to get most things done. As a child my dream was to become a lawyer but unfortunately my dream was ripped to shreds. Having Sickle Cell means you have to settle. Studying was difficult due to frequent crises, pneumonia in my lungs, mobility limitations, poor immune system and constant stressing because I longed for a better life. Choosing to stay unmarried and childless because I don't want to pass my illness to my child. Not wanting them to go through the emotional and physical trauma that I am living. Condemning a child to pain, suffering and death is not something I would wish on my worst enemy if I had one. As I get order my kidneys are likely to get worse and I will need a transplant, which has no guarantee as the donor registration for ethnic minority is limited, my consultant informed me last year at my appointment that I need to consider blood transfusion as I am allergic to Hydroxycarbamide, which again requires ethnically match blood to prevent antibodies. It seems that we are not being given a fighting chance at life and my heart breaks daily knowing this. I hoped for a long time that there would come a day when I would live to see a future where there would be a treatment to cure or give me the chance to live a better life. Where people would be educated and treat myself and many others with Sickle Cell as human beings. Instead, I see the world moving backwards, patients dyeing from neglect in hospitals that are not being made accountable, misdiagnosis of other diseases, being told we are drug addicts and look down on as if we are lower than insects. I wonder if Sickle Cell affected every nationally whether the rejection of the treatment would be about cost. If there's no chance of a future for myself, I am pleading for the youths and newborn babies to be given an opportunity to live. Let them be the voice that says that their ancestors never got to see how gene therapy Exa-cel made an amazing impact on their

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	future. That a cure whom many have waited for since Walter Clement Noel was first diagnose, will give them a quality of life.
6.125	I am writing this email to state my objection to the removal of Gene Therapy as a treatment for Sickle Cell. My aunt had Sickle Cell for 50 years and passed away in January of 2021. She was an amazing person who made an incredible, almost heartbreaking effort not to show her pain. But it was there. This treatment could make the lives of Sickle Cell warriors easier and more pain-free so that people like her wouldn't have to hide their pain. She fought for her community and it's only right that the people who knew and love her carry on that legacy, fulfilling her wish to help people. Removing this treatment option won't help people. Our voices and wishes will be heard. Thank you for your time.
6.126	Please do not eliminate the option of Gene therapy as a treatment for Sickle Cell Disorder. Most of those born with Sickle Cell Disorder (SCD) have so much to give to the society but are limited because SCD crises comes without warning. Gene Therapy could be the answer for some many. Not many for various reasons can go down the bone marrow route. Please do not limit the options available to eradicate SCD.
6.127	Dear Colleagues It has come to my attention that there is a plan or consultation out by NICE to withdraw Gene Therapy as an option for treating patients suffering from Sickle Cell Disease. I would like to express my objection to the removal of Gene Therapy as an option for the treatment of Sickle Cell Disease. Sickle Cell Disease affects mostly people of African origin (Blacks) and as a person of African origin, I believe we cannot afford to allow children born with this disease to go through a lifetime of pain because the treatment is expensive. I have a cousin who is 32 years old and has suffered severely from this disease. Gene Therapy is one of the most successful methods of treating Sickle Cell and this is currently going to be withdrawn as an option. With this treatment, children born with Sickle Cell have a fighting chance to avoid a lifetime of pain. I would like to appeal for a reversal of this proposed decision for the sake of the future generation of black children and others who suffer from this disease.
6.128	I wish to add my voice to the above subject matter. Please reconsider the step. Too many people are suffering from this disease and any step that can help should be encouraged.

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6.129	My daughter is 25yrs old and born with sickle cell disease. I have watched my daughter for the past 25yrs go through crucial pains that my heart breaks down. She had a stroke when she was 5yrs old and has permanent weakness on her right hand. Please do not cancel the gene therapy, as this is one hope, I pray she has to still have a normal life. I beg of you, let this treatment continue to save a lot of life and give these children a normal life.
6.130	Please do not prevent sickle cell patients from getting gene therapy to cure their sickle cell. They deserve to miss out on a lifetime of pain. Thanks.
6.131	Was sad to read about plans to remove this option as a treatment for Sickle cell. I think that this should be reconsidered and made available to as many sufferers as need it. Many thanks.
6.132	I am hereby stating my stand to support the continuation of Gene therapy as an option for patients who have such few treatment options. Why close the door, even though the treatment is expensive, there are other ways of creating awareness and raising support for those in dire need. Please leave this option open. Thank you.
6.133	I passionately object to the removal of gene therapy as an option for the treatment of sickle cell disease. Please let's give the unborn generation of people with sickle cell disease a chance to have a life free of chronic pain.
6.134	I am writing to express my strong support for the inclusion of gene therapy for sickle cell disease within the NHS coverage. As a person living with severe sickle cell, I want to shed light on the daily challenges and worsening conditions that affect individuals like myself. Living with severe sickle cell disease presents a myriad of obstacles that affect every aspect of daily life. From excruciating pain during crises to the constant fear of complications, the burden is relentless. Simple tasks become daunting challenges, and the unpredictability of the disease casts a shadow over future plans and aspirations. Moreover, as we age, the impact of sickle cell only intensifies. The cumulative effects of recurrent crises, organ damage, and other complications take a toll on our health and quality of life. Each passing year brings new challenges and limitations, further exacerbating the already difficult circumstances we face. The prospect of gene therapy offers a glimmer of hope for the sickle cell community. It represents a breakthrough in treatment that has the potential to alleviate suffering, improve outcomes, and enhance quality of life for individuals with this debilitating

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	condition. Access to this innovative therapy through the NHS would not only provide relief to current patients but also offer a lifeline to future generations affected by sickle cell. In light of the profound impact that sickle cell has on individuals and families, I urge you to consider the urgent need for accessible gene therapy within the NHS. By prioritizing the inclusion of this treatment option, we can offer hope, dignity, and a brighter future to those living with sickle cell disease. Thank you for your attention to this critical matter. I trust that you will give due consideration to the voices of those directly affected by sickle cell as you deliberate on this important decision.
6.135	I heard that the gene therapy that could save blacks and Asians from sickle cell is going to be withdrawn. I'd like to say that I'm against that decision. As a sickle cell trait person, I am very thankful to GOD for not letting me marry another sickle cell trait person otherwise my kids would have suffered. So, in any way that this email can help, I stand against its withdrawal.
6.136	I would like to lend my voice as a black man living in the UK that witnessed a harrowing experience with friends that were faced with the possibility of having babies with sickle cell. They lost a lot of babies because of this and removing gene therapy as a treatment option for sickle cell will mean many babies will come into the world infected with this. I would like to plead for this therapy to be retained.
6.137	Please respond on my behalf to recommend Exa-cel for NHS funding because sickle cell can have devastating effects. I'm 32 and have been told I have aneurysms on my brain due to sickle cell, add to that the hospitalisations, the blood transfusions and the extreme, intolerable pain that has made me consider suicide on multiple occasions.
6.138	I'm writing about NICE decision recently to not recommend funding for Gene Therapy as treatment for sickle cell patients. I have several family members impacted and I'd be grateful if you forwarded my comments as needed in support of retaining funding for this treatment.
6.139	I write to VERY STRONGLY OBJECT to your plan to end gene therapy. As you know this is a life saver for many in the Black community, so, although you might not have racism on your mind, BUT, that's exactly what it looks and feels like. So, I join ALL Black folk up and down this land to say VERY LOUDLY and INSISTENTLY, don't take this life saving therapy away from us. Thank you.
6.140	I would like to make you aware of my very strong objection to the removal of Gene Therapy Treatment as a Sickle Cell Treatment Option. I feel that this action does not recognise the extent of pain and discomfort and the corresponding impact on the lives of and overall wellbeing of Sickle Cell sufferers.

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	Additionally, I feel that there is currently not enough being done within the NHS to support the treatment, care and overall support of Sickle Cell sufferers. The removal of this option would be a further slap in the face of the sufferers.
6.141	I have lost more than 4 members of my family to sickle cell related issues. I have a daughter & nephew who suffers from sickle cell. I strongly object to the removal of the gene therapy that would help thousands of sufferers. Please please please do not remove the Gene therapy for sickle cell disease. It is the lifesaving treatment for this extremely Painful condition. Do not take away hope from these patients It will be cruel to do so!!
6.142	I hereby strongly object to the removal of gene therapy as an option for the management of Sickle cell disease by NICE. Sickle cell is a life limiting disease which leads to a lifetime of pain for sufferers.
6.142	To Whom It May Concern I have witnessed over many years the plight that my dear relative, my warrior mentor has gone through over the years due to the painful impact Sickle cell has had on her life. I applaud the nurses and doctors who have helped her through a succession of sickle crises, blood transfusions, brain tumours, kidney failures, kidney transplant, gland removal and further surgery to help with bone loss. Sickle cell ravages the body and whilst my relative has persevered through bad times it would be inhumane to allow any other child or young adult to go through such difficult times due to lack of funding for a procedure that could improve the lives of many individuals. Developing and funding this pioneering procedure, in the long run will help to reduce costs as it will provide independence and a quality of life for individuals who wish to thrive and offer more to the community. There are approximately 15,000 people suffering from this blood condition in the UK but more than 100,000 in the US and 20 million worldwide. Funding Exa-cel would surely help place the UK further on the global map as one of the scientific leaders in the world that not only actions change but is also empathic to inclusivity and the future generation. ‘Nice be Nice, sickle lives matter’
6.143	As a mother and sole caregiver to a 13 year old girl battling sickle cell disease I want to say that the impact of sickle cell on the sufferer, the caregiver and the entire family is

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	unequalled both physically, psychologically and financially and the fear of mortality and a vague outlook on the future is traumatizing. I wish to appeal to the NHS (NICE) board to kindly see the urgency and need to consider the Exa-cel treatment for children 12 and older people living with this emotionally devastating and physically destructive disease. I wish to thank everyone working towards making this remarkable and lifesaving process a reality.
6.144	Most of you know the trauma of being a Sickle Cell patient I myself have sickle cell resulting in hip replacements as well as having to endure the pain of a sickle cell crisis over many years having been injected with morphine pethidine and cyclizine as part of my health care package to recover when I have a severe moment when I need hospital attention...I am now 65 almost and have lived a successful life in my time of many interruptions due to the sickle cell disease and failing health issues over the years. I am writing in support of the new treatment which is now being withheld by NICE...I am in support of the work that has been done in helping sickle cell clients in the future with the gene therapy that has been discovered to alleviate the sickle cell gene it sounds like a dream but too late for me why I am writing because I am supporting this new treatment as will renew life for those who can go ahead and have the treatment it will give them much more then it gave me and I do hope that you look at the decision again to not use this treatment I would think that if it was at risk of end of life then the treatment is not suitable. However, from the research I've done myself it does look as if this new treatment of deleting the gene of sickle cell would have a great impact on our quality of life. I personally have missed out on so much in life that I could have achieved with better health and better health practises. I do hope that the decision can be looked at again and a more successful decision is made for so many others who do need and can benefit from this treatment and for it to be administered successfully. I am a mother and grandmother to four persons who are also part of my journey and also been let down on having their future disrupted having to deal with the issues around sickle cell disease and the difficulty of losing family members to the disease. Friends of mine who have had children and lost their children to sickle cell way too soon needs this. That's why I feel it's important for our voices to be heard on such a delicate subject with such dire consequences. I do hope that in some way my words can be for the betterment of a decision change that can help with the call for a treatment like what's been offered and be available to everyone. I do hope that in some way my words can feed the betterment of a decision. That can help with the call for a treatment like what's been offered I'll be available to everyone. Signed in support.
6.145	I have a very rare form of Sickle Sell Disorder, only one clinical at a well-established [X] teaching hospital had ever seen it and that was 3 years ago when I was an inpatient

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	struggling to fight off an infection. Each year I battle with the same symptoms and the medical team are still unaware why. If we are indeed to be a society of 'levelling up' then why would anyone object to a treatment being available for Sickle Cell Sufferers. I fully support the Exa-Cell treatment. From a voice who knows what it is to live with SC. Thank you in advance.
6.146	Quality of Life is very important and a year free of hospital visits could dramatically improve someone's life. It should be cost effective if it is made free to those with the very severest SCD VOC'S AND/OR "greatest expectancy of improvement", but really as we as African heritage & Mediterranean people are an ethnic minority in the UK how many people would they really need to treat to claim it is "not cost effective?" It is an ethnic specific disease so to refuse treatment immediately creates health discrimination ...as well as saying or assuming older people with SCD would die anyway.... So that discrimination is against age.
6.147	I have Sickle Cell disease and my whole life has greatly been impacted by this inherited disease. Firstly, I had lost 3 siblings to Sickle cell crisis. I personally have had 3 strokes, I have regular painful episodes, and very low Immunity. I am very susceptible to infections and fatigue. Due to Sickle Cell, I have developed other life-threatening problems such as retinopathy, Sickle cell neuropathy, asthma, HBP, spleen removal, chronic kidney disease, etc. I am not able to work or socialise. My emotional psychological and mental health is greatly affected. Sickle cell affects my life and those of my family, friends and community. I spend so much time in and out of hospital that my life revolves around that. My family are anxious all the time whenever I show any sign of any painful episode. I am always in hospital on a weekly basis attending appointments for blood transfusions and blood exchanges and various treatments. Ever since I had the understanding about my condition, I have been praying for a cure. Now that prayer has been answered. It would be a shame and a great crime if this life changing treatment and possible cure is not made available on the NHS. The need and urgent desperate urgency for the adoption of the life changing gene-therapy for thousands of people affected by this dreadful disease cannot be over-emphasized. The lives of thousands of people living with Sickle Cell and their family and loved ones will be positively improved and changed.

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	Adopting Exa-cel (CASGEVY) gene-therapy to be made available on the NHS would give me and thousand others a new lease of life. Thank you.
6.148	I write as a concerned husband, friend and partner of my wife who is a sickle cell patient. The need and imperative for the urgent adoption of Exa-cel (CASGEVY) gene therapy for the treatment of sickle cell disorder cannot be overemphasized. Currently, my wife like other sickle cell patients is faced on daily basis with diverse social, health and psychological issues as a result of the sickle cell ailment. In terms of health, sickle cell is associated with painful episodes(sickle cell crises) and other serious complications such as life threatening infections, acute chest syndrome, anaemia (resulting in tiredness and shortness of breath),lung , kidney , spleen and liver damage, avascular necrosis (death of bone tissue), blood clots, dactylitis (hand-foot syndrome) fever and stroke. Overall, the disease impact negatively on life expectancy and mortality. On the social side, she is incapacitated by the sickle cell condition to get regular job as well as maximize her full potential social interaction as a result of the condition and other associated effects. I strongly appeal for the urgent adoption and implementation of the gene therapy treatment to sickle cell patients to improve life expectancy, improve social and economic impact as well as reduce or eliminate overall health costs by these individuals, family members and the government. Thank you for your consideration.
6.149	I really cannot understand why this is being delayed. If lives can potentially be improved/ saved, then I believe this should proceed. Give the sufferers and their relatives/friends a chance please, NICE.
6.150	I am fortunate to only be a carrier of the sickle cell gene. However, I know people who have SCD and know they suffer on a daily basis. What many don't do and maybe they should, is go to hospital every time they are in pain. Many I'm sure only go when they are in crisis. It is I find a trait of the black community to soldier on for as long as possible before seeking help. This goes against us, as statics can only show how many times someone has been admitted to hospital/ visited the GP/missed days of school. NOT the days they are sitting in work or school unable to be effective at work or unable to concentrate on what the teacher/lecturer is saying.

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	NOT the days they are unable to look after themselves, not the worry that parents/carers have for the future if they are not around to care for them. They don't however, let this limit their aspirations. Those I know are pushing forward with their education and career goals despite the pain. Imagine if they didn't suffer on a daily basis. The extra that they would contribute to society. The less they would be in hospital, off school and work. Unfortunately, my sister lost her university friend to SCD. A life that with this treatment could have been saved. With so few that can be effectively treated with the current options available, I find it heartbreaking to know that there is an effective that could be made available on the NHS. Please make this treatment available. Yours faithfully.
6.151	I would support the provision of this therapy to people who suffer this disease. It is life-impairing and life-limiting, The fact that it only affects people of black or mediterranean ancestry open's NICE'S refusal to a suspicion of racism, I hope this is not the case. I do not have sickle cell, but my late father spent his life working on it.
6.152	I am campaigning for Exa-cel to be made available to Sickle Cell patients just like the following expensive drugs have recently been made available for certain groups of patients like: • cabotegravir and rilpivirine for • Kafrio I hope NICE will change their mind.
6.153	NO ONE CAN EQUATE MONEY WITH CHRONIC SUFFERING AND LIFE!!! The effects of Sickle Cell Disorders is neither HIDDEN nor OBSCURE. Any Measures to REDUCE/ELIMINATE the effects of this Genetically Inherited Disorder, will make a tangible and life enhancing difference to Sufferers and their Families Imagine being freed of the Effects of Sickle Cell Disorders 1: Pain free life 2: Ability to get on with your life, make plans for life and living, 3: NO SUDDEN NEED FOR HOSPITAL ADMISSIONS 4: No Chronic Disabilities, results of chronic Sickle Cell Crises affecting every / any organs in the body, often times resulting to loss of life 5: The emotional impact on Sufferers and their Family of Relatives and Friends

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	IF FINANCE IS AN ISSUE, think and assess the impact it would have on the NHS and the COMMUNITY in General. 1: Reduced Hospital Admissions 2: Reduced Extra Care often needed to help Sufferers and their Families 3: A Boost to School life and Work force The above will SUBSTANTIALLY REDUCE THE EXPENSE on the NHS.EMPLOYERS and the COMMUNITY Lastly, the "Proof of the Pudding is in its eating"!!! Till the treatment is made AVAILABLE and OFFERED to SUFFERERS, NO ONE CAN RIGHTLY SAY, IT IS INEFFECTIVE. TO WITHOLD TREATMENT WILL BE IMMORAL AND UNETHICAL!!! Trusting and hoping that the RIGHT DECISION, TO OFFER TREATMENT, will be made.
6.154	I would like to express my profound shock in reading about NICE not being certain about the severity of Sickle Cell, it's a statement that I do not agree with this statement, sickle cell is a horrible genetic disease which sufferers do not ask for, they are essentially lumbered with it and have to live for the rest of their lives with a debilitating disease, if NICE wants to know how severe sickle cell is, they just need to see someone in a sickle crisis screaming in pain or in my case being in so much pain that I cannot even cry about the pain I am experiencing. I believe this new therapy should be given the green light without any further hesitation, sickle cell sufferers have to pay the full whack for prescriptions because twice parliament have voted against affording sickle patients free prescriptions, however if you have type two diabetes you can get all the medication you need without paying for it, cystic fibrosis patients receive free NHS prescriptions, I cannot help but think this affects an awful lot of ethnic minorities therefore it's not high up on any body's high list and it certainly shouldn't be the case, I am an adult with sickle cell, I am experiencing organ damage, my body relies on other people's blood donations through regular exchange blood transfusion to keep healthy for a mere seven weeks, the down side to this treatment is iron over load and therefore have to wear Desferol three times a week in my stomach for twelve hours a day three times week, a new therapy if not for me but for younger sickle patients is the least NICE can do for these youngsters. It should be a given not for sickle patients to beg for new treatments.
6.155	Dear Committee members, My son has sickle cell for 36 yrs, he has had 3 strokes, an aneurysm in his brain and has been on exchange blood transfusions /top up since age 3 yrs which we are grateful for, and he has very high ferritin level due to his treatment. Watching our son everyday with this condition is devastating. When the news of Exe-cel came we were very happy, but we realised that he will not be able to have it because we cannot afford it but when we had that the NHS is ready to offer it we were overjoyed that our son's suffering is coming to an end very soon and he can leave a fulfilled life free of pain. PLEASE I AM APPEALING TO YOU IN THE NAME

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	OF GOD to offer this treatment to all sickle cell on the NHS to help them achieve their full potential in society. Thank you very much. Yours sincerely
6.156	I am the mother of a teenage boy who has sickle cell. My son, like many other boys his age he loves to play sports and take part in extracurricular activities with his friends. Being a teenager in current times is a challenge for all but with the addition of such a serious condition like sickle cell, life has been extremely challenging. The excruciating pain that my son has to endure during a crisis is heartbreaking. There is nothing worse than watching your son in pain and not being able to stop it. As parents of a child with sickle cell we have been proactive in our research to try to find ways to reduce the number of crises our son has and have always taken extra precautions. We spend a lot of money on monthly supplements and foods to support a healthy lifestyle but no matter what we do there is no avoiding the painful crisis attacks. For the last three years that we have travelled to Europe for our summer holiday, my son has had a crisis each time and spent 90% of each holiday either in hospital or in pain in the hotel room. Due to high levels of stress and anxiety as a result of this, my son is no longer afforded the luxury to look forward to trips and instead now has a period of wetting the bed before trips. One area that I don't think is given enough consideration is the impact on mental health for those who have sickle cell. Many times my son has missed out on school trips, football games and school. He also has to deal with ongoing comments and remarks from his peers about his condition which is emotionally challenging. There is also the long term trauma that needs to be considered which will impact my son into adulthood and although, as parents we will do all we can, there is undoubtedly going to be more of a need for mental health support. My son also has a passion for performing arts. He has had to miss out on many opportunities, such as travelling to Australia for a high profile show. This adds to the impact that sickle cell has on being able to live life to its full potential. The condition doesn't just impact the person with the condition. It impacts the whole family and anyone close to the person. We also live with constant stress and anxiety, never knowing when the next crisis will happen. I have personally been impacted financially due to having to take unpaid time off from work to care for my child. I have also been threatened with disciplinary action for taking time off of work to care for my child and missed out on career opportunities. I would do it all again as my child's wellbeing is of the most importance, but it doesn't take away from the challenges we have faced as parents. The news of exa-gel gene therapy was like a shining light of hope for me and so many who have to deal with the condition. This will generally change the lives of so many! I

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	have often worried about the kind of life my son will have as an adult and the news of the new treatment gave me hope. I understand the cost of the treatment is high, but when considering the cost to the NHS to properly care for someone with sickle cell throughout their life as well as factoring in the mental health for all linked to sickle cell it is worth it for all those concerned. Sickle cell disease has historically been underfunded which has unnecessarily negatively impacted patients. We are finally in a position to make things right and provide a life changing therapy and I would hope to see that our voices have finally been listened to and that there is a genuine commitment to help, like the NHS does for other blood disorders.
6.157	I'm writing to extend my support for the Exa-cel Gene Therapy to be approved and funded by the NHS in the UK. I've a one year old son with the condition and I hope one day he can get a cure for this challenging sickness.
6.158	I would very much like to participate in the consultation of the new hopeful treatment of Exa-cel for the sake of the long term suffering Sickle Cell Warriors such as my son and sister whom I have witnessed spend most of their lives in and out of hospital on a regular basis. • It totally affects their lives immensely, wanting to work and not being able to live a normal life from the time of birth till now, has been an incredible burden on both my son & sister & my immediate family members it has been absolute torture. • This has and still has an adverse effect on their well being to the point of falling into depression, both my son and sister's eyesight being impaired and having to have not just a surgery but surgeries with no guarantee to have it fixed... My son is still undergoing this. He hasn't been able to work due to his lack of confidence, excruciating pain that arises at unexpected times, the mental imbalanced state of mind it actually places them in and being turned down time after time when applying to get some sort of help through the government, i.e. PIP due to lack of work and constant illness as well as the everyday pain they have to withstand. • This ordeal and disease has been incredibly life threatening to the point of their HB being extremely low and not knowing if they'd get through another day whilst enduring the life threatening pain. I believe it would be incredibly wrong, inhumane, cruel and absolutely absurd to deny them a normal life when there lies an answer and solution to all their misgivings, mental and wellbeing and pain since birth to lead and live and have a happier healthier lease of life. This should honestly not even be a negotiation; this is precisely why time and effort has been invested in creating a cure to finally aid their suffering by VERTEX. I sincerely do hope and pray this is the case.

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	Thank you for the opportunity to be given a voice of reason in which I hope will be taken into absolute consideration and heard. PS I hope this will be totally documented.
6.159	To whom it may concern, I have had sickle cell since I was a child. I have removed my spleen, my gall bladder, I have had a total hip replacement. I have a had a pulmonary embolism. I am 37 years old. I have been through so much chronic pain. I don't know how to explain it. I am requesting support for sickle cell disease because it's a very rare health condition. People think it's not that serious, but it is a life-threatening condition and it had ruined my life. Please try to understand our situation and support us as much as possible. Thank you.
6.160	I am writing in support of the sickle cell society for a reconsideration of NICE rejection of Gene-therapy treatment for Sickle Cell Disease (SCD). sickle cell disease (SCD) like cystic fibrosis (CF) are both significant genetic disorders, albeit with different prevalence rates and impacts. SCD in the UK, it is estimated that there are around 15,000 people living with this life limiting disease, compared to CF ~ 11,000. SCD impacts a younger generation who should be economically contributing to society. SCD diseases significantly impact the quality of life and life expectancy of affected individuals. SCD causes severe pain episodes, organ damage, and complications such as strokes, while cystic fibrosis primarily affects the lungs and digestive system, leading to respiratory issues and malnutrition According to estimates, the annual cost of treating an individual with cystic fibrosis can range from £30,000 to £100,000 or more, depending on the severity of the disease and the specific treatments needed whilst according to a study published in the journal "Health Economics Review" in 2020 estimated that the annual healthcare costs for managing SCD in the UK ranged from £7,862 to £13,414 per patient, depending on disease severity and age group. This disparity in healthcare costs between 2 genetic diseases should evaluated to approve gene therapy for SCD. Alongside the fact that SCD affects Black communities who are already impacted by the systemic racism that exists in the UK healthcare system. I suggest that NICE committee members to the recently concluded Blackhealthsummit24 which highlighted the disparity in health outcomes for black patients. While there are treatments available for SCD, they primarily focus on managing symptoms and complications rather than addressing the underlying genetic cause. However, recent advancements in gene therapy voxelotor and Casgevy offer promising avenues for potential cures or significantly improved treatments.

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	Highlight the significant burden of SCD diseases on affected individuals and their families, despite existing treatments. There is the lack of effective cures or disease-modifying treatments for SCD. Gene therapy has been approved as safe and clinical useful by MHRA to give an example here MHRA authorises world-first gene therapy that aims to cure sickle-cell disease and transfusion-dependent β-thalassemia - GOV.UK (www.gov.uk) to address the underlying genetic cause of SCD, offering the possibility of a cure or significant improvement in symptoms and quality of life (this can not be over emphasised for sickle cell patients and their families) Cost-Effectiveness: While gene therapy treatments may initially come with high costs, it's essential to consider the long-term benefits in terms of reduced healthcare utilisation, improved productivity, and enhanced quality of life for patients. Conducting cost-effectiveness analyses can help demonstrate the value of investing in gene therapy treatments. Ethical Considerations: Highlight the ethical imperative to provide access to innovative treatments that have the potential to alleviate suffering and improve outcomes for patients with SCD. Global Leadership: The UK is world renowned for being in forefront of medical innovation and to demonstrate leadership in supporting cutting-edge treatments like gene therapy, please take the opportunity to re-evaluate the decision not to support gene therapy for SCD and make not an economic decision but a wholeness of healthcare provision for SCD patients' and families. In my daily job, I see the significant impact that SCD has on the wellbeing of our patients. I kindly request and plead that The National Institute for Health and Care Excellence (NICE) to support gene therapy treatment for sickle cell disease.
6.161	Yet again NICE want to pull the plug on another Sickle Cell related potential drug that will potentially help Sickle Cell Disease sufferers. This seems to be an ongoing issue with NICE, or is it purely that Sickle Cell Disease does not affect the white population of the UK? NICE pulled the licence on Crizanlizumab, another drug that was determined questionable for use on Sickle Cell patients. I was taking this drug for 19 months and I had never felt as well on this drug in my entire life (I'm 60), and surprise surprise this drug was abruptly stopped in January 2024! I unfortunately believe that due to the fact that Sickle Cell Disease is a ethnic minority related issue for NICE/NHS/GOVERNMENT, and that tells the tale! "No one is listening" yet again raises its head for any person of colour that has a non-White medical problem. Lip service, then NICE will shelve it. CRIZANLIZUMAB was the first Sickle Cell drug in 20 years! Major hullabaloo on launch, 3 years later licence no longer supported, regardless of how well that drug was doing for Sickle Cell patients!

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	The same will happen to Exa-cel Gene Therapy and another costly drug that will provide Sickle Cell patients (circa 17000 UK patients) any hope of any respite from this abhorrent disease. I'm 100% certain that if Sickle Cell affected as many Caucasian patients as possible a cure would have been found by the year 2000! The "no one is listening" campaign had it spot on, alas, no one cares because we (Sickle Cell Disease sufferers) are the wrong colour skin to be listened to or be cared about by NICE or our government.
6.162	We would like to add my voice to this cause as parents of an 18 year old daughter who has been impacted by Sickle Cell Disease (SCD) negatively since her diagnosis at the tender age of 7 months. Over the years, she has lost lots of time in school, has spent countless hours/days in the hospital and in doctors' appointments. She is currently on regular Red Cell Blood Exchange transfusion, travelling outside her town every 5 weeks to the nearest hospital - she needs this to keep the sickled cells at bay, consequently avoiding painful crisis and subsequent hospitalisation. We are adding our voice to this cause because there is some evidence in some studies of the efficacy of gene therapy in chronic conditions which includes SCD. We understand it is not for everyone, but for those who may benefit from it, let it be made available. We believe the overall benefits of an improved and quality of life in individuals living with SCD including its' impact on their families have the potential to outweigh the initial cost implications of this medical treatment on NHS in the long run. As affected families and communities, we will be grateful for a favourable consideration by NICE to allow NHS funding for this treatment. Many thanks
6.163	Could you please forward my support to keep Exa-cel Gene Therapy to Nice. It will be very nice if they can allow us have access to this therapy. I have a one year old son who was born with Sickle cell disease and we are very concerned about his health condition.
6.164	I am writing to strongly advocate for the Exa-Cel Gene Therapy treatment. Sickle-cell is a severe disease that affects carriers more than people know. The awareness surrounding the severity of sickle is nowhere near as understood to the level it should be, with some medical practitioners not considering how painful it is leading to inadequate treatment. And it saddens me how overlooked this disease is. A sickle cell crisis can be brought on by stress, so when a sickle cell patient has to explain to a practitioner their pain and tell them how they are normally treated (with some patients not even being believed) it adds more fuel to the fire, making the crisis more unbearable than it already is. The pain felt during a sickle-cell is one that I can't describe as anything but agonisingly and extremely painful. The pain can occur anywhere in the body and can last for weeks resulting in hospitalisation, myself spending up to 6 weeks in hospital at times. The disease has many triggers which those with sickle cell have to be cautious of such as swimming and things out of our control like cold weather where we wrap up warm. Too much exercise can also trigger a crisis. Therefore, sickle cell significantly limits the quality of our life and dictates how we can live it. Even with all the precautions we take, a sickle cell crisis can still come on for whatever reason.

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	The amount of school missed because of sickle cell puts us at a disadvantage, while it can also affect our concentration as it makes us tired also massively disadvantaging our education. Sickle cell comes with many major complications as well, including a stroke (due to the sickle cells blocking blood flow to the brain), pulmonary hypertension, organ damage etc. Among the complications, sickle cell gives us a shorter life expectancy. The disease can also take a heavy toll on mental health not just for the carriers but the parents and carers who are woken up to the sound of their sons/daughters screams and cries in the middle of night watching them suffer in excruciating pain and putting their life on pause to be with their child for weeks in hospital to witness the agony. This can happen at any given moment. There is a 2013 study that showed people with sickle cell anaemia (SCA) had an average life expectancy of 42 years for women and 38 years for men. The study even suggests this is likely due to lack of access to quality healthcare. All of the points that I have made are to show why Exa-cel treatment is desperately needed for the 17,500 people with sickle cell in the UK. I implore you to implement this treatment to provide at least a chance for a better life for every person that carries this neglected and dreadful disease.
6.165	I've taken Hydroxyurea since 2015. Before I started it, I was having 2-3 sickle cell crisis a year and had 2 hospital admissions over a 3 year period. This was probably the worst it had ever been, and it appeared to be triggered by the stress of being a junior doctor. Since then, I have a blood test every 3 months to monitor my white blood cell count. Hydroxyurea can lower white bloods cells which are important for fighting infections. The dose has to balance not lowering my white bloods cells too much but still be strong enough to prevent me having sickle cell crises. Since I've taken the Hydroxyurea, I've still had crises, but I've been able to manage them all at home with moderate opioid tramadol. Living on hydroxyurea isn't ideal. I stay healthy because I'm disciplined but if I wasn't I'd be a lot worse off. If you offered me the chance to be able to experience true freedom, I would take it in a heartbeat. When you've lived with sickle cell your whole life you take for granted adaptations you've made to survive. You get used to a quality of life that would be considered restrictive by normal people. You accept the futility of complaining about what can't be changed and just get on with it. I'm simply saying that how I rate my quality of life doesn't correlate with the reality of it. In reality, if I was cured of sickle cell my life would change significantly and it's difficult to conceptualise that for someone looking from the outside seeing an apparently healthy person. I've really just repressed a lot of the sadness I felt for the loss of activities and experiences that bring me the best quality of life. I feel like at this point along my personal growth journey my confidence and outlook has improved so much. It's like I know I can do anything I set my mind to but at the same time I can't. Sickle cell hangs over me like the sword of Damocles.

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6.166	It was a joy when my family heard about the cure for sickle after praying for this for a long time and was waiting for it to be approved. Such a disappointment when I heard it's not going to be approved by NICE. Having this disease is a big bother to the person and the entire family, stress, fear, panic of the unknown is rife in our everyday life. Less assistance has been given in this area and NICE has to rethink their decision, everyone has the right to live a good life and giving a cure to one is very important. Thank you.
6.167	Please let NICE APPROVE the exa-cel therapy for sickle cell disease... because the pain experience during crises one cannot explain. Sickle cell crisis is delaying my achievement.
6.168	This is unfair and discriminatory. Sickle cell is always lagging behind in care, medication, government services etc. First you removed DIAMORPHINE, which worked well with sickle cell pain and now this. Hope it's put into consideration.
6.169	Here is my response to NICE: • This new therapy will save lives. • It will provide relief for families knowing that their loved ones suffering from Sickle Cells will have a good quality of life. • Suffers will live with less pain and make them independent most of the time. Please put my consideration forward. Thank you.
6.170	This email is in response to the request for information to support the consultation underway by NICE for gene therapy for sickle cell. My 9 year old daughter has sickle cell and was diagnosed in utero. From the beginning, we were extremely worried about how this would affect her day to day life. It continues to be a real challenge for our family, and I have put some details below to support this: * Over winter months, she is not allowed to play outside at school as the weather is too cold. Instead, she sits in a classroom with 2 or 3 friends to undertake creative activities. We worry that she is missing out on key social interaction time and exercise, but the school cannot provide someone to monitor her constantly at break or lunch times. Similarly, outside of school time, we avoid being outside for long periods of time in winter months.

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	* We often have to buy expensive thermals, jumpers and outer wear for her in the winter months. Cheaper outer wear is not warm enough so we often end up spending more than we would like or can afford to. * She has to ensure she is well hydrated throughout the day. At school she has an alarm that goes off that reminds her to drink and teachers log her intake in a booklet that comes home every day. If she does not hydrate well enough, she ends up in crisis and at hospital or with sore joints at a minimum. * She has had monthly blood transfusions for a year. This means that she has 1-1.5 days off school every month, missing out on both her education and social interactions. These occasions can be quite traumatic for her as it has become increasingly difficult for the team to find a suitable vein. * She has had 3 episodes of spleen sequestration, all of which have been emergency situations. 2 of these happened whilst we were 30,000ft in the air on a plane. She spent a week in a Moroccan hospital instead of on holiday and the other time we thankfully had the foresight to pre book oxygen for her. It is terrifying being halfway across the Atlantic and realising your child is seriously ill. We now have to pre book oxygen whenever we go away and not all airlines offer this. Some do, others do so at a cost, and some do not offer it to children at all. * She has had her spleen removed due to the spleen sequestrations. This was a very traumatic experience for her to go through and has left her scarred for life and at an increased infection risk. * Multiple hospital visits and stays have an effect on the whole family. Often, only one parent can stay in the hospital with her, and we have had to pay ludicrous amounts in hotel stays when the situation has called for it (Great Ormond Street and St Mary's stays when we were away from our home hospital due to the severity of the situation). * She has a weak bladder and still uses pull ups at night. This means that she is unable to have sleepovers at friends houses like other 9 year olds. * She has to be admitted to hospital every time she has a temperature as her hb has been known to drop from 72 to 27 in a 24hr period. * Aside from the obvious trauma, missing school, missing work, financial implications above. I'd like to point out the emotional turmoil and stress that this has put on myself, my husband and our eldest daughter. I have had to seek out therapy twice over some of the emergency situations she has been in and to this day struggle to deal with the guilt I feel over 'giving her' this condition. A safe and accessible cure for sickle cell during my lifetime is something that I wish for every day.
6.171	Yes, I agree with this treatment to go ahead.

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	I have lost 5 siblings & a niece with sickle cell disease. Although I don't have it myself, I believe this treatment will save a lot of unnecessary pain & suffering in the black community.
6.172	Dear NICE, As a member of the African & Caribbean Community, and more importantly a carrier of Sickle cell Trait which means I carry the Gene that causes Sickle cell Anaemia. I am writing to you to state how disappointing it is to hear that NICE have opted to stop the availability of gene editing therapy for Sickle cell patients in the United Kingdom. The majority of my immediate family are also carries of this gene which means any children we conceive, if partnered with another carrier will more than likely develop the full blown symptoms of Sickle Cell which is very painful & distressing for the patient and family, this effects mainly individuals of African and Caribbean descent. Also, Black people are already classed as 2nd class citizens within the health hierarchy this will just add yet more poor health outcomes across a range of conditions. Gene therapy offers an amazing approach to treating Sickle cell disease and could at some time in the future eradicate it entirely. This therapy could modify the stem cells to produce healthy cells as with blood Cancers like Leukaemia. As a mother and Grandmother of 9 grandchildren I implore NICE to please reconsider their decision in regard to the gene therapy relating to Sickle cell disease.
6.173	I would like to voice my strong opposition to the plans to stop the provision of new gene therapy to help the suffering of sickle cell patients. My 26yr old daughter has been living with sickle cell anaemia her whole life and the detriment to her quality of life cannot be underestimated. ○ She has to deal with so many issues we take for granted on a daily basis, including regular crises, constant tiredness, period pains, and of course the fear of the unknown for her future. ○ The deterioration of her organs over time including her liver, and eyes. ○ Of course, her life expectancy is so much less compared to other young adults her age, having already been through so many severe crises where I felt she wouldn't survive. Please do all you can to ensure the gene editing treatment can be made available to sickle cell patients.
	Sickle cell disease is a very severe, incurable, genetic condition with damaging organ damage and pain with cost implications to the NHS greater than thalassaemia untreated. Gene-editing provides a curative approach, which should get even cheaper in time, with

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	further iterations of the technology, therefore bringing about cost-benefit to the NHS and lifesaving changes for the individuals who prior had sickle cell disease.
6.174	As we navigate through the critical phase of advocating for Exa-cel (CRISPR) therapy for sickle cell disease, I want to express my deepest appreciation for your unwavering commitment to this cause. Your dedication to amplifying the voices of those affected by sickle cell is commendable, and together, we can make a tangible difference in shaping the future of treatment accessibility. 1. The Significant Negative Impact of Severe Sickle Cell on Daily Life: It's imperative to underscore the profound challenges that individuals with severe sickle cell face in their daily lives. From debilitating pain crises to limitations in physical activities and social interactions, the impact is multifaceted and deeply disruptive. By conveying these lived experiences, we can provide crucial insights into the urgent need for effective treatment options. 2. How Sickle Cell Worsens Over Time: Sickle cell disease is characterized by its progressive nature, with symptoms often worsening over time. Chronic pain, organ damage, and increased susceptibility to infections are just a few examples of how the condition can deteriorate as patients age. Emphasizing this progression underscores the necessity for proactive intervention to mitigate its detrimental effects on patient well-being. 3. The Effects of Sickle Cell on Life Expectancy and Mortality Risk: One of the most sobering aspects of sickle cell disease is its impact on life expectancy and mortality risk. Studies have shown that individuals with sickle cell disease have a significantly reduced life expectancy compared to the general population, with complications such as stroke and organ failure contributing to increased mortality rates. This stark reality underscores the critical importance of access to innovative therapies like Exa-cel in improving patient outcomes and extending life expectancy. Please can you consider continuing or reducing the funding instead of ceasing it. Please. Thank you once again for your steadfast dedication to this vital cause. Together, we can drive meaningful change and pave the way for a brighter future for sickle cell patients in the UK.
6.175	<u>We must have access to Gene Therapy for the treatment of SCD.</u> This is a miserable condition to live with and at the moment there is no cure, no adequate treatment and many times a horrific condition made worse when you end up in A&E in severe pain and are assumed to be a drug addict because of systemic institutional racism and even in 2024 you have to justify your pain relief. SCD is the commonest genetic condition in <u>British people</u>, yet it gets far less research compared to rare conditions like Cystic Fibrosis as cystic fibrosis a condition that affects white rather than black Britons.

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	Gene therapy may appear to have a large upfront cost but compare that to the cost of a lifetime of blood transfusions, hospital stays, outpatient appointments, renal dialysis, joint replacements, medication and repeated work and school absence and you will see that denying the treatment because of cost is a false economy. In addition, the population of SCD patients who would qualify for this treatment is small so therefore the cost would be minimal compared with treating conditions such as diabetes or cardiovascular disease or some cancer treatments. Having SCD is no life, you live in fear of the pain and are completely demoralised by it. It limits your life chances in every aspect of work, personal social life and financially. This is on top of all the other challenges even healthy black people face. With holding this treatment can be thought of as adding to the discrimination we already struggle within day to day life. If Kate Middleton or King Charles had SCD this treatment would not be denied them. Denying funding for Gene Therapy is a gross lack of insight in understanding the life long burden that is Sickle Cell Disease.
6.176	I have worked in sickle cell psychology services for 24 years and am extremely disappointed to hear the decision from NICE. Severe SCD has a significant financial burden on the NHS and the economy as well as a significant negative impact on individual's quality of life, mood, daily functioning and relationships. It also has an impact on family members. The impact of SCD worsens over time and reduces life expectancy. It is important to consider the role of racism in decisions that are made about people's health care and whether the same decision would have been made if the condition affected a white population. Exa-cel gene therapy is a real opportunity to offer patients a cure and it is imperative that the decision of NICE is reconsidered.
6.177	This is to support the proposed initiative of offering Gene therapy in the treatment of sufferers of sickle cell anaemia. For far too long, this group of sufferers have gone without treatment The gene therapy should be rolled as the science is right.
6.178	I am writing this email as a mother who has a daughter with Sickle cell. Sickle cell as you know is a life-threatening condition that affects the quality of life of those living with the condition. It has had a huge impact on our lives especially on my daughter's life. The crisis can be so unbearable, affects her job and her life in general. The medications at times are all to no avail and they have huge side effects damaging organs.

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	I join the many advocates for the gene therapy treatment to be available on NHS in order to bring an end to the perpetual sufferings of the patients. I plead our voices will be heard and the needful would be done.
6.179	I would like NICE to rethink their decision about CRISPR. Two of my children have the sickle cell trait. Decision may impact the future of generation.
6.180	Every breakthrough in sickle cell research represents a ray of hope and now with the Gene Therapy, for those impacted by this relentless disease. With your support of objecting to the removal of Gene therapy we can continue to drive progress, develop innovative therapy and ultimately make a meaningful difference in the lives of patients their families and friends. Thank you for the attention and consideration. Let us stand united in our commitment to elevate the suffering of patients, their families and friends affected by sickle cell disease by objecting to the removal of Gene therapy. Thank you.
6.181	I am writing with regards to the intention to withdraw Gene Therapy treatment for sickle cell patients. Whilst there may be concerns about the expenses involved in making this treatment available to patients, the effect of not making it available as a viable option resulting in prospective beneficiaries having to undergo periods of treatment and so on when episodes of crises occur can be much more far fetching physically, emotionally and financially both on the individuals and the medical institutions responsible for their care. The impact of living with the disease can be quite debilitating and life limiting for many so where there is the option to avert this completely, it should be considered seriously and offered to the patients that will benefit from it.
6.182	I would like to appeal to NICE to reconsider proposals to withdraw gene therapy as a treatment option for Sickle Cell Disease Gene therapy has been proven unequivocally to help in pain management of people affected by SCD and is in fact a game changer, not only for their quality of life and physical health but also for their mental health and well being. Yes, it may be expensive (as are many innovative treatment options and modalities for most chronic/genetic diseases) but the benefits of treatment far outweigh the cost and in the long run may even be cheaper than the cost of repeated hospital admissions for management of pain crisis. The burden of disease, especially when treatment and/or management is suboptimal and its effects on both patients and their families who have to care for them is enormous. I therefore most strenuously and comprehensively object to its withdrawal as a treatment option for Sickle Cell Disease and seriously hope that NICE will reconsider its position.

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6.183	I am writing in response to the consultation to remove Exa-cel Gene Therapy which is accessible through NHS treatment. As a sickle cell patient, I think this is an erroneous judgement. This life saving treatment gives us an opportunity to live life free from sickle cell crisis pain and it is the chance for several sickle patients to live wholesome lives. Without being able to access this treatment through the NHS denies sickle cell patients accessible treatment for a better life.
6.184	I write to express that I am in support of Exa-cel gene therapy consultation. I am aware of the life changing benefits that this could have to candidates. This subject is close to my heart as I have family members who would benefit if this became possible.
6.185	I would like to present my objection to removing Gene Therapy as a treatment option for Sickle Cell. One of the most successful methods of treating Sickle Cell is Gene therapy. With this treatment children born with Sickle Cell have a fighting chance to avoid a life of pain. A Ray of Hope is being given to the succeeding race. It is one treatment that eradicates a lifetime of pain. I would like to give an example of how underfunded sickle cell disease is. Cystic Fibrosis which mainly affects Caucasians and there are about 10,500 patients has 60 Specialist Centres, fully stocked with Physio, Social Care etc. A ratio of 1 Specialist Nurse to 75 patients and 511 APPROVED treatment options. Sickle Cell has 10 Specialist Centres for about 17,500 patients, little wider medial or social back up. 1 Specialist Nurse to about 400 patients and 4 APPROVED treatment options. It might not be consciously done but the optics do not look good and there is a child struggling to come into this world and lots more who are present on this earthly domain who can and will benefit. Please give them an opportunity to miss a lifetime of pain.
6.186	• Has all of the relevant evidence been taken into account? I believe all available evidence and data has been reviewed and taken into account by the NICE committee. • Are the recommendations sound and a suitable basis for guidance to the NHS? I believe the recommendation are fair. There is not enough evidence proving this safe and effective on a large scale through the NHS. But I think NICE should recommend further research be done under the NHS, NHRI, or HRA, to provide concrete data on this treatment. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

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	A multi arm study should be done to determine clinical and cost effectiveness. It would probably have to be an international study to get enough participants for solid data, this should be done alongside health economics not relying on economic data already out because its not detailed enough for comparison. Costing on care varies between patients and this isn't reflected in the evidence available, more solid costing evidence could be done during a definitive study. The summaries given are a small part of a larger picture that hasn't been represented in its entirety, either the company or an NHS funding body should run a more in-depth study. If you are willing to record every bit of NHS funding a sickle-cell patient used over 15 years, in the treatment, inpatient, etc. and compare that to the companies 15 year observation of participants, that would give the most precise comparison to whether this is cost-effective or not. • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? There is no part of this recommendation that out rightly discriminates against this patient group, but the fact is this patient group is under treated, under served, under studied, and underfunded. This recommendation plays a part in that, as it was stated there was not enough participants, this is a reason patient group hears constantly as to why research isn't being done into sickle-cell. This directly impacts the patients affirming that these governing bodies aren't here to help us, there is no trust being built between governing bodies, research bodies and the patient group to increase engagement into research. As sickle-cell mainly affects black Afro-Caribbean peoples the unwillingness to work with us can be seen as a direct result of our race, social and economic status. To give me an example of cystic fibrosis has 6 treatment/medication plans available for patients under the NHS and people with sickle cell have 2, I can't include Crizanlizumab because it's no longer available under the NHS and Voxelotor is only available to a small group of patients. I did not included transplants in this comparison.
6.187	I have lived in this country with Sickle Cell my whole life and as of this year I will turn 41 which to me is a surprise and a huge accomplishment. To whoever reading this would scoff at this claim as to and normal person without a Chronic disease turning 41 is a standard procedure and they would think they had decades left but from a young age I've been told at least 3 times that my life expectancy is around my current age and much much lower if I was born in Ghana where my parents originated from. Just imagine the knowledge of this hard fact and what it does to your mental health on top of having to deal with regular bouts of Sickle Cell pain, extreme fatigue and the constant highs and lows of your mental health as you have to fight through all of that and at the same time live a normal life that every person deserves. Throughout my years managing this disorder this has been one of the most difficult things to deal with as growing up you start to slowly learn how different you are to everybody else and that you need to live your life totally different if you plan on having some sort of life and that comes down to simple things like how you dress, or how far you're travelling, what's the weather like or having to cancel plans with family or friends at the last minute as a Sickle crisis has decided to take you out.

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	All the things listed above have a major influence on how you feel about yourself and your mental health and you find yourself constantly having to motivate yourself to not feel bad about cancelled plans or to get food as everything requires extra energy to get you through it. Being in regular pain and fatigue impacts a person on so many levels and I always find it sad that my illness isn't given the proper respect by Dr's and nurses and this is always felt when you go into A&E and you're treated suspiciously and questioned over your immediate need for strong pain killers whilst being left to squirm in pain sitting on hard chairs for long amounts of time waiting to be seen or given a bed. As I've gotten older, I definitely notice the impact this illness has had on my body. I get more regular Sickle cell crisis and I feel the fatigue much more than when I was younger, so it takes me more time to do tasks and recover from it. Also, my eyes have deteriorated from Sickle Cell Retinopathy so much so that I have a macular hole in my right eye where the Sickle Cell has destroyed my retina. I definitely take more days off work than I used to so working full time or at all will definitely become something I need to address as working till retirement is not an option for me. Overall, I believe this country needs to address how Sickle Cell sufferers are treated through the healthcare service as we are overlooked in many aspects. I have been sick this past week so I haven't been able to address this as much as I would've liked as this is a serious topic for me and I feel I have a duty to help and make the lives easier for the Sickle cell sufferers just starting out on the path I've had to endure.
6.188	I write to urge NICE to recommend gene therapy Exa-cel for those living with sickle cell. By way of background, I am a carrier of sickle cell and support my 14-year-old sister who lives with sickle cell disease. I have seen how debilitating sickle cell is, and the severity and challenge physically, psychologically, and emotionally that the disease has on daily life. My younger sister, Vivica's, daily living and mobility is severely impacted by her condition. She has spent her life in and out of hospital with severe sickle cell crisis'. Just two weeks ago, Vivica was discharged from hospital after spending 2 weeks in [X] Hospital with a painful bone infection in her leg caused by a crisis of the leg – she was close to receiving a surgery in her leg to alleviate the symptoms. Last year, my sister was hospitalized for 6 weeks and spent much of her time in the Pediatric Intensive Care Unit in [X] and she was prescribed a drug that doctors suggested saved her life, Rituximab and Eculizumab – NICE at the time refused to recommend her Voxeltor. My sister spent the better part of 6 months last year recovering from this specific crisis. My sister, over the course of her lifetime has had acute chest crisis', and crises over her whole body (arms, leg, eye, fingers etc.) since an episode can occur anywhere in a body. She is chronically tired, cannot partake in activities with her friends and often has to miss out on opportunities, such as school (her attendance is consistently low) sports, holidays

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	and even walking to school (which is a 10-minute walk from her home) poses a daily challenge – she often asks, "why me?" and feels helpless to her condition. Vivica uses the aid of a wheelchair when she is having a crisis or is recovering from a crisis. Those with sickle cell are also susceptible to developing hyperhaemolysis, as my sister did, which poses an additional and life-threatening health challenge. For those living with sickle cell, the prognosis is that health will often deteriorate. While drugs such as hydroxycarbamide and penicillin do alleviate some of the symptoms of sickle cell, those with sickle cell will continue to have a life-threatening crises and hospitalizations, which studies show, and I have observed from those around me, increases with age. One of the reasons NICE has cited for not recommending gene therapy to the NHS for sickle cell is on the grounds of finance. In response, I urge NICE to reconsider their approach. Firstly, the severity of sickle cell, which is a life-threatening disorder with very few treatments outweighs the cost of gene therapy which research shows has been very effective in treating sickle cell – the FDA in the US last December approved two new gene therapies to treat sickle cell disease which has already cured patients living with the condition (1). My sister is amongst approximately 15,000 people who live with sickle cell in the UK and sickle cell is the most common genetic disorder worldwide and, in the UK, – there are currently very limited and often ineffective treatments for sickle cell – most people rely on hydroxycarbamide, penicillin and folic acid for relief. Comparably, cystic fibrosis affects approximately 10,500 people and there are various treatment options for cystic fibrosis. Gene therapy cures sickle cell and my sister's life is worth saving. She has plans to become an architect and a disability advocate, but her condition means that her health will severely limit what she can do – access to gene therapy for my sister and other's who have sickle cell will provide a very necessary lifeline, she would be less dependent on medication, the NHS on financial support from the government and she would be able to stand on her own two feet. Further, NICE have accepted using gene therapy for young children living with metachromatic leukodystrophy (2). This is fantastic progress and last year, the first baby received life saving gene therapy on the NHS. I urge NICE to extend this lifeline to those living with sickle cell. While metachromatic leukodystrophy and sickle cell are different conditions, its effects in shortening and reducing quality of life is comparable. If NICE's position is that people should be treated equally and the commission should focus its resources on saving lives, it is imperative to extend the same service to those living with sickle cell. I urge you to consider the severity of sickle cell and the positive effects that gene therapy will have on not only sickle cell patients, but on the black community who are the largest community in the UK impacted by sickle cell. My sister dreams of a future where she is pain free and where she can spend months at a time without being in excruciating pain and visiting hospital. Please consider that the benefits of treating sickle cell outweighs its associated costs. Referenced Sources:

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	1. FDA approval of gene therapies for sickle cell disease: Q&A with NHLBI Director Dr. Gary Gibbons and NHLBI's Division of Blood Diseases and Resources Director Dr. Julie Panepinto NHLBI, NIH 2. NHS England » First baby receives life-saving gene therapy on NHS
6.188	In response to NICE Public Consultation – Please fund the Gene Editing Therapy Exa-cel on the NHS. We are a community of survivors, warriors, fighters, champions, and helpers on the Sickle Cell and Thalassemia journey living in Wales. Sickle Cell Disorder and Thalassemia Disorder are severe and life-long inherited blood disorders that predominantly affect people from Black African, Black Caribbean, Middle-Eastern, and Mediterranean heritage. We have serious concerns about the National Institute for Health and Care Excellence (NICE) as it seems to have neglected its duty to ensure the care of UK citizens in the decision not to continue the research into Gene Therapy for Sickle Cell patients. This new Gene Therapy may have remarkable potential for positive life changing benefits to the health and wellbeing of people living with Sickle Cell Disorder. If NICE were to not rigorously pursue this research, this will disproportionately affect the lives of individuals from certain communities resulting in untold suffering as seen in the recent Covid-19 Pandemic. We feel overlooked and that we are being treated differently because of our race, which impacts our human rights. "Whenever we go to the hospital, we are treated differently, sometimes even being sworn at and told to be quiet during a painful sickle cell crisis." These hereditary disorders have existed for centuries but are often overlooked in the treatment and research compared to other conditions and diseases. We also face health disparities, unlike treatment and research that are readily available for Cystic Fibrosis and other genetic disorders. The unpredictability of the sickle cell crisis – vaso-occlusive further worsens our situation. "My son living with Sickle cell disorder is not treated at the hospital as the same as other children of other genetic disorder". The level of inequality cannot be overruled as my son is being deprived of the support that should be available for him". Due to the lack of awareness, some patients wait in Accident and Emergency for hours without appropriate pain relief. "A nurse was upset with me. She thought I was teaching her job but refused to understand the difficulties of cannulating me. Due to this, I was left in pain until I was seen by a doctor hours later". "Additionally a lack of knowledge and awareness to the severity of the condition led to confusion of ward placement and my loved one becoming terminally ill suffering a crisis and passing away" Furthermore, most people are observing Ramadan and celebrating their major religious holidays, hindering our response. The mainstream media has not shared our struggles, making it difficult for grassroots organizations and community leaders to highlight them. Whenever our loved ones go into the hospital, we fear for their health and well-being. We urge you to reconsider and fund the new gene editing therapy Exa-cel on the NHS. Thank you for taking the time to read our response to your consultation. Please keep us updated on your decision.

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

Draft guidance comments form

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6.189	Thank you for giving me the opportunity to comment on the NICE published draft recommendation NOT to recommend the new gene therapy, exa-cel, for the treatment of severe sickle cell. Not to allow this new gene therapy will be detrimental to those who suffer with severe sickle cell. Severe sickle cell is a very debilitating medical condition for those who suffer with this and if this gene therapy was available will be of great help to those individuals. Sickle cell and crises will not get any better for any individuals and this gene therapy will be beneficial to those who are suffering daily. Life is very precious for those suffering with sickle cell and this gene therapy will be a life saver for the individuals who are suffering with this medical condition. I hope you are able to pass on my comments to NICE. Kind regards.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the [NICE Health Technology Evaluation Manual](#) (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

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comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Some thoughts on the hesitancy over offering gene editing treatment for sickle cell disorder by a retired senior research fellow, 50yrs in the field.

Sickle cell disorder is one of the most common serious hereditary disorders in the world and the first to have a molecular cause identified^{1,2}. It is a life-long condition arising from a single base change in DNA causing a single amino acid change in the beta globin part of the red blood cell protein called haemoglobin, changing it from the usual haemoglobin A to one called haemoglobin S. Haemoglobin is the predominant protein within red blood cells and is responsible for carrying oxygen from the lungs to the tissues (each haemoglobin molecule can carry 4 oxygen molecules) and for transporting carbon dioxide back.

The 200-300 million or so haemoglobin A molecules within each red blood cell are designed through evolution to remain independent of one another at all times and at all stages of oxygenation. However, this is not the case for haemoglobin S. As a result of its amino acid change on its surface, at high enough concentrations and after it has released its oxygen to the tissues, deoxygenated haemoglobin S is able to self-assemble into filaments and fibres that change the shape of the cell to a rigid elongated form called a 'sickle cell'³. Remarkably, on reoxygenation the haemoglobin S goes back into solution, and many of the red blood cells regain their usual shape. However, the red blood cell may be damaged, may remain distorted and may become more likely to stick to the blood vessel wall. All these factors contribute to a tendency for the sickled cells to periodically block blood vessels supplying oxygen to tissues, causing inflammation and pain. These events, known as veno-occlusive crises, are the hallmark of sickle cell disorder. Damaged red blood cells are removed rapidly from the circulation (on average red blood cells of someone with sickle cell anaemia last about 20 days in the circulation instead of the usual 100 days) and severe anaemia also results.

Beginning in infancy, sickling of the red blood cells within blood vessels can cause bouts of the most severe pain imaginable, and may lead to tissue and organ damage in any system of the body ultimately causing organ failures and various disabilities. Disease severity and actual physical outcomes, both acute and chronic, remain so unpredictable that this is an extraordinarily difficult condition for a person diagnosed with sickle cell disorder to confront. Life-threatening drops in haemoglobin level, episodic acute pain, chronic pain, spleen enlargement, spleen atrophy, sepsis, kidney damage, kidney failure, pulmonary damage, pulmonary embolism, pulmonary hypertension, transient ischaemic attacks, strokes, liver fibrosis, liver failure, priapism, gallstones, enlarged heart, heart failure, joint pain, repeated joint replacements, visual disturbance, blindness, hearing loss, painful leg ulcers – we can go on – occurring earlier, sometimes much earlier, in a person's life than might be expected. Nevertheless, the number of complications an individual may suffer varies. A few are pretty universal, for instance: splenic atrophy leading to infection susceptibility, some kidney damage causing increased need to urinate (bed-wetting in infancy for instance) and risk of dehydration, and acute events of severe pain necessitating alleviation with powerful painkillers. Some people have few additional complications for reasons not yet understood, and, paradoxically, many who are more seriously affected look quite well most of the time. An added challenge arises from the fact that most people in the UK with sickle cell disorder are of African, Caribbean, Middle Eastern and Asian Indian heritage and experience varying degrees of racial stereotyping, insult and abuse. It is little wonder that people with sickle cell disorders often express feelings of sadness, isolation, frustration, uncertainty, fear, worry, lack of self-confidence, sometimes even despair. Schooling, further education and employment requires extraordinary persistence by, and additional cost to, the individual and family in order to cope with disruption caused by routine and emergency hospital visits while striving to fulfil personal ambitions and obligations to others. Sickle cell disorder is often also called 'sickle cell disease', despite the term being disliked by many of those affected, in order to emphasise its severity, so often underestimated and misunderstood, when arguing for necessary resources to provide appropriate treatment and care.

Sickle cell disorder is an extraordinarily complex and unpredictable disorder to treat, with very few generally-available, effective therapies despite repeated publicised 'breakthroughs' and promises of 'a cure'. It is actually a group of disorders that range in severity both within and across the groups. Even the best therapies available are not universally-effective and those that extend life may not improve its quality. Important indicators of therapeutic success, e.g. increased Hb, may sometimes be more incidental due to homeostatic mechanism than truly preventative of complications, and may even herald a worsening of other symptoms, e.g. painful crises.

The combination of (i) antenatal screening in order to target pregnancy choices available to parents whose baby is at risk of having a sickle cell disorder, (ii) neonatal screening to diagnose those affected early enough to offer prophylactic information, counselling and therapies, (iii) a network of specialist clinical centres linked both to local voluntary agencies and to expert clinical evaluation thereby available to all, (iv) use of the drug hydroxycarbamide and (v) improvements in delivery of regular blood transfusion for those who need it, has saved money through diminishing the projected increase in the number of births of babies with sickle cell disorder and by improving the health of and support available to many of those affected. Nevertheless, mortality and co-morbidity in the UK (England at least) remains high in the 14-15%⁴ patients who are most severely-affected which is projected to require a considerable increase in treatment resources over time. Besides the need to continue to work on effective and equitable service delivery⁵, more effective therapies are still required.

The only curative therapies available are stem cell transplantation and gene therapy. While stem cell transplantation is available only to the small proportion of people with sickle cell disorder who have a matched donor, this restriction does not apply to the gene-editing therapy proposed here. Furthermore, some of the complications associated with stem cell transplantation will not occur with the gene-editing therapy (graft versus host disease for instance), the high cost of which will surely be driven down with experience of its use. Of course, there is a need for great caution, for detailed face to face explanation with an experienced practitioner of risks to an individual wishing to undergo this therapy, and for detailed long-term follow up of such a novel therapy. Wider education of health professionals throughout the clinical network and of the general public about different types of gene therapy, and their associated risks, must continue. Nevertheless, to have a potential curative treatment available to all who are severely affected by symptoms resistant to current therapies, rather than to the few, seems the right thing to do. It gives hope that promises of therapeutic improvements were not empty ones and, through increasing participation and knowledge, may encourage more people with sickle cell disorder to have faith in the value of their much-needed participation in clinical research.

Sickle cell disorder was the first serious hereditary disorder to have a molecular cause identified. That discovery and its further study has led to advances in understanding the biochemistry and pathophysiology of many other clinical conditions. People with sickle cell disorder should be at the heart of these developments.

1. Pauling L, Itano HA, Singer SJ, and Wells IC (1949) Sickle Cell Anemia, a Molecular Disease. *Science* 110: 543-548.
2. Ingram VM (1957) GENE MUTATIONS IN HUMAN HAEMOGLOBIN: THE CHEMICAL DIFFERENCE BETWEEN NORMAL AND SICKLE CELL HAEMOGLOBIN. *Nature* 180:326-328.
3. Diggs LW & Bibbs J (1939) THE ERYTHROCYTE IN SICKLE CELL ANEMIA. *Journal of the American Medical Association* 110: 695-701.
4. Piel FB, Jobanputra M, Gallagher M, Weber J, Laird SG, McGahan M. Co-morbidities and mortality in patients with sickle cell disease in England: A 10-year cohort analysis using hospital episodes statistics (HES) data. *Blood Cells Mol Dis*. 2021 Jul;89:102567. doi: 10.1016/j.bcmd.2021.102567. Epub 2021 Apr 1. PMID: 33862367.
5. <https://www.sicklecellsociety.org/wp-content/uploads/2021/11/No-Ones-Listening-PDF-Final.pdf>

Some thoughts on the hesitancy over offering gene-editing treatment for sickle cell disorder from a retired Senior Research Fellow, 50yrs in the field.

Sickle cell disorder (also called sickle cell disease) is an extraordinarily complex and unpredictable disorder to treat, with very few generally-available, effective therapies despite repeated well-publicised ‘breakthroughs’ and promises of ‘a cure’. Even the best therapies available are not universally-effective and those that extend life may not improve its quality.

The establishment in the UK of antenatal screening, neonatal screening, a network of specialist clinical centres linked both to local voluntary agencies and to expert clinical evaluation, use of the drug hydroxycarbamide and improvements in delivery and safety of regular blood transfusion for those who need it, has saved money through diminishing the projected increase in the number of births of babies with sickle cell disorder and by improving markedly the health of those affected. Nevertheless, in 2021, Piel et al. reported¹ that mortality and co-morbidity in England remains high in the 14-15% patients who are most severely-affected and is likely to require a considerable increase in treatment resources over time. Besides the need to work on effective and equitable quality service delivery², more effective therapies are still required.

The only curative therapies available are stem cell transplantation and gene therapy. While stem cell transplantation is available only to the small proportion of people with sickle cell disorder who have a matched donor, this restriction does not apply to the gene-editing therapy proposed here. Furthermore, some of the complications associated with stem cell transplantation will not occur with the gene-editing therapy, the high cost of which, one would imagine, will be driven down with experience of its use.

Of course, there is a need for great caution, for detailed face to face explanation with an experienced practitioner of risks to an individual wishing to undergo this therapy, and for detailed long-term follow up of such a novel therapy. Also, wider education of health professionals throughout the clinical network and the general public about the different types of gene therapy, and their associated risks, must continue. Nevertheless, to have a potential curative treatment available to all who are severely affected by symptoms resistant to current therapies, rather than to the few, seems the right thing to do. It gives hope that promises of therapeutic improvements were not empty ones and, through increasing participation and knowledge, may encourage more people with sickle cell disorder to have faith in the value of their much-needed participation in clinical research.

Sickle cell disorder was the first serious hereditary disorder to have a molecular cause identified³. That discovery and its further study has led to advances in understanding the biochemistry and pathophysiology of many other clinical conditions. People with sickle cell disorder should be at the heart of these developments.

1. Piel FB, Jobanputra M, Gallagher M, Weber J, Laird SG, McGahan M. Co-morbidities and mortality in patients with sickle cell disease in England: A 10-year cohort analysis using hospital episodes statistics (HES) data. *Blood Cells Mol Dis*. 2021 Jul;89:102567. doi: 10.1016/j.bcmd.2021.102567. Epub 2021 Apr 1. PMID: 33862367.

2. <https://www.sicklecellsociety.org/wp-content/uploads/2021/11/No-Ones-Listening-PDF-Final.pdf>

3. Smith T (1999) First Molecular Explanation of Disease. *Nature Structural Biology*: 6, no.4, p307.

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

Draft guidance comments form

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Forum on haemoglobin disorders

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: - the name of the company - the amount - the purpose of funding including whether it related to a product mentioned in the stakeholder list - whether it is ongoing or has ceased.	The UKFHD receives no direct funding from Vertex for our routine running costs, however we have applied to a number of commercial companies including Vertex, successfully for unrestricted educational grants to support an educational event (study day).
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
Name of commentator person completing form:	████████████████████ of the UK Forum on Haemoglobin disorders on behalf of the trustees, committee and membership
Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that
1	3.5 Clinical trial evidence: comment of concern <i>"It also noted that more data collection to establish the long-term effectiveness of exa-cel would reduce the uncertainties around durability of the treatment effect."</i>

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	3.9 Long term treatment effects - comment of concern/note: <i>“It understood from clinical experts that the long-term efficacy of exa-cel would be more assured after 2 to 5 years of follow up, but full health may not be restored. So, it concluded that long-term durability of the exa-cel treatment effect may be plausible, but that this should be explored further with additional data collection.”</i> While the UK Forum on Haemoglobin Disorders (UKFHD) agrees with aim for long term data collection for all new therapies including exa-cel, we would like the NICE committee to note that targeting the haematopoietic stem cell has long been shown to be an effective approach in curing sickle cell. The committee should consider that there is also good evidence of using autologous gene therapy targeting haematopoietic stem cells to treat multiple other conditions including primary immunodeficiency syndromes such as Severe Combined Immunodeficiency Disease (SCID) over the past 2 decades with great results and evidence of long term effectiveness. In fact gene therapy in these fields have now progressed to be equal or even better than allogeneic haematopoietic stem cell transplant. So while UKFHD is in agreement about data collection it would strongly recommend that given the amount of evidence on the therapeutic effect of gene therapy that available, this reason should not be used as rationale to not recommend implementation of this technology for individuals with sickle cell disorder (ref included with submission: Kohn LA et al, Gene therapies for Primary Immune Deficiencies. Front Immunol 2021 Feb 25;12:648951). The Forum would also like the NICE committee to note, while it may seem pragmatic, there is no factual basis to base a 2-5 years duration post treatment before determining that exa-cel is curative for sickle cell, this duration seems to us to have been extrapolated from cancer therapy, which is not in any way similar to sickle care. Rather basing the duration on similar haematopoietic stem cell transplant (HSCT) based approaches would seem to make more sense and for HSCT, 1 year seems the duration by which a cure accepted.
2	3.8 Standard care mortality modelling comment of concern/note: <i>“The EAG ran a non systematic search for additional external evidence but reported difficulties in finding data to match the appraisal population. It found data from 6 real world studies that suggested life expectancy is between 43 years and 55 years. The EAG chose to use the mortality rates from Jiao et al. (2023) (life expectancy of 55 years) in its base case”</i> The UKFHD would like the committee to consider that this lack of evidence in the literature it is further evidence of the disparity and inequity that impacts sickle cell, resulting in inadequate research and data sources on the population. Despite studies suggesting improved life expectancy the reality for us the clinicians in our services in the United Kingdom, is each year we have patient deaths across the age span with a peak after 40 years of age. The National Haemoglobinopathy Registry which according to their 2020/21 annual report almost 13 000 individuals with sickle cell registered, reported an equivalent number of deaths in the 19-45 age group as in the 46+ age group. This is real world UK data which the committee should consider when assessing severity and life expectancy measures (NHR report is published on their website). Despite the “non-systematic” nature of the search the EAG carried out it was hopefully clear to them, even when taking into consideration studies with the most positive estimates of life expectancy there is still an overwhelming loss of life in individuals with SCD, at an age well before their ethnically matched birth cohorts in the UK would be expected die. The office of national statistics estimated that for people of Asian and Black ethnicity, women have life expectancy of between 84-88.9 years and males have life expectancy of 81 - 84.5years (ONS data: Ethnic

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	differences in life expectancy and mortality from selected causes in England and Wales - Office for National Statistics (ons.gov.uk)). It is of concern to the forum that the EAG ran a “non systematic search” which found little evidence available in the literature, and this non systematic search seems to have fairly strongly influenced the committee’s decision making. It needs to be taken into consideration the reasons why such evidence is not available, as noted previously this is part of the disparity affecting the sickle population. It is also of concern to the Forum that the clinicians and patient voice present reporting on lived experience, seemed to have less impact than ‘s non systematic search.
3	3.9 Long term treatment effects comment of concern: <i>“VOC after allogeneic HSCTs: people may still have pain events, particularly for the first year after the HSCT. To reflect this, the company applied baseline VOC rates to the entire exa-cel arm for the first year after infusion. The EAG highlighted that these were adjudicated VOCs in the trial and that acute pain is part of the trial definition of VOCs.</i> All studies using an HSCT approach for sickle cell disease, be this allogeneic matched sibling donor or haploidentical transplant, have all reported patient presentation with sickle pain episodes, VOC, after successful treatment (reference included: Leonard A, Furstenau D, et al Reduction in vaso-occlusive events following stem cell transplantation in patients with sickle cell disease. Blood Adv. 2023 Jan 24;7(2):227-234.). In our clinics, broadly speaking the patients who tend to re-present after curative intent treatment with pain, we have found tend to be those whom before the intervention had a high burden of chronic pain from complications such as avascular necrosis of joints (e.g. hip, shoulder etc), high burden of acute presentations and high opioid analgesia use pre-intervention. While the definition of a VOC (pain >2 hours with no other cause) means these presentations may be defined as such, we have found for patient who are post a successful intervention, after a period of stability, with weaning off the opioid analgesia these presentations do cease. The UKFHD would like the committee to consider that given, there is good evidence of such presentations then it is not unexpected after exa-cel and while rightly “adjudicated” as VOC within the trial, some of those presentations may fall into this category, and reflect a burden of chronic pain and or opioid use. It should be expected that similar to other HSCT interventions there would be improvements over time and reduction of opioid analgesia.
4	3.10 Comments of concern: <i>Vaso-occlusive crisis as a predictor of complications: The EAG acknowledged that VOCs are associated with poor outcomes in people with SCD, but stated that using VOCs to predict outcomes is not supported by evidence</i> <i>The committee considered the definitions of VOCs and the inconsistencies highlighted and concluded that the hospitalisation VOC definition was the most appropriate for decision making.</i> The UKFHD would like the committee to note there are multiple data sources that have established the link between multiple VOCs and worsened prognosis including Gardner K et al Survival in adults with sickle cell disease in a high-income setting. Blood. 2016 Sep 8;128(10):1436-8. and Chaturvedi S, et al A retrospective-prospective cohort study. Am J Hematol. 2018 Sep;93(9):1153-1160 which all confirm shortened life expectancy and organ comorbidity with recurrent VOCs.
5	3.12 Comment of concern <i>For people assumed to be ‘functionally cured’, the company used a health state utility value of 0.92 in its model. This was based on a mean change in EQ-5D score from baseline to month 24 (0.11). The EAG highlighted that at month 24, EQ-5D was measured in fewer people than at baseline and so could be affected by selection bias. It said that EQ-5D values recorded earlier in</i>

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	<i>the trial (0.88), which are not affected by loss of follow-up bias or are not statistically different, should be used.</i> The UKFHD found the approach taken by the committee here slightly baffling, as elsewhere the committee had been clear in wanting patients with longer follow up before deeming treatment successful, hence it would seem to fit this approach to use the EQ-5D responses from the patients with the longest follow up, either to refute or confirm improvement. Yet, with the EQ5D it would seem a cohort with a shorter duration of follow up was preferred, which gave less improvement and misaligns with the position taken by the committee till this point.
6	3.15 Comment of concern <i>“The committee acknowledged that all of the following criteria in section 4.5.3 of the NICE health technology evaluations: the manual must be met for a 1.5% discount rate to be used:</i> <i>• The technology is for people who would otherwise die or have a very severely impaired life.</i> <i>• It is likely to restore them to full or near-full health.</i> <i>• The benefits are likely to be sustained over a very long period.</i> <i>The committee concluded that the first criterion for using a 1.5% discount rate was not met because there was insufficient evidence to show that people would otherwise die or have a severely impaired life.”</i> The UKFHD would strongly recommend the committee to reconsider their position on criterion 1. There is plentiful evidence of the severity of Sickle Cell, even the best case data collection still has individuals with this condition dying 20 years before their matched birth cohorts without condition. Our real-world experience is that patients die some 30+ years before their matched unaffected birth cohorts would be expected to die. As noted above the UK National Haemoglobinopathy Registry with 13000 individuals registered as of their 2020/21 report (published on their website) confirmed as many individuals with SCD die aged 19-45 years as do over 46 years. Clinicians from the UKFHD also report this to be their real-world experience. They all report on the high unmet need in this patient cohort with no licensed drug treatments other than Hydroxycarbamide, a 140-year-old drug for this patient population in the UK, blood transfusion or for the <15% of patients with a matched sibling donor and condition severe enough to warrant it a matched related donor HSCT. There is also Hospital Episode data from the UK confirming both the burden and severity. These are all real world UK data which the committee should consider when assessing severity and life expectancy measures. Despite the non-systematic nature of the search the EAG carried out it we hope they also report an overwhelming loss of life in individuals with SCD, well before most of their ethnically matched birth cohorts in the UK would be expected die. As noted above ONS data suggests an individual of black and Asian ethnicity should expect to live into their 80s for both men and women (ONS data: Ethnic differences in life expectancy and mortality from selected causes in England and Wales - Office for National Statistics (ons.gov.uk)). Individuals with SCD in England overwhelmingly are from these ethnic groups and are expected to die even by the very best estimates around long before their 60th Birthdays. Not being able to recognise sickle cell as a severe condition, with individuals who live a severely impaired life after the testimonies heard, the clinician's evidence and from a basic literature search is something we have struggled to comprehend.
7	3.15: Criterion 2: • The benefits are likely to be sustained over a very long period. The committee considered the second criterion was not met, concluding that it may be plausible that exa-cel returns people to full or near full-health. But, it noted the uncertainty

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	was compounded by the short-term follow up of the clinical-effectiveness evidence and that further data could allow the committee to consider if this criterion was met Response: The UKFHD would like the committee to consider that HSCT autograft is standardly undertaken for a variety of conditions including non-cancer diagnoses such as multiple sclerosis, and late graft failure is not a complication that is reported and this would be the expectation with exa-cel.
8	3.18 The committee appreciated that exa-cel could be very beneficial for people with SCD. But it was concerned that if only a small number of people have exa-cel, then the treatment would not address the inequalities experienced by most people The UKFHD would like the committee to take on board the current immense unmet need which individuals with sickle and their clinical teams manage daily, despite being well described condition with it's genetic basis well understood, at the current time in England for individuals with sickle below are all of the treatment options available: 1. For a subset of <15% sickle patients with a matched sibling donor, who also fulfilling current commissioning criteria, there is the option of HSCT to cure their SCD 2. For patients with severe disease and no sibling donors who do not have a rare blood type or multiple alloantibodies and depending on availability of access to apheresis there is the option of regular top up or red cell exchange 3. For all other patients there is Hydroxycarbamide which is not well tolerated by all patients for wide variety of reasons. So for a large group of sickle patients there is no current therapy option, adding exa-cel to the treatment armamentum, with an MDT approach similar to the current practice in England for sickle patients referred for HSCT, where they will be discussed at both regional and national MDT, would go some way to ensuring patients are appropriately selected and there is equity across the country. However, to not consider exa-cel as an option because of fears that too few patients will take up the option simply reinforces the current inequity and ongoing failures within our health systems for this much ignored community.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Do not use abbreviations.

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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Exagamglogene autotemcel for treating sickle cell disease [ID4016]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of Pathologists

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: - the name of the company - the amount - the purpose of funding including whether it related to a product mentioned in the stakeholder list - whether it is ongoing or has ceased.	No disclosures
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[REDACTED]
Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that
1	Vaso-occlusive crisis (VOC) as a predictor of complications: Hospitalisation rates for VOC are not an appropriate model for predicting the risk of complications. Many patients manage severe VOCs either in the day unit setting – this is not coded as an admission, nor would visits to the emergency department. The “No-

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	One's listening Listening" report" highlighted that many patients avoid attending hospital due to fear of substandard care, and are therefore likely to either manage a VOC at home or following attendance at an accident and emergency department and prefer not be admitted to hospital. Using hospitalisations alone is likely to underestimate the risk of complications; and due to the heterogenous nature of SCD there is no universally reliable model to assess risk. VOC in itself has a significant adverse impact on health and quality of life. References: a) The Pain in Sickle Cell Epidemiology Study (PiSCES) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2568749/pdf/jnma00183-0053.pdf b) Brousse et al 2023 Severity and burden of sickle cell disease in France: a nationwide realworld study doi: 10.3324/haematol.2022.282098 c) Darbari et al., 2013 Severe Painful Vaso-Occlusive Crises and Mortality in a Contemporary Adult Sickle Cell Anemia Cohort Study Doi: 10.1371/journal.pone.0079923 d) Drahos et al 2023 The Impact of Recent Vaso-Occlusive Crises on Health-Related Quality of Life in Adults With Sickle Cell Disease ASH 2023 Poster P3678 e) Besser et al 2022 Economic Burden and Quality of Life of Caregivers of Patients With Sickle Cell Disease in the United Kingdom and France: A Cross-sectional Study https://www.ispor.org/docs/defaultsource/euro2022/isporeu22barcelos-pdf.pdf?sfvrsn=3146affa_0 f) Campbell et al 2022 The Burden of Sickle Cell Disease on Children and Their Caregivers: Caregiver Reports of Children's Health-Related Quality of Life and School Experiences, Caregiver Burden, and Their Association with Frequency of Vaso-Occlusive Crises Doi: 10.2147/PROM.S419607 g) Shafrin et al 2021 The Impact of Vaso-Occlusive Crises and Disease Severity on Quality of Life and Productivity Among Patients with Sickle Cell Disease in the US https://doi.org/10.1080/03007995.2021.1897556
2	Exa-cel has the potential to return patients to near normal health 1. Due to the trial inclusion criteria and likely commissioning criteria, patients have not accumulated significant irreversible complications prior to treatment with exa-cel, but do experience frequent VOCs which would lead to multiple complications and poor QoL over time. 2. Therefore, by treating these severe patients before the majority of irreversible complications have set it, exa-cel has the potential to return patients to near normal health. 3. Evidence from patients receiving sibling matched HSCT shows prevention and reversibility of complications and long-term survival. Exa-cel would not lead to GVHD or graft rejection.

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	4. Pan-cellularity of HbF following exa-cel treatment will likely prevent further complications and potentially lead to some reversibility of complications already present References: a. Mahesri et al 2023 VOC-free Status Among Patients With Sickle Cell Disease Following Allogeneic Hematopoietic Stem Cell Transplant: A Cohort Study of Medicaid Enrollees ASH 2023 Poster
3	Mortality in SCD 1. SCD is a severe condition & patients die very prematurely (estimates indicate in late 30s / early 40s) – even with the most appropriate best available treatment. 2. Patients have a very severely impaired quality of life, which will worsen progressively over time as they accumulate more complications and co-morbidities. 3. It is not reasonable to imply the baseline EQ-5D of 0.81 from the trial is the measure of quality of life for all patients with severe SCD for their whole lifetime. This is because: • Patients entering the exa-cel trial necessarily had to meet the trial entry criteria, and therefore were unlikely to have accumulated significant irreversible complications although they were still a severe population with frequent vaso-occlusive crises. However they would certainly go on to develop multiple complications have a much lower QoL in future – it is not reasonable to assume the 0.81 stays constant for patients over their life • EQ-5D, while it is the preferred QoL measure for NICE, does not fully capture the experience of patients with severe SCD due to ceiling effects – EQ-5D has to be taken as a <u>highly conservative</u> representation of QoL, and looking at other measures such as ASQ-ME, FACT-BMT, Pain NRS provides important context for this. References: a) Udeze et al 2023 (Vertex BOI study) Mortality and Clinical Complications Among Patients With Sickle Cell Disease With Recurrent Vaso-Occlusive Crises in England Poster only BSH P0110 b) Desai et al 2020 Clinical outcomes and healthcare utilization in patients with sickle cell disease: a nationwide cohort study of Medicaid beneficiaries https://doi.org/10.1007/s00277-020-04233-w c) Jiao et al 2023 Long-term survival with sickle cell disease: a nationwide cohort study of Medicare and Medicaid beneficiaries https://doi.org/10.1182/bloodadvances.2022009202 d) Piel et al 2021 Co-morbidities and mortality in patients with sickle cell disease in England: A 10-year cohort analysis using hospital episodes statistics (HES) data https://doi.org/10.1016/j.bcmd.2021.102567 e) Di Mauro et al 2023 Males with sickle cell disease have higher risks of cerebrovascular disease, increased inflammation, and a reduced response to hydroxyurea Doi:10.1002/ajh.27074

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	f) Brousse et al 2023 Severity and burden of sickle cell disease in France: a nationwide realworld study doi: 10.3324/haematol.2022.282098
4	Sustained benefit of Exa-cel over a very long period The editing of the haematopoietic stem cells with CRISPR technology are permanent and durable; there is no biological plausibility that the genetic edit will not be permanent. This is supported by data from CLIMB 121 – where the stable proportion of alleles with intended genetic modification (allelic editing) is stable over time Fetal haemoglobin is maintained at around 40% in a pancellular distribution. This would be expected to stop the process of vaso-occlusion. It would also stop progression of existing organ damage and stop development of new organ damage (supported by results from allo grafting and outcomes in HPFH) Acute pain can happen infrequently after allo-SCT due to exacerbation of chronic pain, allodynia and hyperalgesia. The reasons for acute pain events seen after exa-cel in a small number of patients are likely to be similar. These do not represent lack of effect of exa-cel. Reference: Sebastiani, Steinberg 2023 Fetal Hemoglobin per Erythrocyte (HbF/F-cell) After Gene Therapy for Sickle Cell Anemia doi:10.1002/ajh.26791
5	Treatment withdrawals In CLIMB-121 19% of patients in the trial did not proceed to treatment with exa-cel following apheresis. This is much higher than other conditions where an autologous transplant is involved - and this may be due to the patient population (apheresis is more challenging due to the nature of SCD) & the way SCD patients interact with the health care system. The exact figure would be difficult to predict and may be higher than other diseases because of the inequalities patients face, and the unique experience of their disease.
6	

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is **'commercial in confidence' in turquoise** and information that is **'academic in confidence' in yellow**. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the [NICE Health Technology Evaluation Manual](#) (section 5.4) for more information.

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Response to NICE Exagamglogene gene therapy for treatment of sickle cell disease from British Society for Haematology General Haematology Guidelines Task Force

We feel strongly that the NICE appraisers have misjudged the severity of sickle cell disease (SCD).

SCD is a severe condition and patients die prematurely, including many moderately-severely affected individuals dying in their 30s and 40s, even those who have received best currently available treatment such as long-term red cell exchange transfusion and hydroxycarbamide treatment.

The medical literature provides clear evidence for a reduced life expectancy, a severely impaired quality of life, and accumulation of complications and co-morbidities with age.

Regarding the use of the EQ 5D quality of life assessment, it is not reasonable to imply that the baseline EQ-5D of 0.81 (1 is perfect health) from the trial is the measure of quality of life for all patients with severe SCD for their whole lifetime.

Firstly, the EQ 5D over estimates quality of life in long-term conditions such as sickle cell disease and this has been demonstrated in the literature. EQ-5D, while it is the preferred QoL measure for NICE, does not fully capture the experience of patients with severe SCD due to ceiling effects. EQ-5D has to be taken as a highly conservative representation of QoL. Looking at other measures such as ASQ-ME, FACT-BMT, Pain NRS are more validated measures of quality of life assessment in sickle cell disease.

Secondly, quality of life deteriorates significantly with age in sickle cell disease and therefore an assessment at the start of this trial is not reflective of the quality of life in 5, 10 or even 20 years' time for the patients.

Patients entering the exa-cel trial necessarily had to meet the trial entry criteria, and therefore were unlikely to have accumulated significant irreversible complications despite being necessarily a severe population with frequent VOCs. They would have gone on to develop multiple complications and have a much lower QoL in the future had they not been treated with gene therapy. It is not reasonable to assume the 0.81 stays constant for patients over their lifetimes.

Exa-cel has the potential to return patients to near normal health.

Because of the trial inclusion criteria, patients included in the trial have not accumulated significant irreversible complications prior to treatment with exa-cel, but did experience frequent VOCs which are indicative of severe disease which is likely to lead to multiple complications and poorer QoL over time.

By treating these severe patients before the majority of irreversible complications have established, exa-cel has the potential to return patients to near normal health, life expectancy and quality of life, and prevent future complications.

This is extrapolated from evidence from patients receiving sibling matched HSCT which shows prevention and reversibility of complications and improved long-term survival. Unlike sibling matched HSCT, Exa-cel would not lead to GVHD or graft rejection.

Pan-cellularity of haemoglobin F following exa-cel treatment is likely to prevent further complications and potentially lead to some reversibility of pre-existing complications.

The benefits are likely to be sustained over a very long period

There is no biological plausibility that the genetic edit will not be permanent. Genetic edits to haematopoietic stem cells with CRISPR technology are permanent and durable.

This is supported by data from CLIMB 121 in which the proportion of alleles with intended genetic modification (allelic editing) was stable over time.

Acute pain can happen infrequently within the first year after allo-SCT. This can be due to exacerbation of chronic pain, allodynia and hyperalgesia. The reasons for acute pain events seen after exa-cel in a small number of patients are likely to be similar. These do not represent lack of effect of exa-cel.

Fetal haemoglobin is maintained at around 40% in a pancellular distribution. This would be expected to prevent the process of vaso-occlusion. It would also prevent progression of existing organ damage and development of new organ damage. This is evidenced by outcomes in compound hereditary persistence of fetal haemoglobin (HbS+HPFH) in which affected individuals do not suffer the pain and organ complications seen in sickle cell disease and have normal life expectancy.

References

Badawy et al 2020 *A systematic review of quality of life in sickle cell disease and thalassemia after stem cell transplant or gene therapy* DOI 10.1182/bloodadvances.2020002948

Besser et al 2022 *Economic Burden and Quality of Life of Caregivers of Patients With Sickle Cell Disease in the United Kingdom and France: A Cross-sectional Study* https://www.ispor.org/docs/defaultsource/euro2022/isporeu22barcelos-pdf.pdf?sfvrsn=3146affa_0

Brousse et al 2023 *Severity and burden of sickle cell disease in France: a nationwide real-world study* doi: 10.3324/haematol.2022.282098

Campbel et al 2022 *The Burden of Sickle Cell Disease on Children and Their Caregivers: Caregiver Reports of Children's Health-Related Quality of Life and School Experiences, Caregiver Burden, and Their Association with Frequency of Vaso-Occlusive Crises* DOI: 10.2147/PROM.S419607

CLIMB 121 data presented at ASH

Dallas et al 2016 *Long-Term Outcome and Evaluation of Organ Function in Pediatric Patients Undergoing Haploidentical and Matched Related Hematopoietic Cell Transplantation for Sickle Cell Disease* doi:10.1016/j.bbmt.2013.02.010

Darbari et al., 2013 *Severe Painful Vaso-Occlusive Crises and Mortality in a Contemporary Adult Sickle Cell Anemia Cohort Study* Doi: 10.1371/journal.pone.0079923

Desai et al 2020 *Clinical outcomes and healthcare utilization in patients with sickle cell disease: a nationwide cohort study of Medicaid beneficiaries* <https://doi.org/10.1007/s00277-020-04233-w>

Di Mauro et al 2023 *Males with sickle cell disease have higher risks of cerebrovascular disease, increased inflammation, and a reduced response to hydroxyurea* DOI: 10.1002/ajh.27074

Drahos et al 2023 *The Impact of Recent Vaso-Occlusive Crises on Health-Related Quality of Life in Adults With Sickle Cell Disease* ASH 2023 Poster P3678

Drahos et al 2022 *Health Related Quality of Life, Disease Impacts, & Health Equity Concerns in Adults With Sickle Cell Disease With Recurrent Vaso Occlusive Crises* ASH 2022 Oral presentation

Inam et al 2023 *Outcomes and long-term effects of hematopoietic stem cell transplant in sickle cell disease* <https://doi.org/10.1080/17474086.2023.2268271>

Jiao et al 2023 *Long-term survival with sickle cell disease: a nationwide cohort study of Medicare and Medicaid beneficiaries* <https://doi.org/10.1182/bloodadvances.2022009202>

Leonard 2024 *Hematopoietic stem cell collection for sickle cell disease gene therapy* DOI: 10.1097/MOH.0000000000000807

Mahesri et al 2023 *VOC-free Status Among Patients With Sickle Cell Disease Following Allogeneic Hematopoietic Stem Cell Transplant: A Cohort Study of Medicaid Enrollees* ASH 2023 Poster

NHS commissioning policy <https://www.england.nhs.uk/wp-content/uploads/2020/02/clinical-commissioning-policy-allogeneic-haematopoietic-stem-cell-transplantation.pdf>

Osunkwo et al 2022 *Burden of disease, treatment utilization, and the impact on education and employment in patients with sickle cell disease: A comparative analysis of high- and low- to middle-income countries for the international Sickle Cell World Assessment Survey (SWAY)* DOI: 10.1002/ajh.26576

The Pain in Sickle Cell Epidemiology Study (PiSCES) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2568749/pdf/jnma00183-0053.pdf>

Piel et al 2021 *Co-morbidities and mortality in patients with sickle cell disease in England: A 10-year cohort analysis using hospital episodes statistics (HES)* data <https://doi.org/10.1016/j.bcmd.2021.102567>

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Sebastiani, Steinberg 2023 *Fetal Hemoglobin per Erythrocyte (HbF/F-cell) After Gene Therapy for Sickle Cell Anemia* doi:10.1002/ajh.26791

Shafrin et al 2021 *The Impact of Vaso-Occlusive Crises and Disease Severity on Quality of Life and Productivity Among Patients with Sickle Cell Disease in the US* <https://doi.org/10.1080/03007995.2021.1897556>

Udeze et al 2023 (Vertex BOI study) *Mortality and Clinical Complications Among Patients With Sickle Cell Disease With Recurrent Vaso-Occlusive Crises in England* Poster only BSH P0110

Walters et al 2010 *Pulmonary, Gonadal, and Central Nervous System Status after Bone Marrow Transplantation for Sickle Cell Disease* DOI:10.1016/j.bbmt.2009.10.005

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Cell and Gene Therapy Catapult

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[REDACTED]
Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
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1	Many advanced therapy medicinal products [ATMPs] are delivered as a single treatment providing lifelong change and impact. It appears that Casgevy is facing the same challenges with many gene therapies. Where patients are expected to achieve a life expectancy of the general population it is not considered realistic to extrapolate at the time of launch a lifetime treatment effect. There are other

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	types of evidence that can be leveraged in the decision-making process, including expert opinion, biological plausibility, and clinical evidence from therapies with similar mechanism of action at the genetic and cellular level. However, in this case there are no other CRISPR Cas9 therapies approved to compare to and limited evidence on long term response using this technology in-vivo. The first CRISPR Casgevy treated patient was Victoria Gray, who at nearly 5 years after receiving her dose is still VOC-free as per most recent interviews. VOC-free status for a defined time frame such as two years has been found reliable indicator of continued treatment response with other intervention such as allogeneic HSCT. This has been seen Mahesri et al. which found that after SCT 90% of patients were VOC free for at least two years, This suggests that two years without a VOC episode is an appropriate time frame to suggest a long term response in sickle cell disease given that this was considered a long term follow up. However, we acknowledge that the mechanisms behind gene therapies are newer and further follow up data would be needed to consolidate this. (Mufaddal Mahesri, Su Been Lee, Raisa Levin, Suzan Imren, Lanju Zhang, Lina Titievsky, Rishi J Desai; VOC-Free Status Among Patients with Sickle Cell Disease Following Allogeneic Hematopoietic Stem Cell Transplant: A Cohort Study of Medicaid Enrollees. Blood 2023; 142 (Supplement 1): 3674. doi: https://doi.org/10.1182/blood-2023-189427)
2	While difficult to establish long term effectiveness in cell and gene therapies, we believe that this uncertainty could be alleviated by a managed access scheme. We understand that the price and cost-effectiveness of Casgevy is a limiting factor in the committee considering whether appropriate for a managed access scheme. Allowing managed access could further alleviate uncertainties and establish long term safety alongside long term follow up. Further discussion on establishing a confidential discounted price will be beneficial to establishing a managed access scheme which in turn would also allow further data to be collected.
3	The EAG stipulated that frequency of VOCs does not appear to be an adequate predictor of complications in SCD. Cell and gene therapies often use surrogate endpoints as a proxy to measure a clinical response or complications. It is often challenging for a gene therapy in the absence of high-quality data or a condition with various outcomes to illustrate the various impacts the therapy will have on a patient's life. VOC frequency was used to predict the risk of complications. The EAG outlined that VOC frequency to predict complications is not supported by evidence. Therefore, we agree using VOC frequency may not be a suitable predictor in relation to other complications. Given that this mechanism of this therapy increases the availability of foetal haemoglobin, it has been noted that adults with persistent foetal haemoglobin continue to have the other complications as those without persistent foetal haemoglobin It may be more beneficial to capture any other changes or biomarkers in these complications as a separate endpoint individually in a long term follow up or capture surrogate endpoints that may reflect the mechanisms of these complications. (National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Forum on Regenerative Medicine; Beachy SH, Alper J, Hackmann M, et al., editors. Exploring Novel Clinical Trial Designs for Gene-Based Therapies: Proceedings of a Workshop. Washington (DC): National Academies Press (US); 2020 Apr 9. 4, Developing Endpoints for Gene Therapy Clinical Trials.).
4	There were 35 SCD patients in CLIMB-121. While clinical experts suggested that the size was adequate to reflect clinical efficacy and safety they highlighted that this may be due to the novelty and initial side effects in the initial phases of delivering the therapy. This is a common challenge in clinical trials across gene therapies. Small sample sizes can over or under estimate clinical effectiveness. In this context, the uncertainty regarding the trial size and its impact on the results could be alleviated through a manage access scheme. A managed access would increase the

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	number of patients who undergo the therapy and further consolidate the clinical efficacy and duration of response. This would inevitably lead to further follow up data alongside the long term follow up in the CLIMB-131 trial. Stronger relationships with patient representation groups early on in the clinical trial design process could alleviate this issue in future trials.
5	With long term safety, we note that compared to other gene delivery mechanisms there is a higher risk of in unexpected mutations with the delivery mechanism of CRISPR Cas9. There has been no recorded development of damaging mutation or oncogenesis in any of the clinical trials with Casgevy. However, the risk is apparent and should potentially be collected in a long term follow up trial. A registry similar to those found with CAR-T therapies would be useful in determining any further complications as a result of these novel therapies.
6	Casgevy could be reference point to represent how NICE implements interventions based on equality. NICE has not explicitly added modifiers to any TA with respect to alleviate health inequalities in a disease. While not a rare disease, we understand that a majority of those with SCD dare from ethnic minority backgrounds. Research has shown underrepresentation in clinical trials of ethnic minorities thus, the company's position is understandable when finding difficulty in producing high quality data for trial recruitment. Recent history has shown contempt towards novel therapies in ethnic minorities in the UK. The uptake of the COVID-19 vaccines were notably low in ethnic minorities, with much of the commentary focussed on a lack of understanding of the technology itself and some distrust towards the companies and manufacturers. The COVID era revealed many health inequalities with a disproportionate mortality rate skewing towards ethnic minorities. COVID-19 vaccine hesitance was driven by personal beliefs and mistrust of healthcare organisations. Patient access to Casgevy presents an opportunity for NICE as an organisation to practically illustrate its commitment to alleviating health inequalities by showing they will represent the unmet need in ethnic minorities, and has the potential to rebuild trust with the scientific community.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Whittington Health/Anthony Nolan

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil						
Name of commentator person completing form:	Dr Emma Drasar						
Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.						
Example 1	We are concerned that this recommendation may imply that						
1	I do not believe that all relevant evidence has been taken into account particularly around severity and QOL measurements or at least that the committee has not understood the impacts and clinical diversity of sickle cell disorder and the clinical impact of the intervention..						

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2	Quality of life: EQ-5D is the preferred base case for NICE however it is not appropriate for chronic lifelong disorders. Multiple studies including “No one is Listening” clearly lays out the impacts on patients lives of sickle cell disorder, particularly those with recurrent acute pain episodes and those with chronic end organ damage. This again impacts on life expectancy and number of pain episodes is clearly linked with poor outcomes. It also fails to take into account the iceberg under the water of those patients who manage pain at home and also days missed from work and education and reduction in life opportunities due to their underlying condition.
3	Summary of clinical and cost effectiveness: This does not take into account the long term benefits of reduction/removal of the polymerisation of Hb S. We know from trial data that stem cell transplant and use of hydroxyurea reduce end organ damage and therefore this intervention will have at least the same impact on longer term outcomes. I am also unclear as to why we are including the patients who did not receive the infusion – we have policies and processes in place in the UK to make sure that this does not occur and is very unlikely to occur due to the stringent nature of the review process via the national haemoglobinopathy panel that is present in the UK.
4	Severity: I was very shocked and disappointed that the committee did not seem to understand that sickle cell is a severe, lifelong and unpredictable condition which ruins people's health and lives. Patients die early and with significant impacts on their morbidity. Again this impacts on quality of life. Patients who entered into the trial had to meet the trial criteria and therefore were from a non “end stage” population of patients. However all patients with sickle cell disorder will reach this stage at some point during their lives, even those with “mild” disease. The vast majority of my patients will die significantly younger than their ethnically matched controls as a result of their sickle cell disorder. This intervention could enable patients to achieve near normal health, massive reduction in pain and prevention of irreversible complications. We know from transplant and patients with Hb SHPFH that this is possible and achievable. There are also the removal of the transplant related complication of GVHD and the widening of a curative therapy to those patients without appropriate donors.
5	Recurrent pain: Patients who have had recurrent acute pain or chronic dysregulated pain will take time to recover from the hyperinflammatory environment in which they have been existing. Patients post hip replacement still have pain – we don't refer to those patients as having “relapsed”. When we start patients on red cell exchange they still can be admitted and have pain – this in particular due to the fact that they have 10-30% fully HbS cells and therefore polymerisation can still occur. Due to the pancellular nature of Hb F achieved with this therapy that directly inhibits polymerisation this is likely to be more successful than the above interventions which are approved by NICE.
6	Discrimination: The majority of patients with sickle cell disorder are of African or other immigrant heritage. They have existed in an uncaring healthcare environment and have been subject to racist and discriminatory practice by healthcare professionals throughout their lives. I think that the race of patients and the impact of their health condition cannot be ignored as they are far more likely to encounter negative attitudes in a recurrent manner throughout their lives

Insert extra rows as needed

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- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Name of commentator person completing form:	Funmi Dasaolu
Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that
1	No, I feel the committee have not fully understood the nature, severity, and impact of Sickle Cell Disease on the quality of life of those affected. This relates to bullet point one.
2	The committee demonstrated an understanding of the impact and effects of Vaso-occlusive Crises on individuals with Sickle Cell Disease, however, I feel that have the fully appreciated or understood Sickle Cell Disease is so much more than Vaso-occlusive Crises and it's complications. This relates to bullet point one.
3	Using Vaso-occlusive Crises that result in hospitalisation as a measure of severity is flawed, and fails to acknowledge the full impact of the condition. It does not take into consideration the vast

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	majority of individuals who try and manage crises at home and avoid seeking treatment due to previous negative experiences, stigmatisation and discrimination. This relates to bullet point one.
4	I do not believe, the long-term cumulative effects of Sickle Cell Disease has been considered by the committee. Irrespective of Vaso-occlusive Crises resulting in pain and/or hospitalisation, the 'silent' sickling that is constantly occurring within the body leads to significant and irreversible organ damage and complications. As such, individuals may not present with frequent crises, but this does not negate the damage occurring (hence the need for regular screening and preventative care). This relates to bullet point one.
5	The committee has not appreciated or taken into consideration the preventative strategies or lifestyle changes/adjustments individuals with Sickle Cell are forced to make in order to try and live a 'normal life', nor the impact this has on quality of life whilst trying to manage the condition. This relates to bullet point one.
6	The EQ-D5 is not suitable, effective, or accurate in measuring quality of life in individuals with Sickle Cell Disease. There is need for a better suited tool when exploring impact on quality of life in this population. As the condition is congenital individuals are only able to truly understand the impact on quality of life once the negative effects of the condition have been removed. This relates to bullet point one.
7	No, I do not believe the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. The committee has not fully understood the results from the trial sample size indicate Exa-cel is safe, effective and the results can be generalised to the specific population in question. The safety and efficacy of Exa-cel is what people with lived experience care about the most. This relates to bullet point two.
8	No, I do not feel the provisional recommendations are sound and a suitable basis for guidance to the NHS. My concern is Exa-cel offers a possible cure, which would give much need hope to desperate individuals. However, the provisional recommendations leave a gap in the treatment pathway for individuals with Sickle Cell Disease. The question remains what alternatives are there for individuals who have tried all options available via the currently available standard pathway of care, yet still experience severe disease. This relates to bullet point three.
9	Given the nature of Sickle Cell Disease it falls into the category of a disability, as per the Equality Act 2010. As disability is a protected characteristic, I personally feel the preliminary recommendations needs amendment to ensure adherence with the aim of fostering good relations between people with a particular protected characteristics and others. Although, preliminary this recommendation does not come as a surprise to many within the Sickle Cell community. Sadly, it further exacerbates inequality, and feelings of insignificance and discrimination. Many feel Sickle Cell is not a priority for the NHS, and see this decision as a reflection of the racial undertones which have plagued Sickle Cell care and treatment over the decades. Moreover, it further widens the gap between Sickle Cell and the treatment landscape of other similarly inherited conditions, and amplifies feelings of mistrust towards healthcare professionals. This relates to bullet point four.
10	The preliminary recommendations adversely impact those already disadvantaged because of their disability. Exa-cel offers a potential cure, where no other treatment has been effective. As it is not recommended for treatment of Sickle Cell Disease, it leaves many with the condition with no viable options for curative treatment, thus, negatively impacting quality of life. Many feels this recommendation compounds the inequality already experienced. This relates to bullet point five.
11	In regards to cost-effectiveness, whilst there is a significant cost to the NHS should Exa-cel be recommended, this has to be balanced with the cost incurred over the lifetime of an individual with Sickle Cell Disease taking into consideration management of the condition day-to-day, acute pain episodes resulting in hospitalisation, the complications and associated treatments, medicines, transfusions, and management of chronic pain, as well as the impact on society and the welfare state. I am not sure this has fully been considered by the committee. This relates to bullet point two.

Insert extra rows as needed

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Has all of the relevant evidence been taken into account?

Please see responses to subsequent questions.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I believe the recommendations fail to take into account the severity of sickle cell disease. I was present as a Clinical expert and much of the debate hinged upon interpretation of the variable quality data available to guide both EAG and NICE committee. As a consequence, we are in danger of failing this patient group once again. By failing to acknowledge the disease severity and impact we will be failing to provide a low risk, effective cure for those most severely affected. As a clinician with over 30 years of experience caring for patients with sickle cell disease, I have witnessed the physical and psychological toll of the disease first hand. Normal life expectancy in the UK is around 80 years of age and, although studies of life expectancy give differing results there is no argument that individuals with sickle cell disease have a life expectancy that is around two to three decades less than the general population. Quality of life studies such as PISCES (McClish DK, doi:10.1186/1477-7525-3-50) and SWAY highlight the severe restrictions associated with sickle cell disease. I therefore do not see any grounds to continue to debate the severity of this disease.

For decades sickle cell disease services have been under funded/provided and research funding minimal. This has severely affected access to the kind of high-quality data that we are used to for haematological malignancy or inherited haemorrhagic diatheses. Much of the data we have to work with does not fully clarify the clinical severity, the mortality and morbidity risk or the impact on patients' quality of life and equality of opportunity.

As an example of the problems we face, despite small improvements in sickle care within the NHS, good epidemiological data remains hard to come by. The inadequate funding for sickle services and data input into the National haemoglobinopathy registry leaves us with an incomplete picture. In Europe the French have experienced similar issues (Haematologica 2023 Sep 1;108(9):2476-2486).

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I am not qualified to comment on the economic and cost effectiveness modelling so will concentrate this response on the effects of sickle cell disease from the perspective of survival, severity, quality of life and the benefits of exacer.

Survival and severity:

There are numerous reports highlighting the severity and early mortality of this disease (Udeze C. British Journal of Haematology 2023, Piel FB, Blood Cells Mol Dis. 2021;89:102567, Di Mauro M, Am J Hematol. 2023;98(11):E341-e4., Brousse V, Haematologica. 2023;108(9):2476-86. Jiao B, Blood Adv. 2023;7(13):3276-83.). Similar survival rates are seen in the Jamaican

cohort study, a case controlled study established in the 1970s which shows 55% of the population alive at the age of 40 years (<https://doi.org/10.1371/journal.pone.0192710>).

The frequency of organ specific chronic organ dysfunction is likely to be high but data is limited and this aspect of the disease an evolving story. Definitions of chronic organ dysfunction in sickle cell disease are unclear, partly because many organs eg kidney, liver, heart, lung show evidence of altered function early in life. What is certain is that the process of HbS polymerisation is lifelong and attritional to the microvascular circulation and hence organ function. Hydroxycarbamide does not reverse this process.

Pain remains the most frequent symptom and, despite the difficulty of using this subjective symptom as a measure of disease severity, remains the most commonly used marker of severity. Pain diary studies document that most pain is experienced outside the healthcare setting with almost a third of patients reporting pain every day (<https://doi.org/10.7326/0003-4819-148-2-200801150-00004>). This must be recognised when evaluating both severity and response to treatment. Failing to do so undermines the meaningful evaluation of any new treatment.

Quality of life:

The SWAY study clearly articulates the challenges faced by those with sickle cell disease across all aspects of their life. Studies consistently demonstrate that individuals with SCD experience lower HRQOL compared to the general population. Moreover, comparisons with other chronic diseases such as cystic fibrosis and asthma reveal similar or even lower HRQOL scores among patients SCD patients. Further study from the Comprehensive sickle centres in the US documents the substantial impairment of HRQOL in adults with SCD suggesting that more effective treatments of persistent pain and depression would provide the largest HRQOL benefit.

Benefits of exacer:

The CLIMB 121 trial evidence suggests an effective cure. This is unsurprising considering the very high levels of HbF achieved, the pan-cellular nature of the distribution and the effect this will have on polymerisation of HbS (<https://doi.org/10.1182/blood-2013-09-528067>). That a trial patient had an episode of pain post treatment has raised questions of the effectiveness of the treatment. However, pain is a complex and subjective phenomenon. Experience suggests that in those rare patients with frequent acute or chronic pain, with a history of high or frequent opioid analgesic use, develop central sensitisation or opioid hyperalgesia. This maybe further complicated by the knowledge that pain similar to sickle cell can occur on reduction of opioids particular if this is done too quickly. In such patients it would be wrong to assume all pain is vaso-occlusion driven. Once again this highlights the difficulty of severity markers in sickle, there being no clear measurable biological marker of disease activity. The phenomenon of pain post treatment is also seen in patients post stem cell transplant (Br J Haematol. 2019;184(4):690-3).

).

There is also the debate regarding eligibility for the 1.5% discounted rate. I would strongly suggest that this case does meet the criteria as set out below:

1) *Without treatment people would die or have a severely impacted life:*

Please see previous section on survival and severity.

2) *Treatment will restore full or near full health*

The trial data show an increase in total haemoglobin accompanied by a reduction in markers of red cell breakdown, prevention of further sickle complications and improved quality of life. Whether the treatment will reverse all aspects of chronic organ damage present before conditioning is uncertain but seems unlikely. In younger patients the risk of significantly disordered organ function is much lower.

3) *Benefit likely to be sustained*

Thus far trial participants have shown consistent and stable high levels of the edited gene, and as a consequence very high levels of HbF at a level that will prevent the key pathogenetic event; the intracellular polymerisation of HbS (ref). There is no biological reason to believe that transcription levels will decline appreciably with longer follow up. Re-reading the NHSE commissioning documents on sibling stem cell transplantation (<https://www.england.nhs.uk/wp-content/uploads/2020/02/clinical-commissioning-policy-allogeneic-haematopoietic-stem-cell-transplantation.pdf>) it is clear that, using similar evidence of disease severity, this expensive treatment was approved risk on the basis of it being a *potential cure* despite a significant risk of early and late graft failure, graft versus host disease and no analysis of cost effectiveness. Whilst I understand the NICE processes maybe more detailed, it would seem we are adopting different standards to the approval of curative treatments for use in the same setting. This is confusing and inconsistent.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

It seems to me that the difficulties experienced with the assessment of exacel relate to the lack of high-quality evidence on the natural history of the disease and the absence of a highly reliable marker of severe disease. Uncertainty with respect to the paucity of high-quality evidence of severity, impaired QOL or impaired survival must not be confused with absence of early death, impaired QOL for this disease group. The effect is particularly marked for those who have frequent complications who are unlikely to survive much beyond their fifth decade (<https://doi.org/10.1002%2Fajh.23683>).

The issues around evidence described are themselves a result of discrimination and inequality within the NHS, society and research funding prioritisation. A recent publication in the US highlighted the 10-fold financial disparity per patient between national research funding on sickle cell versus cystic fibrosis. (*J Clin Transl Sci.* 2023; 7(1): e65). My point being that NICE have reached their conclusion based on an inadequacy of good evidence which is, in itself, a result of longstanding inequality in

service provision and research. The “no” decision therefore risks amplifying this discrimination. That we are still debating the severity of the disease is an example of such discrimination. Whilst the published report comments that patients may be less likely to engage with research and correctly stresses the effects of deprivation, less emphasis has been placed on adverse effects on health of the decades of limited research funding. Using the example of cystic fibrosis once again to highlight the impact of poor funding; the last decade or so has seen major changes in the understanding of the disease, developments of new classes of therapies and multiple clinical trials and consequent changes to prognosis and survival. In comparison during that period Sickle cell patients saw a small handful of new drugs reach phase 2-3 trials (excluding exacer) most of which have proved to have a limited or inadequate effect. None have had ongoing NICE approval.

I am not qualified to comment on the DCEA models used but feel I need to highlight the hidden effects of discrimination, not just in healthcare provision but also in research funding.

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Name of commentator person completing form:	Toby Bakare
Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
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1	Has all of the relevant evidence been taken into account? No. From having attended the meetings I believe there were some fundamental misunderstandings about what the disease is and what the symptoms are. As someone who has

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	experienced VOCs that had Acute Chest Syndrome and VOCs that didn't include Acute Chest Syndrome it was frustrating to hear the committee struggle to understand the difference between the two and issues around double counting in the data etc. I think that the seriousness of the disease and the wide variety of symptoms are misunderstood. That leads to a not understanding the potential for the treatment or the reality for people currently living with Sickle Cell. The dramatic difference between having the faulty gene that causes Sickle Cell, VOCs and everything that comes with it is something that I don't think is understood. It's something that I'm only fully understanding now that I am post-transplant. The difference in my own life is that my blood doesn't sickle, there is no pain when performing my daily activities, I can be active even putting my body through rigorous physical exercise and not have physical pain. That's a fundamental difference in my quality that's more drastic than any previous measures, i.e. standard of care. I am dealing with the legacy of Sickle Cell and the organ damage that accompanies it but the fundamental flaw that was there before of a gene that causes Sickle isn't there and it has changed my life hugely.
2	Are the recommendations sound and a suitable basis for guidance to the NHS? I don't believe that they are. It has to be considered that there is a lack of treatments for Sickle. The current standard of care options do offer improvements but in the case of blood transfusions they are temporary and cumbersome and in the case of Hydroxyurea, in my own experience, it left me with less frequent crises, but when they did occur they were more painful and severe than when not on taking hydroxyurea and thereby the risk of Acute Chest Syndrome, Sepsis, etc did rise. Standard of Care i.e. Hydroxyurea still leaves a sufferer of Sickle Cell with blood that can and does Sickle. What percentage of that blood sickles will determine on any given day whether a sufferer will have a severe VOC and be hospitalised. But a certain percentage does Sickle every day. That leads to host of other complication from kidney damage to avascular necrosis, other chronic pain condition and extreme fatigue. This will all need to treatment on the NHS.
3	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes in part. It would be helpful to know the cost of Standard of Care as I believe that a lifetime of treatment does a create a burden on the NHS. The cost of Exa-cel treatment is expensive, but if the potential is drastic with the potential to improve the lives of thousands of people, then I believe it needs consideration as a treatment, at least with a view to managed access. The cost of hospital admissions, transfusions, and of course the economic impact of having people not work needs to be understood. I can speak from myself that the difference in my quality of life has been drastic. I expected this as I discussed the procedure with my medical team but the reality of being fitter, healthier, pain -free and able to do what I want is still a huge adjustment for me and in the best possible way a huge surprise!
4	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? The committee did give consideration for the fact that this is a disease that affects mainly black people of African origin, but the reality is that they may not appreciate the lack of options for treatment for people.

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Consultation on the draft guidance document – deadline for comments 5pm on 11 April 2024. Please submit via NICE Docs.

	I hope the committee is aware of funding discrepancies between Sickle Cell and similar medical conditions such as Cystic Fibrosis, which according to recent parliamentary has twice the amount spent on it for research. In terms of possible treatments, it's believed that there are 511 treatments for Cystic Fibrosis while for Sickle Cell the number is 3 (The Lancet, Vol 10, April 2023) this is before the recent decision not to make Crizanlizumab available on the NHS. I believe equality considerations are not compatible with having a curative option that is unavailable for people who need it.
5	Comment on section 1.1 (Recommendations), "long-term": It's not clear to me here if the science is being disputed or not. If the blood produced post transplant isn't HB SS, i.e blood that sickles, then why would the the patient experience symptoms of acute pain. I feel this is again science around the disease not being understood.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is **'commercial in confidence' in turquoise** and information that is **'academic in confidence' in yellow**. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the [NICE Health Technology Evaluation Manual](#) (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Single Technology Appraisal

Exagamglogene autotemcel for treating sickle cell disease [ID4016]

Comments on the draft guidance received through the NICE website

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	
Yes	
Are the recommendations sound and a suitable basis for guidance to the NHS?	
Yes	
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	
Yes	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?	
No	
Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	
The evidence appears sufficient to roll out the treatment to those who urgently need this treatment.	
Are the recommendations sound and a suitable basis for guidance to the NHS?	

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Get it over with. Who is worrying about the cost? I have not worked since last December struggling with the side-effects of Hydroxycarbamide and someone is worrying about cost. Please save me the trouble and get on with it.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

Comments on consultation:

This is a welcome treatment consultation on Sickle Cell Anaemia. Any treatment that will alleviate the impact of this disease and suffering of the affected individual would always be considered as top priority. Who feels it knows it as the saying goes. This treatment will improve the quality of life of the sufferer and their carers. It will indeed mark a new epoch in the treatment of this disorder. The outcome of this whole process will be generational with many living a longer but stress free life.

Name	
Organisation	East Midlands Haemoglobinopathy Co-ordinating Centre
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

Caring for patients across the East Midlands HCC region, we feel that the severity for those living with sickle cell disease has not been fully appreciated. We have experienced numerous instances where people living with sickle cell have suffered consequences as a result of their condition that have a significant impact on their quality of life, as well as life threatening complications which endanger their life. The impact that this has on their ability to live and work as a valuable member of society is significant. Many people with sickle cell disease have lived most of their lives not expecting to live past the age of 40 and whilst care has improved to address this, there are still those who have not been so fortunate and lost their lives to this condition. The potential for there to be a curative therapy to address this for those who have not the fortune to have a sibling donor is life changing for some who wish to undergo curative treatment.

Are the recommendations sound and a suitable basis for guidance to the NHS?

As above, we feel that the severity of living with sickle cell and therefore the potential benefits in terms of quality of life as well as impact on life expectancy is not addressed. The NHS is currently managing the consequences of a lack of curative and effective treatments for those living with sickle cell disease. This includes the inpatient burden for those requiring frequent admissions, as well as the consequence of managing complex co-morbidities due to the long term organ damage that can occur. Wider society is also impacted; the impact of loss of earning potential not just for those directly affected but also for those in caring roles is also important to consider.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The clinical effectiveness is not reasonable if you fail to interpret the clinical severity of living with sickle cell disease.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

It is well recognised that those who live with sickle cell are more likely to be from a black and minority ethnic group. This can make those living with the condition feel that when such decisions are taken, it is a reflection of their race and not a reflection of the evidence being presented. It is important that this is recognised.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

Though the recommendations are sound. The study is not extensive enough to shelf the drug within the NHS.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, the cost effectiveness does not take into account the cost of VOCs when a patient is admitted to hospital. The cost effectiveness is not calculated with this in mind.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes it's very obvious that as the condition predominantly affects black African and Caribbean people we are being ignored. This drug has the ability to reduce VOCs and help save lives from complications of the disease.

Name	
Organisation	N/A
Conflict	N/A

Comments on the DG:

I wanted you to know how important treatment like this is for people living with sickle cell disorder.

I was one of the first adults to have the allogenic stem cell transplant on the NHS just over 2 yrs ago.

I now have a new life. This is because I had a 100% HLA match who was my sister.

I no longer live with the fear of dying from any number of complications sickle cell presents on a day to day basis.

I am no longer in pain daily.

I don't have to find someone to look after my kids on short notice.

I no longer have to live on the breadline to provide for my family.

I am now able to work more and contribute to society.

Sickle cell is a terrible disease. It is a disorder that caused my whole life to be out of order! It impacts the black community disproportionately and it is time to move forward with treatments so that we too feel seen and valued in society.

Thank you for the hope this treatment will offer to many.

Name	
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

No. There is a fundamental misunderstanding about how the debilitating symptoms of SC manifest differently and their impact on day to day life for those living with the disease and it's far reaching physical, social and mental effects.

I also do not think that the long term organ damage is fully appreciated. The physical manifestation of Sickle Cell exists on a spectrum, whilst some patients may not experience regular crises, blood transfusions, pain etc, this is not to say their organs are not being damaged with each day and the legacy this causes for their long term health. What doesn't affect people today, affects them tomorrow. They are also unable to participate in normal physical activities, which can leave them on the fringes of society.

The earlier the gene therapy is offered the less the long-term damage will be experienced both mentally and physically.

The detrimental effect on the mental health of SC patients has not been fully appreciated, particularly for Black males who have a high incidence on untreated mental health challenges.

Furthermore, the existing social & health inequalities experienced by the African Caribbean communities have not been considered. Coupled with SC, those living with the disease are often experiencing poverty which makes managing the disease challenging and difficult to manage. Treatment for SC disease is not consistent and there is still a huge lack of knowledge and understanding within medical settings outside of the major cities i.e. London/Birmingham. This leads to further exacerbation of health inequalities.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I don't believe that they are. Without gene therapy, patients are left with therapeutics that alleviate symptoms somewhat, however their quality of life is still impacted.

There is a lack of accessible cures for SC that do not require donors, which bring their own challenges when trying to acquire a suitable match.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Whilst the cost of treatment is challenging at present, the impact on people's lives will be revolutionary. The cost of managing the disease must be considered- hospital stays, transfusions, drugs, support services. As mentioned, the long term implications of SC on organs, creates further pressure on the NHS as they have to be treated.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Within the Afro Caribbean community, there is a huge stigma of having sickle cell disease. Whereby people are dissuaded from reproducing with someone who has the disease/trait. This has a profound effect on those living with the disease who are sometimes viewed as social pariahs. This has a profound effect on their mental health how people negotiate their adult life, how they see themselves and their understanding and acceptance within their community.

Together with the existing health inequalities experience by Afro Caribbean societies, and the impact of SC disease on daily life and mental health, SC serves to push those living with the disease further onto the fringes of society, with little hope. As a parent of a child with SC, this is something already at the forefront of my mind, even though my child is only in primary school.

A cure for SC would be freeing for so many and give them an opportunity to live a life free of debilitating pain, hospital stays and constant fear of when their next crisis will happen.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

As a former medical practitioner from the black African community, I have seen at first hand the severe physical pain every single person afflicted with SCD goes through. I have seen the devastating impact on loved ones. I have seen some die. I am very familiar with the health economic arguments and modelling as someone with a Master in health management degree from Imperial College. However this is one of the flaws of the health economic modelling used when determining whether a drug or therapy should be approved by NICE. It can be a very cruel way to determine how they should be applied. I believe that giving the opportunity for human consultation as this should mitigate that. NOTHING a can justify withholding this therapy for use. At the very worst you classify the sufferers into how severe their conditions are the most severe have access to the therapy. It is a travesty to decline the use in any form at all. It is simply a cruel decision.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Comment on section 1 (Recommendations), 1.1, “The acceptable cost-effectiveness estimate for exa-cel is higher than what NICE normally considers to be a cost-effective use of NHS resources.”:

Cystic Fibrosis has had several medication approved since 2021, which on par was not considered too expensive. The licence has also been extended.

Comment on section 1 (Recommendations), 1.1, “This is a reasonable adjustment to account for health inequalities and the innovative nature of the technology. Even when taking this into account, the cost-effectiveness estimate for exa-cel is still above this. So, it is not recommended for routine use.”:

This is one of the first treatment option available for people with Sickle Cell Disorder for three decades. How is this equitable never mind cost effective?

Comment on section 3.1 (Details of condition), “The committee heard that the complications affect people's mental health and daily activities, in particular their ability to work, go to school, to exercise, to travel and to live with spontaneity.”:

The Socioeconomics also impacts on parents and carers who often have to take time off from employment or education to support their child. Some even at risk of losing their jobs or not fulfilling assignments whilst at university or college.

Comment on section 3.1 (Details of condition), “This is because there is a large variation in the care offered from one hospital and region to another and people with SCD often feel stigmatised by healthcare professionals (see section 3.17).”

Discrimination and Health Inequalities on the grounds of Race is a major factor in this condition. Pain is rarely managed appropriately in the hospital setting leading to further complications, longer stays, infection and fear of utilising treatment.

Comment on section 3.1 (Details of condition), “They noted that they could not remember a day without pain, whether that be mild, moderate or severe.”:

Can we really justify that 2024 in the UK we are allowing individuals to come into our hospital and be left in pain for long periods against NICE Recommendation. Is this acceptable? Certainly having Gene Therapy in the short term may very well be expensive, however long term it would be cost effective.

Comment on section 3.1 (Details of condition), “It also concluded that there is high unmet need for effective treatments that improve outcomes and QoL.”

In 30 years only Hydroxycarbamide is the only acceptable medication and how many have been turned down in the last 6 years, this is not fair or equitable.

Comment on section 3.2 (Treatment options), “Patient experts highlighted that people with SCD want choice and e”

Where is the choice when the only option of drug is Hydroxycarbamide. and It has taken over 30 years to see the benefits or side effects.

Comment on section 3.5 (Clinical trial evidence), “It also noted that more data collection to establish the long-term effectiveness of exa-cel would reduce the uncertainties around durability of the treatment effect.”:

More research and data collection is needed. How will this be achieved if any forward thinking treatment options are declined?

Comment on section 3.9 (Long-term treatment effects), “but that this should be explored further with additional data collection.”:

Hence the need to support such therapies so data and research can be collected.

Comment on section 3.16 (Identified health inequalities):

Recommendations is bias on the grounds of Race. Black African Caribbean people have suffered for decades Sickle Cell predominately affects this group. What treatments have been available in 30 years and how many have been turned down where is the equal or equitable? Racism comes to mind.

Name	
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes sickle cell affects people of Afro-Caribbean only, therefore discriminating against them by denying them treatment that can change their lives

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

All evidence has, but not to their full extent. (Summary of thoughts in the Comment below)

Are the recommendations sound and a suitable basis for guidance to the NHS?

As they currently stand, no. (Summary of thoughts in the Comment below)

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. (Summary of thoughts in the Comment below)

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes. (Summary of thoughts in the Comment below)

Comments on consultation:

My name is [REDACTED]. I am a 24 years old female Sickle Cell patient (HbSC). I have suffered through VOCs, hospitalisation and other medical conditions caused by my sickle cell conditions. I am grateful for the opportunity NICE has given patients to comment on their draft recommendation on the NHS funding Exagamglogene autotemcel for treating sickle cell disease.

I wish to submit a comment in response to the overall draft recommendation, covering two main points and a summary of additional thoughts set out by the subheadings below.

1. The negative impact that severe sickle cell has on the day to day life of people living with the condition

Sickle Cell is systemic and can affect all parts of the body, there is currently no one-treatment-for-all. This can lead to daily complications such as the ability to walk, work, be in school and wash and care for oneself. There is often significant financial costs such as equipment for disability adjustments, medicine due to not automatically entitled to the Med-Ex card, reduce in assets to qualify for certain disability allowances, missed days off work, and many more examples). There is also a cost a physical and mental cost of the daily upkeep in health for sickle cell patients.

The negative impact does not begin and end in the event of a VOC, many suffer symptoms leading up to a crises such pain, nausea and chronic fatigue; and are often left with a weakened body which must take time to heal once the crisis is over. For example, I had a crisis in my leg which had me admitted into hospital for only under a day but left me be unable to walk properly for almost four months after being discharged.

The negative impact of SCD would be significantly lifted with the introduction of Casgevy. Eliminating VOCs from the lives of SCD patients would lead to less hospitalisations, less time off sick and less costs to mitigate the debilitating effects of pain crises (before, during and after). Quality of life would improve greatly due to no longer worrying of the uncertainty of tomorrow which SCD often brings.

2. The worsening impact that sickle cell has over time

It is well documented the worsening impact SCD has with age. As aging often brings its own set of health complications, these can be aggravated by SCD. Often is the case of older SCD patients having to take early retirement due to the illness becoming debilitating to work despite being decade(s) away from the actually retirement age, and often not even in the financial position to do so.

However, this does not only occur when reaching middle-age or becoming elderly. For example, my Sickle Cell was more severe during childhood, improved in my teenage years and has started to get worse again in my later teens to early adulthood, all under the age of 25 years old. Therefore the progression of SCD (or better put, the regression of the health of the SCD patient) must be taken into account to build a more accurate picture of the severity of the disease and its worsening impact over time.

Casgevy can make things better by allowing us to age more steadily and gracefully. I would not want my future children become early care-givers.

Life won't feel like a ticking time-bomb, and we can have a future to look forward to with hope.

3. Additional Thoughts:

Innovation: This is the first time as a lay person hearing innovation be an inhibitor. I believe the innovative aspect should highlight the milestone is research, and excite new possibilities of curable chronic diseases. Mainly highlighting the uncertainty seems a slight pessimistic read of this aspect. Treatments have been known the breed treatments, as seen in hydroxyurea's origins as a drug for cancer patients now also used for Sickle Cell. The possibility of a domino-effect of funding this treatment leading to other possible cures could be considered instead.

Discrimination: Sickle Cell is one of the most common genetic disorders in the country. Another common genetic disorder, Cystic Fibrosis has a population of 11,000 patients and 511 treatments available, Sickle Cell's population is at almost 17,000 with currently only three treatments. Why is there such disparity between the treatments available for one condition over the other? It cannot be ignored a main difference between the average patient of CF and SCD which is race. I implore the committee to ensure that this decision be made completely unbiased, free of prejudice and of fair and sound judgement. Often we as patients have had our voices ignored, despite being the ones to experience the disorder ourselves. This experience, as seen the case of Tyrone Airey has been known to be fatal. I implore the committee to not make another fatal mistake in judgement today.

Thank you for taking into consideration our comments, and we hope NICE are able to come to the correct decision by recommending the NHS funding of this vital, life-changing and life-saving treatment.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
As a sickle cell sufferer after working for a long time i have had to retire early. The impact of sickle is greater than you know pain, anxiety fatigue. Anxiety depression you feel like ending your life. Nausea means unable to eat and drink no nutrition. Cannot socialise too depressed. Physical impact mobility issues need walking aids. Over time sickle and thalassemia impacts heart, spleen, bones eyes gallbladder skin teeth other issues to manage Functional neurological disorder fibromyalgia. Financial impact is greater to manage condition additional costs as well as perscription cost holistic approaches that help but too costly. Unable to work so rely on benefits struggle to pay	

bills by the right food. Its hard to know you could have a crisis and die. Also challenges with the right care at the right time

Name

Organisation

N/A

Conflict

N/A

Comments on the DG:

Dear NICE Committee,

I write in response to your consultation regarding the use of exa-cel in sickle cell disease. I write as a practicing haematologist specialising the care of individuals with haemoglobin disorders, and as

[REDACTED] Sickle Cell Haemoglobinopathy Coordinating Centre. I appreciate that you have already been presented with a significant amount of evidence on these matters but must recommend that the initial decision not to make this treatment available for this patient group be reconsidered.

Sickle cell disease is a serious condition which detrimentally affects both quality of life and life expectancy of sufferers. I have many patients who experience weekly or even daily pain, some of which is extremely severe. Most patients manage the majority of their painful crises at home, and therefore data on hospitalisation will inevitably underestimate the frequency of pain and its effect on patients' lives. I see high rates of anxiety and depression, inability to work or to manage usual activities of daily living due to the effects of this condition. I understand that evidence relating to reduced life expectancy has already been presented, and accords with our regional experience of untimely death and life-threatening complications in a significant proportion of young adults. I have no doubt that this condition is a serious one and should be acknowledged to be such during this consultation.

The second point I wish to comment on is the anticipated longevity of exa-cel treatment. As this form of genome editing works by permanently disrupting a region of the BCL11A gene, there is no plausible biological mechanism by which edited cells might revert to their pre-editing genetic sequence. The genetic modification of these cells should be considered to be permanent. Stability of editing levels seen in the peripheral blood and bone marrow 2 years after treatment in the relevant clinical trial indicates that the longer-term repopulating haematopoietic stem cells were successfully edited. This is a strong indication that the treatment will be effective in, at the very least, the long term.

In terms of treatment efficacy, based on the high foetal haemoglobin percentages achieved by trial participants, with pancellular distribution of this haemoglobin, there will be meaningful clinical benefit. We have well established data, presented already, which demonstrates the correlation between HbF level and severity of disease including life expectancy, and there is no reason to believe that attainment of such high HbF levels via

genome editing would not be as beneficial as where they are conferred by inherited genetic polymorphism.

Finally, I acknowledge that exa-cel treatment is an intensive procedure with all of the risks we usually associate with myeloablative busulphan chemotherapy. Therefore, if available as a treatment option, it would be reserved for those with the most severe disease which is not adequately controlled by hydroxycarbamide treatment. There would be a rigorous and systematic assessment and review process for any patient in whom exa-cel therapy would be considered, such as there is currently for sibling bone marrow transplantation for adults, for which all potential cases are discussed by the National Haemoglobinopathy Panel with numbers of patients proceeding with that treatment option in practice being low. Based on my experience of considering other novel or intensive therapies with patients, such as crizanlizumab (when available) or allogeneic stem cell transplant for adults, I anticipate a low take-up of the option of exa-cel even in eligible patients, were it to be made available. This is due to a number of anxieties many patients hold regarding less well established treatments, as well as their personal priorities which often include maintenance of fertility.

In practice, therefore, numbers receiving this therapy would be only a small fraction of the total percentage of patients with sickle cell disease. However, there is a significant minority of patients with very severe disease and frequent crises, for whom current treatment options are inadequate or inaccessible, and who have an intolerable level of suffering, for whom exa-cel now represents their only chance of long-term amelioration of disease. It is on behalf of this minority of patients, who have no other option and a high burden of unmet need, that I write to request reconsideration of the committee's initial decision and that this therapeutic option might be made available to them.

Yours sincerely,

, Sheffield Teaching Hospitals NHS Foundation Trust

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	
Please refer to my comments	
Are the recommendations sound and a suitable basis for guidance to the NHS?	
No. Please refer to my comments	

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. When you consider the cost of hospitalisation of sickle cell patients (which for some they have spent a significant proportion of the life in hospital), surely have a drug that could cure sickle cell would be more cost effective- has this been considered?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Given the health inequalities that exist within the black community along with the recognised and acknowledged medical racism, it could be argued that the recommendations by NICE have not fully looked into this area- leading many to conclude that perhaps the aspect of race has not given due consideration. Please also refer to comments.

Comments on consultation:

Dear NICE,

As a member of the African and Caribbean community, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom.

This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease.

Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent.

In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage. Making this disorder one of the most (if not the most) common genetic disorder in England.

This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years.

The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people.

Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18.

These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community.

The health inequalities faced by the African and Caribbean community in the UK are well-documented.

Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare.

A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts.

Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease.

Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition.

By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease.

This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run.

It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition.

Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future. Such health inequalities tragically highlighted by the covid pandemic now urgently needs to be addressed.

Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system.

It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be.

This is unacceptable and goes against the principles of equality and fairness that should underpin our society.

I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible.

The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group.

By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long.

Thank you for your attention to this critical matter.

I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.

Name	
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

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This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run.

It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition.

Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future.

Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system.

It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be.

This is unacceptable and goes against the principles of equality and fairness that should underpin our society.

I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible.

The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group.

By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long.

Thank you for your attention to this critical matter.

I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.

Yours sincerely,

[Redacted Signature]

Carer

Name	[Redacted Name]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

I believe further discussion at the second stage of consultation is required as further evidence should be evaluated regarding the impacts of sickle cell disease on individuals physical health- acute chronic episodes of pain and fatigue, intellectual needs- children missing out on education due to the symptoms of this disease and people unable to attend work, emotional wellbeing- health anxiety and depression, and social needs- unable to meet with friends and family and feeling isolated, this highlights the severity of the disease. When considering the holistic needs of patients with Sickle Cell Disease it is evident that this impacts many areas of an individuals life. Considering evidence from patients in the US who have received this treatment and given their account on the experience and the positive impacts of this treatment also indicates the benefits of this approach.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, after reading the review of an individual who had undergone this treatment, the benefits of this new treatment option were highlighted whilst also understanding the physical and psychological impacts of this treatment, it was concluded to be a beneficial treatment and improved energy levels, feeling of control and quality of life. I believe that further research should be undertaken and that this treatment option should not be ruled out.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Whilst it is important to consider the cost effectiveness of this treatment, it is also important to consider the impact this treatment could have on many individuals and families quality of life. Whilst currently individuals who experience sickle cell crisis present to A&E for treatment have repeat infections and admissions to hospital as a result of this disease, which costs the NHS, the treatment could help to reduce these admissions and patients quality of care and trust in the NHS after years of reporting poor quality care for sickle cell disease.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Socioeconomic factors should be considered within this study as this correlates to poorer health outcomes. It is important to consider the current health inequalities which impact an individuals health and wellbeing. Care for sickle cell disease has been reported as being poor and individuals have stated feeling judged and stigmatised when requesting pain relief, it is important to consider how this currently impact individuals mental health when accessing services in vulnerable circumstances.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	
I am not assured that the committee fully understand and appreciate the negative impact of living with sickle cell, the every day mental and physical burden and exhaustion of living with sickle cell. The unpredictability and fear of vaso occlusive crisis.	

This treatment should be available from about 6 months of age. We know that children have strokes, infections etc which can end up being fatal.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I have read the recommendations, but realistically not everyone that has SCD, will be offered this treatment. A criteria will be imposed as it is for most treatments, for the most severe patients. But this must be made available to all. Someone may not be severe now, but in a few years things could change.

I am aware that zolgensma is available for SMA patients at a cost higher than exagamglogene, so I do not understand this difference in treatment. I also do not understand why it will be offered to patients 12 and over. Why would you not seek to improve the lives of those under 12 living with sickle cell.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No.

It is much better to cure us from our suffering, allow us to live better lives and contribute to society the way we want to. 58% of SCD patients are no longer able to work, 76% have to reduce their hours. These are very significant.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes

The fact that this is a condition that mainly affects black African and Caribbean people. The fact that sickle cell is not understood by professionals, politicians and the like. The fact that there is huge disparity with how we are treated. We don't even get free prescriptions, compared to other conditions like cystic fibrosis and diabetes. We are asking for to be listened to and for help to cure this condition. Additionally, there have been other treatments made available and they also have been withdrawn. Researchers are not going to want to invest time and money into sickle cell, if everything that is presented is then withdrawn or not approved.

It is very clear the disparities with managing sickle cell for the NHS is down to race. If this is something that mainly affected the white population, as is cystic fibrosis, we would be much further ahead in managing and curing this condition.

It is clear the level of discrimination due to race and sickle cell.

Comment on section 1 (recommendations):

This is extremely disappointing that with such a major break through in curing sickle cell; a most debilitating condition to live with, can now not be offered to sickle cell patients in the UK. Given the lack of treatments available for people with sickle cell, compared to a genetic condition like cystic fibrosis (CF) this would have brought some hope to us. There are 511 treatments available to the 10,500 people with CF who are mainly white people, compared to 3 treatments available to the 18,000 people living with sickle cell, who are mainly black people. Additionally, 2 major treatments were made available voxelotor and crizanlizumab for sickle cell, and then latterly withdrawn. As a sickle cell patient myself, it is very discouraging to know this decision is a finance one, when infact it can be life changing for many of us.

Whilst it is a finance one, the huge health inequalities, stigmatisation and prejudice for a condition that mainly affects the African and Caribbean community is vast. This would help to start redress some of that balance and enable us to live a better lives.

Treatments must be fair and equitable.

Comment on section 2.1 (Marketing authorisation indication):

This treatment should be available from about 6 months of age. We know that children have strokes, infections etc, which can end up being fatal. Why would we not want to make a child free of suffering and pain. Why would we not want to cure them.

Comment on section 2.3 (Price):

No price can be put on a cure for saving hundreds of people's lives.

Comment on section 3.25 (Recommendation):

It's safety has already been approved, so now it is just to do with cost effectiveness.

How can we put a cost on our lives. Lives that are cut short, full of pain and suffering, anxiety, fear, diminished quality of life and complications.

I would hope that the committee would see the severity of the impact on our lives and not make this a finance decision.

This has been approved for use in the USA.

Do sickle cell lives matter more in the USA, than the UK?

Comment on section 3.1 (Details of condition), “SCD is a debilitating and life-limiting condition. It also concluded that there is high u”:

Yes, absolutely. It has changed my life completely. I am one of the 58% that needed to stop work. I was 56 when I stopped work. As an older person the years of suffering, damage too my body and complications, ending with a chest crisis, all took its toll on my health and I was no longer able to work.

I live with daily pain, fear of having a severe vaso occlusive crisis, chronic suffering from avascular necrosis in both my hips and both my shoulders; which affects my mobility and restricts my activities, retinopathy, breathing issues, exhaustion, autosplenectomy; leading to reduced immunity. Needless to say my quality of life is diminished. The impact on us of seeing our peers dying, and knowing this condition could shorten our lives is devastating. The impact on me physically and emotionally is exhausting and a price can not be put on this. The financial impact is also a strain.

If the clinical experts show an understanding of the pain, the physical complications, the debilitating and life limiting condition, and the full effects of SCD, then please help us and approve this cure

Comment on section 3.1 (Treatment options):

The few treatments available help in part. Often pain relief does not touch the pain. We know to keep ourselves well hydrated etc.

Exa-cel could drastically change the lives of those of us living with SCD, significantly improve our QoL and provide much needed hope. Clinical experts have already noted that exa-cel could offer a chance at a disease-free survival, improved organ function, reduced symptoms such as VOCs and reduced healthcare use.

This is what we need to make a huge change and impact on our lives.

Comment on section 3.3 (Treatment positioning of exa-cel):

This is a remarkable, innovative lifesaving and life changing procedure, which would make a change to the lives of sickle cell people.

Comment on section 3.3 (Treatment positioning of exa-cel), “The committee was also aware that exa-cel would only be available to people with severe SCD who have recurrent VOCs. It acknowledged the difficulty in accessing the severity of SCD (see section 3.1) and heard that recurrent VOCs would be identified in clinical practice based on visible VOC episodes, as used in the trial (see section 3.4). The committee concluded that exa-cel could potentially address the unmet need.”:

Sickle cell is a very unpredictable and complex condition.

Somebody may be relatively well and free of complications, and then suddenly they become seriously unwell.

This must be made available to all who want this cure.

Yes give the most severe treatment first.

Comment on section 3.16 (Severity):

If the severity modifier exists and the committee acknowledges the severity of SCD, its complications; life reducing impact then its approval should be automatic.

The severity of this condition is absolutely devastating on our lives.

Giving more weight to the health benefits should mean the committee will approve this treatment option.

Comment on section 3.17 (Identified health inequalities):

The issues of inequity, discrimination, racial bias, stigmatisation, inequalities in accessing treatment, and the lack of understanding and prioritisation towards people with SCD is endemic.

The No one's listening report highlights all our struggles, very well.

We are let down time and time again with treatment options.

This cure would help to redress some of the imbalance and inequalities.

Comment on section 3.19 (Innovation):

Too many treatments for us with SCD are introduced and then taken away.

Researchers are not going to want to continue with researching; investing time and energy if everything is going to be rejected.

This potential cure is innovative, remarkable, life changing and life saving for us.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender	

reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

With so many black and ethnic children and adults being affected by SCD in the UK, we have very limited resources. The ones we do have have advanced barely over the years compared to USA. My child is admitted yearly with serious infections but we deal with pain caused by SCD regularly at home. She's only 6 she has a lifetime of this, her lifetime might not even be as long as mine. She's a fighter as are all the little children that live with this disease. They just need more chances. If there is a potential cure to this life shortening disease to save these little children's lives a life of pain and suffering, I'd like to think that by the time she's 12 there will be options for her. Just like there are options for cancer, and other life shortening illnesses. Please make this an option to save our children's lives.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I don't think so. Has any consideration been given to the cost of recurrent admissions and long term treatment and management of the resulting serious co-morbidities as against the cost of Casgevy? Will there not be some benefit overall to the NHS in helping to reduce hospital visits and treatments for the SCD community?

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. There doesn't seem to be enough guidance to the NHS on when Casgevy would not be used.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Somewhat reasonable. Where NICE is not satisfied with sample size or cost benefit analysis, further evidence or supporting documentation could be requested.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes, Consideration needs to be given to the fact that the reported number of SCD sufferers is highly probably underestimated due to the nature of the

demographic. Many SCD sufferers can be undocumented but still end up seeking hospital admission and treatment in a crisis, which impacts health costs, but does not help in correct estimates of the population group when allocating resources or budgets.

Additionally there are not many treatments available for SCD treatment or management, so it is not as if we have many choices. At the moment it is a question of very limited choices so if even one of those is denied on cost effectiveness alone, it just seems like another hurdle in an already extremely difficult uphill climb.

More weight ought to be given to the discretion and skill of clinicians to decide when the treatment will be efficacious or not, when all risks have been weighed up. The fact that it will be available on the NHS does not mean clinicians will indiscriminately recommend it. But to not have it available at all reduces an already very limited pool.

Comments on consultation:

Section 3.18

Both the company and the clinicians are right about sample size and fear of novel treatments within the SCD community. If you are suffering so heavily from a complex, debilitating and potentially life threatening lifelong condition, you are very unlikely to do anything to destabilise your status-quo. At least you know what your status-quo is, and there is just no room or capacity to contemplate any other side-effects. This naturally has an effect on sample sizes for trials and it will not be significantly any different with another innovative drug.

Considerable weight needs to be given to clinicians point that this was the same situation when hydroxy-carbomide and transfusion therapies were first introduced but they are now very routine therapies

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I'm not sure if the real life data that people living with sickle cell disease tell us about has been fully taken into account. In particular the concept of the severity of the disease and quality of life. People living with sickle cell disease have never known a normal life or can compare to what an expected / normal quality of life is. Even patients living with 'mild' SCD need regular medical reviews, tests and can live with episodes of pain. We know many people have disrupted lives even if not coming into hospital. They are also at risk of unexpected and unpredictable episodes of severe pain or life threatening complications such as stroke, chest syndromes, sudden death.

Patients in trial data will not represent fully those not in the trial in these aspects.

Sickle cell disease is a life limiting condition still with early deaths still recorded. Life expectancy is reduced.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I would argue that this treatment should be offered to some patients with SCD given the severity of the condition and the impact on patients and the limited treatment options available.

SCD is a severe condition with patients subjected to hospitalisation, risk of life threatening conditions and reduced quality of life.

This condition is likely to have long lasting / life long benefits at reducing sickling and crises. With the expectation that patients will be able to achieve a near normal life (particularly if treatment accessed before long term organ complications develop) - it is difficult to describe return to normality as this is a life long condition and patients living with SCD will never have had what is often considered a normal life.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The benefit of this condition will offer long term improvement - and benefits will be accumulated over time. The treatment will reduce long term complications that would otherwise increase medical requirements and decrease quality of life

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We know that patients living with SCD report fear of hospitals, distrust of medical care and experience discrimination due to the invisible nature of pain and the ethnic background that patients living with SCD predominantly come from. Patients tell us that their pain is often not believed.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
These are general comments on this consultation.	

The first being to highlight the negative impact to the lives of people living with SCD. Not only does living with SCD undermines the quality of life of people living with SCD, but it also adds considerable strain to the lives of close friends and family informally caring for and supporting patients.

This also has knock on effects on healthcare and the economy as individuals living with SCD are a continuous burden on the healthcare system, and they and their carers are unable to effectively contribute to society and the economy a double negative. This appears as something that may also be underestimated.

I urge NICE not to underestimate the severity of SCD on people and families living with SCD. This extends beyond the physical pain experienced by patients, but the psychological and emotional aspects in relation to uncertainty over day-to-day options as well as the ability to plan over the medium to long term.

There is a desperate need for a suitable cure and therapy for this disease, and the lack of progress in developing cures for this disease is of great concern.

Name	
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

No. People with sickle cell disease are typically from marginalised communities, may also be from socioeconomically deprived neighbourhoods and suffer health inequity in access to health care. Consequently they tend to have poorer health outcomes. Access to exagamglogene could significantly improve health outcomes, and help them to be able to stay in work and education, thus improving economic productivity.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes, as stated above, people with sickle cell disease typically experience racial discrimination and poorer pregnancy outcomes. They may also suffer from disability due to the long term effects of sickle crises, so theoretically, access to the drug could prevent long term disability.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. There already not many treatments not available for those with SCD. This type of treatment will still be available for those other conditions that need it, if that is the case it makes no sense to stop offering it to people with SCD when there has been no further developments in the treatment of SCD in the UK and in the NHS especially

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Cystic Fibrosis which mainly affects Caucasians and there are about 10,500 patients has 60 Specialist Centres, fully stocked with Physio, Social Care etc. A ratio of 1 Specialist Nurse to 75 patients and 511 APPROVED treatment options.

Sickle Cell has 10 Specialist Centres for about 17,500 patients, little medical or social back up. 1 Specialist Nurse to about 400 patients and 4 APPROVED treatment options.

The numbers, the complaints the stories down to what is available for benefit and to how the Healthcare system is historically racist as to this day people are still being taught that black people are stronger handle pain better when there is no such scientific evidence to support that claim.

If the treatment is not completely being taken away from others there's no legitimate reason why it shouldn't be offered to those with SCD and basing it off a study of 30 ppl but not even a long term study to see how it will effect them into adult hood is insane and the fact that the nhs does not promote and inform the community of the treatment is all more why ppl have been hesitant to proceed with it

Name

Organisation

N/A

Conflict

N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

No.

Sickle-cell anaemia is the most common inherited condition in the UK and compared to other gene disorders it has not been given the same priority.

This disease has an impact all through life and starts at birth. It is not just the individual but the whole family that suffers.

The burden of disease is pain and disability both physical and psychological.

Sickle cell crises can happen acutely. It adds a significant burden in terms of cost and resources to the NHS - affecting primary care, secondary care as well as emergency services.

It is difficult to overstate the effect on the individual's ability to be socially integrated, hold down a job and undertake normal daily tasks.

An acute sickle-cell crisis can damage any internal organ of the body and the person is at risk of permanent disability or death.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No.

There is unacceptable variation in the quality of care given to people with sickle disease. Many primary care centres and hospitals are not geared up to give the best quality care for this group of patients.

Treatment options are limited compared to other inherited conditions e.g. breast cancer and cystic fibrosis.

There is now increased recognition of the effects of sub-optimal care for people with learning disability leading to premature disability and death. The same should apply for people with inherited blood disorders.

It is not acceptable that little has been done to take steps to promote avoidable disability and improve life expectancy.

Quote:

Party Parliamentary Group (APPG) on Sickle Cell and Thalassaemia Report - No One's Listening, 2022.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The economic cost and the burden of this illness could have been better reviewed e.g. cf. screening and treatment of other conditions such as cervical screening, breast screening, bowel screening, immunisations etc.

There is also a significant race inequality issue that has not been properly considered.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Race - as described above.

You may not like to hear this but when I worked as a junior doctor in Liverpool, we were aware of a haematology planning meeting where a consultant was heard to say, ""We don't need to worry about sickle disease much as it mainly affects the blacks.""

Name	
Organisation	Caribbean & African Health Network
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	
No, there are so many omissions on the impact of sickle cell on the lives of the sufferer	
Are the recommendations sound and a suitable basis for guidance to the NHS?	

No, the sample of those suffering from severe sickle cell needs to be greater. There needs to be evidence collated from those that care for sickle cell patients and the VCSE and faith community were omitted. As a VCSE organisation working at strategic and operational level my organisation which is the largest Black led organisation in the country was not consulted. We also lead campaigned for sickle cell review of services in Greater Manchester due to the terrible treatment of those with sickle cell. Patients are suffering and unable to uphold a good quality of life. QALYs does not work for this community

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No QALY is a bias method to assess cost effectiveness and quality of life outcomes. Black patients with sickle cell cannot live a quality life without appropriate treatment

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We need a bigger sample of organisations like mine, we need health professionals like myself and those that care for people with sickle cell everyday to really highlight the impact of sickle cell on those affected. We need the impact from pregnant women and how their lives are not lived in the way most of us can look forward to having a baby. The cultural and religious impacts also need to be taken into account as well as the moral imperative that should be to provide equitable access to treatments for over 17,000 people suffering. It cannot be that MS has more cost benefits. Black people who are largely affected will not have the financial capital to pay for this treatment and they too are tax payers. We need equity in treatments

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
I would like to present my objection to removing Gene Therapy as a treatment option for Sickle Cell. One of the most successful methods of treating Sickle Cell is Gene therapy. With this treatment children born with Sickle Cell have a fighting chance to avoid a life of pain. A Ray of Hope is being given to the succeeding race. It is one treatment that eradicates a lifetime of pain. I would like to give an example of how underfunded sickle cell disease is. Cystic Fibrosis which mainly affects Caucasians and there are about 10,500	

patients has 60 Specialist Centres, fully stocked with Physio, Social Care etc. A ratio of 1 Specialist Nurse to 75 patients and 511 APPROVED treatment options.

Sickle Cell has 10 Specialist Centres for about 17,500 patients, little wider medial or social back up. 1 Specialist Nurse to about 400 patients and 4 APPROVED treatment options.

It might not be consciously done but the optics do not look good and there is a child struggling to come into this world and lots more who are present on this earthly domain who can and will benefit. Please give them an opportunity to miss a life time of pain.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I just feel that more time should be spent on this, as sickle cell disease is such a life threatening disease and so many die from this. So many lives have been cut short from living with this condition.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I believe more time should be given before making a solid decision.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I believe when it comes to life, money should not be a factor. Sickle cell is not taken as serious as it deserves to be taken. Lives are cut short and children and adults suffer.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Sickle cell has always been on the back burner, I just feel that those with sickle cell which predominantly affects the black race deserve the chance to live a healthy life just like everyone else.

Comments on consultation:

To whom this may concern, being a mother to a 5-year-old son with sickle cell disease SS, is very challenging, a constant worry and causes mental

health issues in the form of depression and anxiety. What myself and other parents go through with dealing with this disease I wouldn't wish on anyone. The hurt and pain you feel as a mother knowing that there is nothing you can physically do to help your child screaming in unimaginable pain is just unbearable. This therapy is something that myself and other parents can look forward to when our children become of an age when they can be accepted for this. All I want is to be able to see my son live, grow and be the best that he can possibly be without the added debilitating effects that this awful disease brings, such as the sudden excruciating pains and infections that left untreated is extremely serious. Please reconsider your decision.

[REDACTED]

Name	[REDACTED]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Yes and it made no sense to why it is being disapproved.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, what does it mean by cost effectiveness? They won't make money out of this? But what about the thousands of people who'll be cured? Do they not care about us? Is money above humanity now?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

This treatment should be provided to everyone regardless of them being poor. What I understood from this was that it won't make them profit so they're rejecting it? That's considered discrimination. Rich people can afford the treatment but what about middle class people like us who only had faith in the funding and people with genuine good hearts who want to see people like me be cured and live a healthy life rather than being sick and transfusion dependent, with life threatening chelation affecting her organs!

Comments on consultation:

The only hope we see is now being rejected. Being born with a gene defect wasn't our fault but not letting the cure reach us is your fault. If there is a way for me to be cured, why is it being disapproved? Does this world not like to see people healthy and cured? Is this world really cruel to use ill people to make money by selling them the medicines they need to live.

To be cured, healthy is honestly a blessing that some people are with. I want to be cured, I want to live a life where I'm not tired and exhausted 24/7 nor am I on verge to damaging my organs cause of the excessive iron overload. Where I have to take so many medications in a day. I take 15 tablets a day! Just to manage the iron overload. 15!

Name	
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

Yes.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes. The information provided is supported by evidence from clinical trials that displays the treatment as a substantial alternative to more invasive treatments.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No.

Name	
Organisation	Sickle Cell Society
Conflict	N/A

Comments on the DG:

Dear NICE,

As a member of the African and Caribbean community, I am writing to express my deep concern and disappointment regarding the recent decision

by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom.

This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease.

Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent.

In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage.

This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years.

The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people.

Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18.

These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community.

The health inequalities faced by the African and Caribbean community in the UK are well-documented.

Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare.

A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts.

Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease.

Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition.

By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease.

This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run.

It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition.

Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future.

Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system.

It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be.

This is unacceptable and goes against the principles of equality and fairness that should underpin our society.

I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible.

The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group.

By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long.

Thank you for your attention to this critical matter.

I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.

Yours sincerely,

Full Name

[Redacted Signature]

Name

[Redacted Name]

Organisation	Next Generation Initiative
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account? Yes Are the recommendations sound and a suitable basis for guidance to the NHS? Yes Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? No	
Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account? NO, The impact on people living with this chronic relapsing condition needs to be better articulated with empathy: Sickle-cell anaemia is by far the most common inherited condition in the UK and the numbers are rising. It begins to have a significant impact on physical health within the first year of life It is a life-long chronic condition which causes multi-morbidity, disability and premature death - It is characterised by: - repeated unpredictable sickle-cell crises which require emergency medical treatment in A&E, the most inefficient, costly way to manage chronic conditions - frequent long stay admissions costing the NHS hundreds of thousands of pounds each time - chronic excruciating pain experienced at multiple sites around the body, often simultaneously - inability to either get a job or keep a job due to frequent sickness absence	

- stigma, loss of self worth, impaired mental health impacting social / family life.^{[1][1][1]}_{[SEP][SEP]} Each time a person has an acute sickle-cell crisis they risk complications of infection, damage to any internal organ of the body - lung, brain, liver, kidney, skin, eye, gallbladder, spleen, bowel - and most frightening of all for the individual, a significant risk of death during each hospital admission.^{[1][1][1]}_{[SEP][SEP]} After each sickle-cell crisis, physical and mental health deteriorate, increasing a person's morbidity, resulting in a poorer quality of life.^{[1][1]}_[SEP]

Are the recommendations sound and a suitable basis for guidance to the NHS?

No given that - The quality of care for the significant population of people in the UK, living with sickle-cell anaemia as a chronic condition, typically does not meet requirements in terms of the 6 domains of quality - safe, effective, patient-centred, timely, efficient, equitable. Statistics highlight annually preventable and premature deaths in people living with sickle-cell anaemia.^{[1][1]}_[SEP] There is unacceptable variation in service provision and deterioration in standards across the board continue to occur as budgetary cuts deepen.^{[1][1]}_[SEP] Treatment options are extremely limited compared to other inherited conditions such as cystic fibrosis.^{[1][1][1]}_{[SEP][SEP]}

It is unacceptable that although we have known about this condition for more than a century so little has been done to radically transform the quality of life and life expectancy for the significant population who live with this condition (see the All-Party Parliamentary Group (APPG) on Sickle Cell and Thalassaemia's Report, No One's Listening, 2022). This context of inadequate care provision should influence the recommendations

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Sickle-cell anaemia is by far the most common inherited condition in the UK and the numbers are rising.

It begins to have a significant impact on physical health within the first year of life

It is a life-long chronic condition which causes multi-morbidity, disability and premature death - It is characterised by:^{[1][1]}_[SEP]- repeated unpredictable sickle-cell crises which require emergency medical treatment in A&E, the most inefficient, costly way to manage chronic conditions.^{[1][1]}_[SEP]- long stay admissions costing the NHS hundreds of thousands of pounds each time

- chronic excruciating pain experienced at multiple sites around the body, often simultaneously

- inability to either get a job or keep a job due to frequent sickness absence

- stigma, loss of self worth, impaired mental health impacting social / family

life.^{[1][1][1]}_{[SEP][SEP]} Each time a person has an acute sickle-cell crisis they risk complications of infection, damage to any internal organ of the body - lung, brain, liver, kidney, skin, eye, gallbladder, spleen, bowel - and most frightening of all for the individual, a significant risk of death during each hospital admission.^{[1][1][1]}_{[SEP][SEP]} After each sickle-cell crisis, physical and mental

health deteriorate, increasing a person's morbidity, resulting in a poorer quality of life.^{[1][SEP]} I don't think sufficient predictive costings have been made over life course for the number of people living with sickle cell, including social and societal costs. This then needs to be compared with the costs of treatment and figures around proportion who will experience a 100% cure if treatment is completed and no longer need care for acute relapsing illness

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Discrimination on the grounds of race - The quality of care for non-white people, living with sickle-cell anaemia as a chronic condition, typically does not meet requirements in terms of the 6 domains of quality - safe, effective, patient-centred, timely, efficient, equitable. Statistics highlight annually preventable and premature deaths in people living with sickle-cell anaemia.^{[1][SEP]} There is unacceptable variation in service provision and deterioration in standards across the board continue to occur as budgetary cuts deepen.^{[1][SEP]} Treatment options are extremely limited compared to other inherited conditions such as cystic fibrosis.^{[1][SEP]} The above is an outline of the devastating impact of sickle-cell anaemia on an individual and their loved ones in the current context of access to services, care and outcomes.^{[1][SEP]} It is unacceptable that although we have known about this condition for more than a century so little has been done to radically transform the quality of life and life expectancy for the significant population who live with this condition (see the All-Party Parliamentary Group (APPG) on Sickle Cell and Thalassaemia's Report, No One's Listening, 2022).^{[1][SEP]} 'Reducing inequalities' is repeatedly set out as a key priority for integrated health and care systems - Given that Casgevy results in 100% success for those who can complete the treatment and it has been use since 2019 in the USA, the evidence is surely overwhelming and the time is now, for a step-change in care. NICE must reconsider and rule in favour of Casgevy to make it available on the NHS forthwith.^{[1][SEP]}

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	
I do not think so. I do not think that this consultation takes into account the severity of sickle cell or the magnitude of the long-term benefits to patients of exa-cel.	

Are the recommendations sound and a suitable basis for guidance to the NHS?

Again, no - I would question the level of knowledge, and perspective taken from Sickle Cell sufferers, when making this decision, and would urge a rethink. In particular, I would ask the following is considered:

The negative impact that severe sickle cell has on the day to day life of people living with the condition

The worsening impact that sickle cell has over time

The impact of sickle cell on life expectancy and the risk of mortality

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Absolutely not. In terms of clinical effectiveness, based on studies from the US, there is a valid case for the use of exa-cel. In terms of cost effectiveness, I would suggest that benchmarking the use of this treatment should be considered in comparison to other diseases that are equated to Sickle Cell in terms of clinical treatment - for example, severe Sickle Cell crises and related issues are generally treated in the same way as severe cancer patients, in Oncology wards. This should be what is used when looking at the cost effectiveness of the treatment. How much were radiology and chemotherapy treatments initially?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Absolutely. Sickle Cell is a disease that mainly affects people of African origin, and this has created a massive stigma in the way that it is treated, perceived and taken seriously as an illness, despite the fact that there are numerous case studies on how cripplingly severe it can be. If cost effectiveness is the reason given for not going ahead with exa-cel treatment, this needs to be fully and transparently compared with similarly debilitating diseases that primarily affect people of European ancestry, and the initial cost of treatments for these - otherwise there is a clear racial bias at play.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	

As a lay person, the evidence detailed in this initial consultation seems very detailed and contains detailed medical explanations and reasoning behind why the treatment should not be considered at this time.

However, have any links between other treatments of this kind (for other genetic diseases) and small trials of this kind been investigated and the results been looked into? are there similar, trials that could be studied and conclusions made.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I'm sure the detailed analysis is sound and is trying to protect patients interests. But it has been pointed out that Sickle Cell Disease has many negative socioeconomic factors and despite this treatment only having a small number of trials- if proved successful this treatment could have a massive impact on the QoL outcomes for the people it affects and would also reduce the medical needs and impact on services by these people in the long term.

So although the recommendations are sound, some strategic consideration needs to be given to how more trials and feedback can be conducted -so that the limited trials so far can be extended and also longer term feedback from patients who've already received the treatment can be analysed and used to determine which patients would benefit from the treatment in the future.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

As it's a small sample the summaries are initial interpretations and these would need to be reviewed over a much longer term with more patients in the sample before a definitive cost could be assigned to the treatment.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The main aspect that needs to be taken into consideration is that as the report mentions, SCD mainly affects ethnic minorities disproportionately. It then compounds the socioeconomic disadvantages of many of these people. Any potential treatment that could reduce the severity and life long impact of the SCD needs larger trials in this country, before recommendations against the treatment should be made.

No treatment will ever have 100% successful, but in this day and age advances in technology mean that any gene therapy should be considered as a potential treatment. No links to other ground breaking gene therapy treatments have been mentioned in the report - could some parallels be made, or at the very least lessons be learned?

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Dear NICE, As a member of the African and Caribbean community, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom. This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease. Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent. In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage. This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years. I have sickle cell disease and it has had a significantly negative impact on both my physical and mental health. It has also been difficult for members of my family to watch me suffer and struggle because of this debilitating condition. The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people. Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18. These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community.	

The health inequalities faced by the African and Caribbean community in the UK are well-documented.

Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare.

A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts.

Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease.

Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition.

By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease.

This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run.

It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition.

Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future.

Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system.

It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be.

This is unacceptable and goes against the principles of equality and fairness that should underpin our society.

I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible.

The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group.

By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long.

Thank you for your attention to this critical matter.

I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.

Yours sincerely,

[REDACTED]

Name	[REDACTED]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

It is very low numbers in the clinical trial so offering it as a treatment would allow for there to be more robust evidence to be collected over the coming years and then you could conclude a much more solid and informed cost effectiveness

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. We are losing too much money in terms of days taken off work, unemployment, recurrent hospital admission. Approving this decision would definitely be cost effective for the UK in the long run

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I think we need to gather more evidence and more work needs to be done to recruit patients, for this very life changing and impactful disease

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

yes - the conclusion will further alienate and reduce trust from Afro-Caribbean patients - the committee has underestimated the positive impact approving this drug would have on patients from this demographic, which would then have countless benefits for the NHS in the long run

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Are the recommendations sound and a suitable basis for guidance to the NHS? There may be 'lack of available evidence' resulting in an unfortunate, unintended bias occurring in this field. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? It is important to ensure that all is being done to continually reduce the multiple health inequities experienced by people living with SCD Comment on section 3 (details of the condition): As a GP I have been very aware of the impact of Sickle Cell disorders on not only the person living with the condition but also the family. It impacts both individuals physically, socially, mentally and in all aspects of life. The associated morbidity is significant and life-impacting and I feel that sometimes under-reporting of symptoms/ signs may result in an underestimation of the full cost and effect of these conditions. Comment on section 3.4 (CLIMB SCD-121 trial), text “. The trial was done across multiple sites globally, including 1 UK site. At an April 2023 datacut, the trial had recruited 43 people and 29 had been followed for 16 months or more after exa-cel infusion and for at least 14 months after the last red blood cell transfusion for post-HSCT support or SCD management. This data was used in the economic model (see section 3.6). The latest datacut presented during the appraisal (June 2023) included 1 more person. After exa-cel infusion, people were followed for up to 2 years in the CLIMB SCD-121 trial and then asked to join the CLIMB-131 trial, a phase 3 long-term follow-up study, where people will be monitored for up to 15 years. The primary outcome measure in CLIMB SCD-121 was the proportion of people achieving an absence of severe VOCs for at least 12 months after exa-cel infusion. The key secondary outcome measure was the proportion of people free from inpatient hospitalisation for severe VOCs, for at least 12 months after exa-cel infusion. Both outcomes were measured from 60 days after the last red blood cell transfusion for post-HSCT support or SCD management. 28 out of 29 (96.6%) people who had been followed for 16 months or more after exa-cel infusion were severe VOC-free for at least 12 months and remained	

VOC-free for an average of 20.7 months of follow up (range: 13.6 months to 43.6 months). All 29 (100%) people were hospitalisation-free for at least 12 months. Of all the people who had exa-cel, 86.0% were VOC-free and 97.6% were hospitalisation-free for between 1.3 months and 43.6 months”:

these are impressive results when taken in the context of a person experiencing extreme painful crises without treatment and how these VOCs affect a person's life and livelihood

Comment on section 3.17 (Identified health inequalities):

inevitably, denying this treatment to people with SCD will increase health inequalities, given the demographic of the population most commonly impacted by SCD.

It is important to ensure that all is being done to continually reduce health inequities experienced by people living with SCD

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Dear NICE,

My son has sickle cell disease and I have seen him suffer both physically and mentally because of it. It's heart-breaking.

As a member of the African and Caribbean community and a parent of someone with sickle cell disease, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom.

This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease.

Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent.

In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage.

This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years.

My son has sickle cell disease and I have seen him suffer both physically and mentally because of it. It's heart-breaking.

The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people.

Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18.

These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community.

The health inequalities faced by the African and Caribbean community in the UK are well-documented.

Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare.

A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts.

Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease.

Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition.

By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease.

This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run.

It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition.

Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future.

Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system.

It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be.

This is unacceptable and goes against the principles of equality and fairness that should underpin our society.

I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible.

The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group.

By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long.

Thank you for your attention to this critical matter.

I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.

Yours sincerely,

[Redacted Signature]

Name	[Redacted Name]
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	
No	
Are the recommendations sound and a suitable basis for guidance to the NHS?	
Yes	
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	
Yes	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender	

reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Sickle cell affects a minority but should not be treated with levity

Name

Organisation

N/A

Conflict

N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

NO. I believe that the impact on people living with this chronic relapsing condition needs to be

better articulated with compassion.

I have family members and loved ones who suffer daily with Sickle-cell disease. It is by far the most common inherited condition in the UK and the numbers are rising.

It is a life-long chronic condition which causes multi-morbidity, disability and premature death.

Each time a person has an acute sickle-cell crisis they risk complications of infection, damage to any internal organ of the body - lung, brain, liver, kidney, skin,

eye, gallbladder, spleen, bowel together with a frightening significant risk of death during each hospital admission

After each sickle-cell crisis, physical and mental health deteriorate, increasing a

person's morbidity, resulting in a poorer quality of life

Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not believe that the quality of care for the significant population of people in the UK

living with sickle-cell anaemia as a chronic condition, meets requirements in terms of the 6 domains of quality - safe, effective, patient-centred,

timely, efficient, equitable. Statistics highlight annually preventable and premature

deaths in people living with sickle-cell anaemia.

There is unacceptable variation in service provision and deterioration in standards

across the board continue to occur as budgetary cuts deepen.

Treatment options are extremely limited compared to other inherited conditions

such as cystic fibrosis.

It is unacceptable that although we have known about this condition for more than

a century so little has been done to radically transform the quality of life and life

expectancy for the significant population who live with this condition (see the All-

Party Parliamentary Group (APPG) on Sickle Cell and Thalassaemia's Report, No

One's Listening, 2022).

. This context of inadequate care provision should influence the recommendation

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

In the UK, 15,000 people are affected by sickle cell disease (SCD) and more than 300 babies are born with the condition each year. It affects a lot of different races and the two largest populations in the world are in Africa & India.

SCD is the UK's largest genetically inherited disorder and fastest growing. Around five years ago the UK needed 150 donors per day to treat patients with SCD. Now the need is around 250 donors per day.

It is a life-long chronic condition which causes multi-morbidity, disability and premature death - It is characterised by:

- repeated unpredictable sickle-cell crises which require emergency medical treatment in A&E, the most inefficient, costly way to manage chronic conditions

- long stay admissions costing the NHS hundreds of thousands of pounds each time

- chronic excruciating pain experienced at multiple sites around the body, often simultaneously

- inability to either get a job or keep a job due to frequent sickness absence

- stigma, loss of self worth, impaired mental health impacting social / family life

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Discrimination on the grounds of race - The quality of care for non-white people,

living with sickle-cell anaemia as a chronic condition, typically does not meet

requirements in terms of the 6 domains of quality - safe, effective, patient-centred,

timely, efficient, equitable. Statistics highlight annually preventable and premature

deaths in people living with sickle-cell anaemia.

There is unacceptable variation in service provision and deterioration in standards across the board continue to occur as budgetary cuts deepen.

Treatment options are extremely limited compared to other inherited conditions such as cystic fibrosis.

The above is an outline of the devastating impact of sickle-cell anaemia on an individual and their loved ones in the current context of access to services, care and outcomes.

It is unacceptable that although we have known about this condition for more than a century so little has been done to radically transform the quality of life and life expectancy for the significant population who live with this condition (see the All-Party Parliamentary Group (APPG) on Sickle Cell and Thalassaemia's Report, No One's Listening, 2022).

'Reducing inequalities' is repeatedly set out as a key priority for integrated health and care systems - Given that Casgevy results in 100% success for those who can complete the treatment and it has been use since 2019 in the USA, the evidence is surely overwhelming and the time is now, for a step-change in care. NICE must reconsider and rule in favour of Casgevy to make it available on the NHS forthwith.

Comment on consultation:

Sickle cell is a chronic relapsing condition, resulting in multi-organ morbidity and consequent impact on mental health, capacity to work and contribute society. The treatment if tolerated has 100% success.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	

All relevant evidence has been taken into account. However, I do not believe that the fact that the condition gets progressively worse over time has been appropriately weighted in determining the severity modifier.

As an individual suffering from sickle cell disease, with knowledge of many friends and families that have died from SCD at the age of 30 or above, the mortality risk is extremely high the older the patient gets and this should be appropriately factored in determining the severity modifier weight

Are the recommendations sound and a suitable basis for guidance to the NHS?

Most of the recommendations are sound. However sufficient consideration has not been given to inequalities in determining if a recommendation should be given for managed access.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The recommendation for managed access should be reconsidered. The benefit of exa-cel could be potentially life changing to people living with SCD and an inappropriate amount of weight has been placed on cost effectiveness versus the change in QALY of patients living with SCD.

It should be noted that the systematic discrimination which exists in the UK against ethnic minorities is the reason why there hasnt been sufficient research and advancement into SCD in the first place. Had there been sufficient research into SCD and advancement in the treatment options available, exa-cel could potentially be made available at a more cost effective price. Therefore, continuing to focus on cost effectiveness inadvertently continues to perpetuate this systematic discrimination.

No groundbreaking innovation and change can occur if cost effectiveness is always the focus.

I would suggest that this discrimination is reconsidered and overall a recommendation for managed access should be given

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	
from what i have read the information is there and should be recommend.	

Are the recommendations sound and a suitable basis for guidance to the NHS?

from what i have read i would say yes
this would help an already lower wage earners get access to vital medical help.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

over the long term of a patient the cost to the NHS will be well worth it.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

as this effects mainly black people if not recommended it would discrimination not to fund it.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? Have you put funding into research as you would have done with other groups? Comment on draft guidance consultation: As a mother with a daughter with sickle cell. I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom. This decision is a blow to my daughter and to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease. This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years.	

The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people.

Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18.

These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community.

The health inequalities faced by the African and Caribbean community in the UK are well-documented.

A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts.

Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease.

Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition.

By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease.

This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run.

It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition.

Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future.

The decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system.

It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be.

This is unacceptable and goes against the principles of equality and fairness that should underpin our society.

I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible.

The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group. There are about 11 thousand suffers of Cystic Fibrosis in the UK and over 33 treatments available to them. Compared to 17 thousand suffers of Sickle Cell with less than 5 treatments available to them.

I hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account? I feel that the cost effectiveness calculation did not (fully) take into accounts the costs to the NHS, economy and persons if the treatment would not be implemented. The costs of treatment, support and economical defects per person living with Sickle Cell are high. The treatment costs include prolonged periods in hospital, regular treatments (for instance blood exchange), and emergency treatments often needed multiple times a year (ambulance, etc). The economical costs are high as most people living with sickle cell are qualified disabled, hence are on disability support and have reduced ability to work. In addition, this often also effects the economical situation of family and carers. Lastly, results from Sickle Cell VOCs often results in adaptations needed to a person's living situation, support, etc, which provides an economical burden to the person, support network and the government. I feel that the cost effectiveness should be balanced to the decrease in costs as mentioned above. Ofcourse, together with the importance of having a treatment for Sickle Cell. Are the recommendations sound and a suitable basis for guidance to the NHS? I feel that at least the treatment should be recommended with managed access, with potential full consideration in the future. As Sickle Cell has a tremendously high burden to the people living with it and the people around them, having a treatment would be essential to help them. As a friend of someone living with Sickle Cell, I know the horrendous effects this disease has on a person. Every day is a struggle, or can be a struggle, on the level of pain, disability, mental health and uncertainty. VOCs are unpredictable, and patients have to prepare that they can happen any moment, turning their lives upside down, their jobs, their family situation, their housing stability, etc. Many people living with Sickle Cell have, after years of fighting, a disability status as they cannot function like normal people can and they will never be able to. Moreover, this even worsens over time, for instance my friend now has to live with (all caused by Sickle Cell): mental health issues (including post traumatic stress disorder), rheumatoid, deterioration of her joints (including her hip and shoulder which need to be replaced). This will all get worse over time, making it harder to do day-to-day activities (sometimes just having a shower or getting dressed) and further and further disabling people who will not receive treatment like exa-cel. Moreover, the effects on the support network are mentally and financially. Knowing that every time their loved one has a VOC and it is so bad they have to be taken into hospital, they might never see them again. The daughter of my friend has developed anxiety syndromes as a result of having to experience her mother having to go through all the VOCs in her life, and moreover having	

to understand that her mother could die younger than other's as a result of Sickle Cell. As, luckily, the life expectancy has increased, still people die (very) young with Sickle Cell, and if they do manage to stay alive, it is with high levels of disability which are caused by the repetitive VOCs suffered over their lifetime. The VOCs can be stopped by treating patients with exa-cel!

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Please see my comments above. Also, the lives of the support network of people living with Sickle Cell are highly disrupted by this disease. Therefore, treating one patient will positively benefit a large group of people in terms of their ability to work and the costs to the treatments which the support network will need as a result to having to care for and being exposed to the effects of Sickle Cell.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes, the group of people having been faced with Sickle Cell - the patients and their support network - have faced racism and other unequal treatments over many years. As stated in the No One's Listening Report, and many other investigations, scientific papers, etc, the Sickle Cell community has been faced by racism for many years. What I found shocking is that the committee members and NICE project team seem not have include even one person with Black heritage background. This further suggests racism at play, and inaccurate understanding of the sensitivity of this issue including the lack of trust by the Black community in healthcare and research settings. Having been faced by racism throughout their lives, which has only been increased by having to live with Sickle Cell as this group is often stereotyped as "drug seekers" or inaccurately identifying their pain and discomfort. Policies and politics have also been racially inclined by not supporting the Sickle Cell community. And with this decision of NICE, there is another big influence of racism. The report states that racism is been taken into account but details are unclear and this report could very well been read as another racist act.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	

I don't think so because all the recommendations from NICE are not a cure for Sickle Cell disease, this would be the only cure at moment and they are putting costs over life. They need to hear or see what Sickle Cell patients endure every day to be able to make relevant recommendations.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, because every single sickle cell crisis is as dangerous as a heart attack or stroke which can happen to the patient as well during crisis and I don't think they factored that into their recommendation, that every Sickle cell crisis can be viewed as your last day of being alive.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Not at all, if all human beings are equal, no matter what your skin colour is, and also updating the number of Sickle Cell patients in the UK, and not using the over ten years statistics, they will know that the NHS will save more money by having a cure for Sickle Cell disease because, they can multiply one hospital stay by how many patients a day and for how long they have to stay because crisis and complications and compare the costs.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes, when they talked about cost, it feels like they are not thinking about the group of people in question, I know it's not cheap but they can not put price on human life, and if they could give the go ahead for one group without talking about the cost, why can't they do the same, unless it's because it's not affecting people they deemed as important.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	
No. You cant list the challenges of the condition then say that this treatment will be beneficial then recommend against it.	
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	

No. Considering there are over 17,000 UK sufferers of SCD the trial sample was small. However, its results were successful. It would be worth doing a larger trial and it would be worth following up the current cohort over 2 year - 5 years.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

There was no anonymisation process, the therapy was already used on a condition that mainly affects people from a particular race. I doubt that there were no biases or prejudice regarding the specific group of people who suffer with SCD specifically Black African and Caribbean ethnicities. It had been noted that this group disproportionately experiences health inequalities and are more likely to live in more deprived areas of the UK.

Comment on section 2.2 (Dosage in the marketing authorisation):

This link does not work. "This XML file does not appear to have any style information associated with it."

Comment on section 3.25 (Recommendation):

I implore the committee to reconsider its decision not to recommend Exa-cel.

As a sickle cell patient, I was excited to learn of a new life changing gene therapy. The prospect of living a normal, pain free life was in the horizon. Unfortunately, it is highly disappointing to read that this hope may be short lived. The prospect of a cure on a debilitating condition that causes severe pain, complications, organ damage and death. With treatment either being hydroxyurea to reduce VOC or prevention and treating complications. Now it seems that the only possible cure for sickle cell disorder is bone marrow transplant, but this is only possible for a limited number who have a suitable donor.

Surely the positive clinical results are an indicator that over 17,000 sickle cell sufferers deserve the opportunity, chance and lifeline to experience the life changing effects of the innovative Exa-cel?

Claiming to consider health inequalities, life and race inequalities, socio-economic inequalities and yet conclude that the UK population would rather extend the life of a wealthy individual, without challenging this is not how you effectively make reasonable adjustments. Research already provides examples on unequal experiences in health care settings between black and white communities. Here we have SCD a condition that disproportionately affects black people and it now seems to be unimportant to find a solution.

Comment on section 3.4 (CLIMB SCD-121 trial):

Despite a small sample size the results already sound promising and will be life-changing for those who participated.

Comment on section 3.5 (Clinical trial evidence):

Considering approx over 17,000 people suffer with sickle cell disorder in the UK alone, its disappointing to see the low number for trial participation or to read that there was difficulty to drive participation.

I do wonder what the recruitment process was? (Also linked to 3.18)

Comment on section 3.8 (Standard care mortality modelling):

If little information is known or little research provided regarding mortality age. Why lead with "The company's BOI study reports a mean age of death for people with severe SCD of 40 years."..(in 3.7)?

Comment on section 3.9 (Long-term treatment effects):

The results from the trial, whether seen as a 'functional cure' or 'cure' is still a success. To effectively be VOC free, free of daily pain, regular pain that stops you from functioning is definitely worth following up. Long term effects and the ability to follow up over 2yrs - 5years should be explored further with additional data collection.

Comment on section 3.20 (Equalities):

Despite claiming to have taken into account health inequalities, socio-economic backgrounds, race etc highlighted in 3.17. It just feels as though the Company, Stakeholders, experts etc don't seem to care enough. Or maybe because the patient's are not what "the UK population prefers" regarding "extending quality-adjusted life expectancy for a poor individual compared with a wealthy individual". (3.18)

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	
A sickle cell crisis can have a life changing impact on the wellbeing of an adult and child therefore, everything possible should be done to relieve symptoms and prevent it happening	
Are the recommendations sound and a suitable basis for guidance to the NHS?	

It appears that Black people are again unable to access treatment that would improve the quality of their life, by reducing pain and numerous episodes of hospital admissions. I do not have sickle cell but as an health care worker I have witnessed its impact on a young lady who had a stroke also a man receiving dialysis and his family as he struggled to work, socialise and lead a normal life, due to the impact of having sickle cell. it is vital that this medication is available for those who need it.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The cost of medication for pain, lost days off work, college, university, school also for family and carers furthermore, in patient and out patient hospital appointments, A&E admission, quality of life, mental health also health care staff involved, is evidence of the cost effectiveness, in prevention.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The reason why people withdraw before having the infusion should be addressed as there may be something a black organisation like CAHN (Caribbean and African Health Network) could do to support patients with this treatment.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Dear NICE,

As a member of the African and Caribbean community, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom.

This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease.

Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent.

In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage.

This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years.

The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people.

Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18.

These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community.

The health inequalities faced by the African and Caribbean community in the UK are well-documented.

Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare.

A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts.

Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease.

Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition.

By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease.

This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run.

It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition.

Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future.

Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system.

It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be.

This is unacceptable and goes against the principles of equality and fairness that should underpin our society.

I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible.

The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group.

By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long.

Thank you for your attention to this critical matter.

I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.

Yours sincerely,

[Redacted Signature]

Name	[Redacted Name]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Are the recommendations sound and a suitable basis for guidance to the NHS?

Allow more funding to reach education surrounding the illness and improving racism and cultural bias in the system. Hospitals take an oath to teach and be a teaching hospital. If they are unwilling to improve on an illness that has been around for a long time, are they really doing what they publicly claim they are. Less performative and more internal dialogues with staff that want to learn and do more

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Price is a huge factor with this treatment and understandable why it can be questioned. But if funding was accurately distributed without bias and it's accounted for, a little goes a long way in the sickle cell community

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I think medical staff should have repercussions for sickle cell abuse. There's no repercussions for sickle cell patients that lose their lives due to ignorance and pure neglect.

Comment on draft guidance consultation:

- The negative impact that severe sickle cell has on the day to day life of the condition

Sickle Cell Disease (HbSS) is an inherited disorder present from birth. The sickle haemoglobin becomes rigid and sticks together causing the long premature breakdown of the red blood cells resulting in low blood count (haemolytic anaemia) and 2) vaso-occlusion which is the sticking of red blood cells in small blood cells resulting in down-stream lack of oxygen to the tissues and therefore damage to the organs affected. Information around sickle cell has not fully been grasped therefore information needed to help the patients are suppressed. For instance the severity of our blood cells imploding rapidly in our bodies and releasing haem (can be seen as poison in the blood stream) which has severe impact on our day to day lives.

Sickle cell severely impacts our activities of daily living. Such as cooking, cleaning, remembering to take medication, laundry, shopping, managing our personal finances, communication and taking transport. Because patients have learnt to cope with their daily lives because of the lack of education and knowledge surrounding the illness due systemic racism, we've adapted to being unsupported. Not only is the physical impact of sickle cell crushing, the emotional and mental challenges are worse. The emotional and mental impact of sickle cell is what is medically ignored the most because of lack of funding that goes into adequate teaching and global recognition. Therefore this means the day to day challenges of sickle patients is intensified because the challenges are ignored and suppressed by the medical industry. Sickle cell patients are relied on to teach, be volunteers for the medical industry while also being gaslighted about the condition. This means sickle cell patients are most likely to be discriminated against.

- The worsening impact that sickle cell has over time

The mental and emotional turmoil developed over time by realising that we are scape goats in the medical industry and no one truly cares despite the performative activism we are constantly exposed to. The damage to our organs from being exposed constantly to a sickle cell crisis that is severely under managed by health professionals we are meant to trust and be grateful for. Sickle cell patients are constantly abused and discriminated against which leads to severe emotional damage that can lead to severe depression or worse, suicide.

The worse impact is realising nobody is really coming to help or save us and the performative help is nothing but politics. The fact that pharmaceutical companies are willing to invest millions in research for medication but not thousands for proper training and education speaks volumes to the sickle cell community. Sickle cell receives low and unfair equity as opposed to cystic fibrosis that receives up to 9 times more funding and education. The exposure to racism and discrimination is directly linked to poor health management as you realise we are the sole authors of our care and health.

•The impact of sickle cell on life expectancy and risk of mortality

The risk of mortality is extremely high in the sickle cell community because of the exposure to systemic racism, discrimination and ignorance. Because of the lack of equity and funding that goes into sickle cell patients, we are more exposed to premature deaths when we visit Accident & Emergency department. The lack of resources and education given at university stage for medical students perpetuates the ignorance shown in hospital. Our life expectancy has direct links to being exposed to sickle cell abuse and poor treatment. If that is combined with inadequate funding, that then becomes the perfect cocktail for a shortened life expectancy and a high rate of mortality.

For further comments please contact sickle cell campaigner Lowlah Bloom

[REDACTED]

Name	[REDACTED]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Although NICE acknowledges some pertinent evidence, its decision does not correspond with the evidence provided for approving the treatment for NHS use. This suggests potential gaps in knowledge and evidence concerning the disease's severity and the impact on sufferers' quality of life. If there are no gaps in the relevant evidence, then it appears that such evidence and considerations were disregarded leading to NICE's decision against recommending the use of this curative method. This is why I urge

NICE to revisit their decision and reconsider, as failing to do so may tragically shorten or burden numerous lives with unnecessary pain.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is inconsistent to acknowledge both the absence of alternative options and the urgent necessity for additional treatment avenues to enhance the quality and longevity of life for those afflicted by this disease, yet dismiss the handful of promising healthcare advancements. Given this, the recommendations put forth by NICE lack merit and appropriateness unless they acknowledge and advocate for the imperative of progressing of this curative method.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Upon reviewing the consultation and considering the shortened lifespan of individuals with severe Sickle Cell, it becomes apparent that the lifetime cost of treatment may actually be less than that of a cure due to the shorter life expectancy associated with the condition. Therefore, the summaries of clinical and cost effectiveness may not offer reasonable interpretations of the evidence in this particular scenario. I urge NICE to revisit their approach, engaging with and researching a broader spectrum of sufferers to gain a more comprehensive understanding of why it is imperative to provide a cure for those who have no alternative options. NICE's reluctance to prioritise approval overlooks the imperative of providing effective care, and proactive measures to rectify disparities in treatment accessibility within the UK healthcare system for sufferers of Sickle Cell.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The consultation rightly acknowledges the challenges faced by Sickle Cell sufferers in accessing adequate management and treatment, whether due to intentional barriers or lack of awareness. However, the rejection of this curative method risks perpetuating the same injustices faced by those whose lives and struggles are deemed unworthy of available treatments. Whether intentional or not, this recommendation inadvertently discriminates against Sickle Cell sufferers, denying them access to a cure that is available to others worldwide. It's imperative to ensure equitable access to treatments for all individuals, regardless of their demographic background, and to prevent any form of unlawful discrimination. We must not only acknowledge instances where this equity is lacking, such as in the 'No One's Listening' report, but also take proactive steps to provide access to cures, as demonstrated by this curative method now available in the UK.

Comment on draft guidance consultation:

As a mother of a two-year-old living with Sickle Cell, I am deeply disheartened by the apparent lack of understanding from NICE regarding the profound challenges faced by those born with this condition. My son was born just weeks after 'Crizanlizumab' was greenlit for NHS use. By 10 months old, he had already undergone three blood transfusions and was placed on hydroxycarbamide to manage his condition.

Both sufferers and healthcare professionals assured me that the landscape was changing, offering hope for a more manageable life. Gene therapy is now here as a potential cure. Yet, in just two short years, it's become painfully clear that progress has not matched expectations. While progress is being made in other countries, the availability of treatments for the Sickle Cell community in the UK seems to be falling behind. Despite the availability of treatments and potential cures, there's a glaring disparity in access and understanding, even within our own healthcare system.

The fact that treatments exist to alleviate pain and prolong life isn't reason enough for approval here, despite their adoption in other countries. The NHS should set the gold standard for care, yet reports like 'No One's Listening' and tragic cases like Evan Nathan Smith's death underscore the urgent need for a reevaluation of our stance on making these curative methods accessible.

I urge you to reconsider your position and make these curative methods available to those who desperately need them. Additionally, measures should be taken to streamline access to existing treatments for those fortunate enough to have HLA-matched donors. I am more than willing to provide further insights if needed.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Sickle Cell is a rare disease so It is difficult to generate evidence from studies with sample sizes large enough to be capable of detecting clinically meaningful differences using conventional clinical trial, designs such as as expected by drug regulator, authorities and evidence based medicine bodies.

However In the one published study the observed difference in the endpoint of reduced veno occlusive episodes was impressively large (93.5%)

NICE should therefore adopt a more flexible and collaborative paradigm for addressing clinical evidence and values in rare diseases such as sickle-cell disease

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations are not a sound or suitable basis for NHS guidance in a rare disease, such as sickle-cell disease - an inherited chronic debilitating life, shortening disorder,

A more collaborative and flexible approach should be employed, including consensus, building methodologies, such as Delphi studies, which were favoured by the EU, which funded considerable research into their use in public health matters in the 1990s. In addition consensus methodology is acceptable for the generation of SIGN guidelines

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The methodology which the NICE process routinely follows is not appropriate for assessing drugs or treatments for use in rare diseases because of the issue of sample size which indeed dogs research in rare diseases.

The patient numbers which are typically achievable in studies of novel treatments for rare diseases such as sickle cell are small. When sample sizes are small confidence intervals are bound to be wide. As a result, uncertainty becomes the inevitable outcome of health, economic evaluations based on clinical trials of new treatments for rare diseases. Unfortunately evidence based medicine, judges treatments, whose effectiveness is surrounded by economic uncertainty, unsuitable for routine use.

This in turn means that for methodological reasons, new treatments are not recommended, even though as in the case for casgevy the one study so far showed clinically interesting results with a 93.5% reduction in the endpoint of veno occlusive episodes

As stated previously NICE perhaps needs to adapt the methodology, it is using me to assess drugs such as Casgevy to match the clinical settings in which drugs for rare diseases are researched and could be used to change lives

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

This decision by NICE despite MHRA approval is already perceived as racially discriminatory

I hear this firsthand from people who endure living with sickle cell disease in my role as the [REDACTED] of the Croydon Sickle Cell and Thalassaemia Support Group (registered charity, 110 0,120)

I have also heard from nursing staff, that it seems to them clinically inequitable and racially discriminating that this potentially curative treatment should not be available when they see so many other patients having expensive cutting edge treatments in cancer therapy.

I worked as a haematologist in the NHS and this decision will add to the perception that people with sickle cell suffer racial discrimination in the treatment they receive as documented in the report from the Sickle Cell Society and the APPG 'No One is listening'

Finally, the fact that the FDA approved Casgevy in December 2023, as the first gene editing cell based treatment using CRISPR-CAS9 and that it may not be used here is seen as inequitable even racially discriminatory by the UK

Name	[REDACTED]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I believe not all relevant evidence has been considered. I feel the benefits of Exa-cel are not considered.

There is no clear evidence why people should not have the opportunity to be offered Exa-cel. This potentially will be life changing for the individual and they need to be given the chance of a better life, living with sickle cell.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendation should be for people suffering with sickle cell are offered Exa-cel

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summaries of clinical and cost effectiveness are not reasonable interpretation of the evidence.

I believe there is too much consideration given to the cost of this and not the benefits to children/young people and older people suffering from sickle cell. We do not want to see unlawful discrimination of this group of people. I want to ask if NICE believe the voice of the person suffering from sickle cell is clearly represented? I do not believe this is the case.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender

reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I do not believe the full picture of what a person living with Sickle Cell is represented.

Their lives are affected by this disease.

Sickle Cell is a condition which is not readily known about. More publicity is required to ensure the people in power understand the affects of living with sickle cell.

Sickle cell can have such a negative impact on people suffering with the disease.

Sickle cell shows it has a worsening impact on peoples lives over time.

Sickle cell has an impact on life expectancy and has a high risk of mortality.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

-

Are the recommendations sound and a suitable basis for guidance to the NHS?

-

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

-

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes.

Sickle cell anemia affects persons of color and racism in medicine has been deeply documented in the United Kingdom.

The severity of sickle cell as it affects daily life not only with pain that cannot be described but also with continuous damage of organs the longer one is alive are not debatable.

To not pursue a life-altering cure developed in our lifetime due would be unforgivable, and given the levels of racism in medicine in the United Kingdom, that is the only possible reason, as far as I'm concerned.

If cancer treatments are not turned down, there is no reason to turn down such a life-changing treatment for people with sickle cell.

It would be highly disappointing for medicine to once more berate the experiences of persons of color in 2024.

Name

Organisation

N/A

Conflict

N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

NO, The impact on people living with this chronic relapsing condition needs to be better articulated with empathy:

Sickle-cell anaemia is by far the most common inherited condition in the UK and the numbers are rising.

It begins to have a significant impact on physical health within the first year of life It is a life-long chronic condition which causes multi-morbidity, disability and premature death - It is characterised by:

- repeated unpredictable sickle-cell crises which require emergency medical treatment in A&E, the most inefficient, costly way to manage chronic conditions

- frequent long stay admissions costing the NHS hundreds of thousands of pounds each time

- chronic excruciating pain experienced at multiple sites around the body, often simultaneously

- inability to either get a job or keep a job due to frequent sickness absence

- stigma, loss of self worth, impaired mental health impacting social / family life

Each time a person has an acute sickle-cell crisis they risk complications of infection, damage to any internal organ of the body - lung, brain, liver, kidney, skin, eye, gallbladder, spleen, bowel - and most frightening of all for the individual, a significant risk of death during each hospital admission

After each sickle-cell crisis, physical and mental health deteriorate, increasing a person's morbidity, resulting in a poorer quality of life.

Besser M, Jarvis S, Hamlyn M, Brown JP, Barcelos G, Beaubrun A, Binns M, Rice CT. 5613022 SOCIETAL BURDEN OF SICKLE CELL DISEASE IN THE UK: EMPIRICAL ESTIMATES OF PRODUCTIVITY LOSS AND LOSS OF FUTURE INCOME USING REAL-WORLD EVIDENCE.

Hemasphere. 2023 Apr 10;7(Suppl):5. doi:

10.1097/01.HS9.0000928160.37824.27. PMID: PMC10112497.

Dormandy E, James J, Inusa B, Rees D. How many people have sickle cell disease in the UK? J Public Health (Oxf). 2018 Sep 1;40(3):e291-e295. doi: 10.1093/pubmed/idx172. PMID: 29294057.

Are the recommendations sound and a suitable basis for guidance to the NHS?

NHS?

No given that - The quality of care for the significant population of people in the UK living with sickle-cell anaemia as a chronic condition, typically does not meet requirements in terms of the 6 domains of quality - safe, effective, patient-centred, timely, efficient, equitable. Statistics highlight annually preventable and premature deaths in people living with sickle-cell anaemia.

There is unacceptable variation in service provision and deterioration in standards across the board continue to occur as budgetary cuts deepen. Treatment options are extremely limited compared to other inherited conditions such as cystic fibrosis.

It is unacceptable that although we have known about this condition for more than a century so little has been done to radically transform the quality of life and life expectancy for the significant population who live with this condition (see the).

. This context of inadequate care provision should influence the recommendation

For Q2

Piel FB, Jobanputra M, Gallagher M, Weber J, Laird SG, McGahan M. Co-morbidities and mortality in patients with sickle cell disease in England: A 10-year cohort analysis using hospital episodes statistics (HES) data. Blood Cells Mol Dis. 2021 Jul;89:102567. doi: 10.1016/j.bcmd.2021.102567. Epub 2021 Apr 1. PMID: 33862367.

Health inequalities for patients with sickle cell disease. 2022 March; EDM (Early Day Motion) 1114: UK Parliament

All Party Parliamentary Group (APPG) Sickle Cell and Thalassaemia. . No one is listening. London: APPG Sickle Cell and Thalassaemia, 2021

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Sickle-cell anaemia is by far the most common inherited condition in the UK and the numbers are rising.

It begins to have a significant impact on physical health within the first year of life It is a life-long chronic condition which causes multi-morbidity, disability and premature death - It is characterised by

- repeated unpredictable sickle-cell crises which require emergency medical treatment in A&E, the most inefficient, costly way to manage chronic conditions^{[L]_{SEP}}
- long stay admissions costing the NHS hundreds of thousands of pounds each time
- chronic excruciating pain experienced at multiple sites around the body, often simultaneously
- inability to either get a job or keep a job due to frequent sickness absence
- stigma, loss of self worth, impaired mental health impacting social / family life^{[L]_{SEP}}

^{[L]_{SEP}}

Each time a person has an acute sickle-cell crisis they risk complications of infection, damage to any internal organ of the body - lung, brain, liver, kidney, skin, eye, gallbladder, spleen, bowel - and most frightening of all for the individual, a significant risk of death during each hospital admission^{[L]_{SEP}}

^{[L]_{SEP}}

After each sickle-cell crisis, physical and mental health deteriorate, increasing a person's morbidity, resulting in a poorer quality of life^{[L]_{SEP}}

. I don't think sufficient predictive costings have been made over life course for the number of people living with sickle including the social and societal cost. This then needs to be compared with the costs of treatment and figures around proportion who will experience a 100% cure if treatment is completed and no longer need care for acute relapsing illness

Fuggle P, Shand PA, Gill LJ, Davies SC. Pain, quality of life, and coping in sickle cell disease. Arch Dis Child. 1996 Sep;75(3):199-203. doi: 10.1136/adc.75.3.199. PMID: 8976657; PMCID: PMC1511691.

Fuggle P, Shand PA, Gill LJ, Davies SC. Pain, quality of life, and coping in sickle cell disease. Arch Dis Child. 1996 Sep;75(3):199-203. doi: 10.1136/adc.75.3.199. PMID: 8976657; PMCID: PMC1511691.

Miller MM, Rumble DD, Hirsh AT, Vervoort T, Crosby LE, Madan-Swain A, Lebensburger J, Hood AM, Trost Z. Pain-Related Injustice Appraisals in Youth with Sickle Cell Disease: A Preliminary Investigation. Pain Med. 2021 Oct 8;22(10):2207-2217. doi: 10.1093/pm/pnab001. PMID: 33723587; PMCID: PMC8677454.

Pizzo E, Lavery AA, Phekoo KJ, AlJuburi G, Green SA, Bell D, Majeed A. A retrospective analysis of the cost of hospitalizations for sickle cell disease with crisis in England, 2010/11. J Public Health (Oxf). 2015 Sep;37(3):529-39. doi: 10.1093/pubmed/fdu026. Epub 2014 May 5. PMID: 24796312; PMCID: PMC5896799.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Discrimination on the grounds of race - The quality of care for non-white people, living with sickle-cell anaemia as a chronic condition, typically does not meet requirements in terms of the 6 domains of quality - safe, effective, patient-centred, timely, efficient, equitable. Statistics highlight annually preventable and premature deaths in people living with sickle-cell anaemia.

There is unacceptable variation in service provision and deterioration in standards across the board continue to occur as budgetary cuts deepen. Treatment options are extremely limited compared to other inherited conditions such as cystic fibrosis.

The above is an outline of the devastating impact of sickle-cell anaemia on an individual and their loved ones in the current context of access to services, care and outcomes.

It is unacceptable that although we have known about this condition for more than a century so little has been done to radically transform the quality of life and life

expectancy for the significant population who live with this condition (see the All- Party Parliamentary Group (APPG) on Sickle Cell and Thalassaemia's Report, No One's Listening, 2022).

'Reducing inequalities' is repeatedly set out as a key priority for integrated health and care systems - Given that Casgevy results in 100% success for those who can complete the treatment and it has been use since 2019 in the USA, the evidence is surely overwhelming and the time is now, for a step-change in care. NICE must reconsider and rule in favour of Casgevy to make it available on the NHS forthwith.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	
Definitely not. Why are the costs not disclosed? Public access to the costs would give us even more insight into what NICE considers to be cost effective use of NHS resources. I believe there is a strong link to the health inequalities African and Caribbean people continue to face. How much is the quality of SCD patients life worth? And surely long term suffering has a huge impact on NHS resources.	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender	

reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

There is already a problem with very few African and Caribbean people giving blood, being donors etc exacerbating the problem of finding suitable donors for SCD patients. Therefore I believe there is a strong need to allow Exagamglogene autotemcel into the UK to treat sickle cell disease.

Name	

Organisation	N/A

Conflict	N/A

Comments on the DG:

Funding and utilizing Exagamglogene autotemcel for treating sickle cell disease is crucial for several reasons. Firstly, it offers a groundbreaking approach by targeting the underlying genetic cause of the disease, potentially providing a long-lasting cure rather than just symptom management. Secondly, investing in this innovative therapy aligns with our commitment to advancing medical science and improving patient outcomes. Lastly, by supporting the development and use of this treatment, we can significantly alleviate the burden of sickle cell disease on individuals, families, and healthcare systems worldwide.

Name	

Organisation	N/A

Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

1. Patients do not seek medical help early enough with a VOC due to the barriers and inequalities in the health care systems . This drives patients to manage these VOCs at home as much as possible.

Since the set up of the first rapid access sickle unit in England in Manchester in Jan 2024 , the number of admissions with VOCs have gone up in the 3 months. This is not due to more patients but these are truly acute pain episode. Patients have more confidence in the system to attend and seek help early as they do not need to go to Emergency departments. They have direct access to a 24/7 triage number and having a team who understands their pain.

There is a definite underestimation of the true VOC patients experience and therefore the data on severity of disease definition with hospital admission. This is now more reflective and is coming out a bit more.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Exacel certainly has a role to play as a curative option for patients with severe sickle cell disease. In Manchester we have done 2 sibling matched transplant in adult patients. Their quality of life has improved tremendously.

Quote from one patient seen in March 2024

'I cannot go back to the life I had pretransplant with red cell exchanges. I have a much better life now. I work with NHS and am now able to do a full-time job.' Even though I am still on some immunosuppression 2 years on, I still have a good quality of life.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No.

1. The severity of organ damage as patients age is not fully appreciated by NICE. The cost implications of ageing sickle cell population has not been taken into account.
 2. Impact of quality of life of a sickle cell patient with sickle cell disease has not been fully understood by NICE.
 3. There is a definite role for Exacel in a subset of patients with sickle cell disease who will benefit from this treatment especially those with recurrent VOCs who struggle with transfusions programme due to vascular access issues, and no matched sibling for consideration of stem cell transplant.
- There is a definite clinical utility in a subset of patients well defined to have access to this treatment.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I do think perhaps the impact on QOL has not projected well on the data collected and this may well be due to cultural aspects from patients, uniqueness of the disease and patients' attitude of 'I just need to get on with my life' and not expressing their views very openly as they should. This is something I see on a daily basis as a clinician looking after these patients.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	

While evidence was considered, it does not appear to have been fully comprehensive. It's important to recognise that living with sickle cell disease (SCD) can be incredibly challenging. Black individuals are disproportionately affected by this disease, and there's extensive research showing that they often face difficulties in articulating their pain and health challenges. This is largely due to systemic racism, lack of trust in healthcare systems that are still structurally biased, and inadequate health literacy.

Having worked in health sector, I've witnessed firsthand how SCD tragically impacts many young lives, often preventing them from working or maintaining personal relationships or healthy mental well-being. The excruciating pain associated with SCD affects the entire body, permeating through the blood and impacting all organs of those affected. Therefore, it's clear that not all pertinent evidence has been taken into account.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, the recommendations should support the approval of funding. Diseases that disproportionately affect Black communities are often under-researched and under-funded. It's time to change this pattern and prioritize funding for treatments like this within the NHS. Let's take a step towards closing the gap in health inequalities.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summaries of clinical and cost effectiveness may not fully represent the evidence. It's crucial to ensure that interpretations are comprehensive and consider all aspects of the evidence to make informed decisions about the effectiveness and value of treatments.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes, there are concerns regarding accessibility to this consultation for communities that may lack literacy or technical skills needed to participate effectively. However, the critical need for this treatment remains irrespective of these barriers to engagement.

Name	National Haemoglobinopathy Panel
Organisation	National Haemoglobinopathy Panel
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	

1. Audit transplant related consultations in patients 1 years post-BMT:
A key issue in the assessment of efficacy is whether a 12-month assessment is an appropriate and representative time-point to assess the long-term effects of a myeloablative therapy. To address this, Dania El Tabech & Josu de la Fuente audited the relationship of allogeneic transplantation for sickle cell disease to long-term outcomes in 65 consecutive transplants at St Mary's Hospital, Imperial College Healthcare. This can be treated as a representative cohort, not only because over two thirds of all allogeneic transplant in the UK have been conducted in this centre, but also because approximately 50% of the allogeneic transplants with complete data in the European Society for Blood & Marrow Transplantation (EBMT) come from this centre. Six transplants were excluded due to not having reached a minimum 12 months follow-up and five due to transplant related mortality. The transplant procedures included a combination of related, unrelated and haploidentical stem cell sources, and both myeloablative and reduced intensity approaches, avoiding the outcomes to be skewed by a particular approach. With a median follow up of 3 years (range 1-8 years) 54 consecutive transplants with a minimum 12 months follow-up were audited with a median age of 15.24 years. No patient with successful engraftment had sickle related complications at 12 months. One patient had a subsequent secondary graft failure at 3 years. None of the 54 patients without sickle related events at 12 months went on to develop a sickle related event at subsequent follow up, indicating that the 12 months assessment is an appropriate and sufficient time point to assess efficacy.

2.
The NHP was established in 2019 to provide a team of experts in the management of sickle cell disease SCD and dedicated experts in cellular therapy (bone marrow transplantation and gene therapy) to assess and screen complex patients presented by specialist centres across the country, including discussion and selection of cases to be referred for bone marrow transplantation. The monthly video MDT started in April 2020 and by March 2024 total of 109 cases had been discussed. Following discussion by experts, 76 cases (an average of 20 cases per year) were approved for referral for BMT. However, following an audit of those approved to proceed to BMT, 75.5% are proceeding with the recommendation for stem cell transplantation and 22.45% declined to proceed with transplantation for various reasons. This shows that sickle cell patients given adequate information and enabled to participate in shared decision making are able to choose an option most suited to their individual situation.

OUTCOMES OF CASE APPROVED

Bone marrow transplantation:

Cases for proposed for SCT- 76

Responses so far (10.04.2024)- 49

Patients deciding not to proceed to SCT despite panel approval- 11 (22.45%)

Procedures awaiting patient decision despite panel approval: 1 (2.04%)
Numbers proceeding to SCT: 37 (75.51%)

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendation should reflect the fact cases that are considered for gene therapy are those who despite the severe phenotype do not have another option to receive proper care. The recommendation should carefully offer those patients with severe VOCs that are not eligible to for bone marrow transplantation and may not be amenable to other high-risk therapies. Gene therapy uses endogenous graft and therefore free of graft versus host disease complication.

Lugthart S, Ginete C, Kuona P, Brito M, Inusa BPD. An update review of new therapies in sickle cell disease: the prospects for drug combinations. Expert Opin Pharmacother. 2024 Feb;25(2):157-170. doi: 10.1080/14656566.2024.2317336.

Epub 2024 Mar 4. PMID: 38344818.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Sickle Cell Disease – Burden and Quality of Life

Research indicates that individuals with Sickle Cell Disease (SCD) face significant challenges that impact their quality of life across various domains. A systematic review focussing on the effects of hematopoietic stem cell transplant (HSCT) and gene therapy on health-related quality of life (HRQOL) in patients with SCD and thalassemia revealed that these therapies are associated with positive effects across most HRQOL domains for SCD. Notably, in SCD, HSCT was linked with large positive effects in all HRQOL domains, suggesting improvements in HRQOL outcomes following gene therapy in addition.

Reference:

Sherif M. et al. A systematic review of quality of life in sickle cell disease and thalassemia after stem cell transplant or gene therapy. Blood Adv 2021; 5 (2): 570–583.

<https://doi.org/10.1182/bloodadvances.2020002948>

Pain is a hallmark symptom of SCD and has a profound impact on the HRQOL of affected individuals. A recent global study emphasised this profound impact of SCD on HRQOL, particularly among adults with recurrent vaso-occlusive crises (VOCs). It was found that these individuals experience significant disruptions to daily life due to recurrent pain crises and chronic pain, leading to substantial impairments in their ability to work and overall HRQOL. The study, which included surveys and interviews, reported lower than average scores in several HRQOL domains, including physical and emotional well-being, compared to the general population. A

notable percentage of respondents also reported experiencing pain, discomfort, anxiety, depression, and mobility impairment.

Reference:

Jennifer Drahos, et al Blood 2022; 140 (Supplement 1): 1387–1388.
<https://doi.org/10.1182/blood-2022-157818>

Furthermore, chronic pain, acute pain crises and hospitalisations significantly reduce physical functioning, emotional well-being, and social activities, leading to a deterioration in overall HRQOL and decreased QALYs.

References:

Anie KA, et al (2012). Patient self-assessment of hospital pain, mood and health-related quality of life in adults with sickle cell disease. BMJ Open, 2, e001274. doi:10.1136/bmjopen-2012-001274.

McClish DK, Penberthy LT, Bovbjerg VE, et al. Health related quality of life in sickle cell patients: The PiSCES project. Health Qual Life Outcomes. 2005;3:50. doi:10.1186/1477-7525-3-50.

Smith WR, Penberthy LT, Bovbjerg VE, et al. Daily assessment of pain in adults with sickle cell disease. Ann Intern Med. 2008;148(2):94-101. doi:10.7326/0003-4819-148-2-200801150-00004.

Comparison with General Population and Other Chronic Diseases
Studies consistently demonstrate that individuals with SCD experience lower HRQOL compared to the general population. Moreover, comparisons with other chronic diseases such as cystic fibrosis and asthma reveal similar or even lower HRQOL scores among patients SCD patients.

Reference:

McClish DK, Penberthy LT, Bovbjerg VE, Roberts JD, Aisiku IP, Levenson JL, Roseff SD, Smith WR. Health related quality of life in sickle cell patients: the PiSCES project. Health Qual Life Outcomes. 2005; 29; 3:50. doi: 10.1186/1477-7525-3-50.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

SCD is a chronic, life-limiting, and debilitating condition that causes significant morbidity and mortality. In patients with severe SCD (with frequent vaso-occlusive episodes) mortality and morbidity are increased even further. SCD is characterised by haemolytic anaemia, widespread organ damage, unpredictable episodes of severe pain called VOC ('vaso occlusive crisis') and shortened life expectancy SCD has significant negative emotional, social and quality-of-life (QoL) effects on patients, and also their families on a daily basis.

The committee asked for additional data on mortality and QoL: British Journal of Haem VOLUME 189 SUPPLEMENT 1 (Baba Inusa, John James et al, 2020) shows that patients with SCD are affected by a myriad of complications and associated chronic multi-organ comorbidities. There is extensive recent literature (including studies from the UK) that consistently demonstrates that SCD patients have a significantly reduced life expectancy which is further reduced for patients with severe SCD/recurrent VOCs.

These figures are consistent across cultures and over time with a lack of significant improvement over the last few decades even if optimal treatment is available see summary from SWAY study. In light this, it is clear that a whole population of patients is being gravely underserved.

The main aim of treatment is to achieve cure but there is currently no such therapy available and therefore the main therapy is to prevent infection by using penicillin prophylaxis, vitamin supplementation using folic acid and the only disease modifying therapy is hydroxyurea which has been in use for over 35years. Current therapies offer only palliation but do not eliminate the symptoms and even though treatment improves the quality of life in many, not all patients respond to treatment.

While in 2017 L-Glutamine, and 2019 both Crizanlizumab and Voxelotor were FDA approved, neither L-Glutamine, Voxelotor nor Crizanlizumab have been supported by NICE.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Disappointing conclusion. It appears we can pick and choose when consideration of long term effects applies. The primary reason for this rejection is simply, that the lives of the primary intended recipients of this treatment, are not valuable enough to justify costs. Its primary users being people from African Caribbean backgrounds. I have heard too many stories of people within my community who have suffered at the brutal hands of SCD. We have a treatment that potentially can improve the lives of individuals who have been living in chronic pain, and this committee has concluded they need more data? Where was this request when we were fast tracking vaccinations ?	
Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

NICE Exagamglogene (Casgevy) Consultation for Treating Sickle Cell Disorder having not been recommended by NICE on 14.3.24. Submission before 11th April 2024

Dol – [REDACTED] was part of the MHRA marketing authorisation

Dear NICE,

I live with Sickle Cell Disorder (SCD), [REDACTED] the award-winning UK Sickle Cell Society for a decade, and have been a member of multiple NICE steering Committees, as well as NHS Boards and Groups evaluating and approving medicines, pathways, specifications, assurance etc, across different medical conditions, but including SCD, and other rare diseases. I have written articles published from the Guardian to Elsevier. Please note rejecting treatments with great efficacy for any condition de-incentivises funders, pharmaceutical companies, researchers, and the whole medical ecosystem from investing.

I am the longest serving member of the SC and Thalassaemia All Party Parliamentary Group and Chaired the same when needed. Please accept my deep concern and disappointment regarding NICE's decision on the 14th March 2024, to reject Exagamglogene (Casgevy). This is a devastating blow to my community of fellow sickle cell Warriors and their families across the UK, a community that remains long suffering, and continues to face extreme health inequality.

[REDACTED] 'The Sickle Cell Guide' which was reviewed and highly acclaimed by the Lancet Medical Journal who say it is essential reading for medical professionals, I wonder how many on the NICE Committee have read this book? ('The Sickle Cell Guide' is available at Amazon <https://www.amazon.co.uk/dp/B0BJ84YHGY> Lancet Review April edition of the Lancet Medical Journal Hematology <https://www.sciencedirect.com/science/article/abs/pii/S2352302623000704>). In December 2023 the FDA Approved the world's first CRISPR gene editing drug.

[REDACTED]

In the UK structural and systemic inequality has contributed to little, to no change in sickle cell care, because no one in the NHS with any power cares, resulting in the utter stagnation we see today. Of course, we would welcome the opportunity to debate this, but even that offer gets rejected and dismissed with impunity.

My reports highlighting the testimonies of many patients and their complaints are ignored. Government and other reports on sickle cell disorder (SC) are ignored, Black, Achison, Marmot, etc are ignored. Other peer conditions race miles ahead in the care and treatments they receive.

The disparity occurs in plain sight, complaints are ignored, and patients are abused with impunity. Nearly 50% of patients, fearing to go to hospital, because of the abuse and harm they experience, ref SWAY and 'The Sickle Cell Guide'! In their Vaso-Occlusive Crisis; which is a 'Medical Emergency', the majority of patients say, they prefer to suffer at home, than suffer conflict with white authority!!!!

The above is important, there is so much I could do to save the NHS money, but it just does not care! People living with the condition know it, have voiced it for decades, and have little trust in the NHS and its clinical professionals at every level. This breaks my heart, and I think it would break anyone's heart if they really cared. They would understand that human beings in a civilised country should not be having totally avoidable, harmful, unsafe, distressing experiences, at a greater rate, and higher severity than their white counterparts.

As a public for good I have tirelessly encourage my SC community to engage in the consultation <https://www.youtube.com/watch?v=E20-z3qOeio> if only the NHS and its associates demonstrated such leadership, ethics, and sincerity. This at the time of the Hilary Cass Report, where puberty blockers untested, that reportedly do not work, have unethically been prescribed on the NHS to vulnerable children.

The link sets out the flaws on the decision including the. abject lack of choice and failure to develop healthcare, decade upon decade for people living with SC. The pain of a VOC likened to being repeatedly hammered or axed, indeed mothers from around the world report child-birth hurts less than a sickle cell crisis.

I and the majority of people living with this life limiting, unpredictable, multi-system disorder; experience accumulative organ, tissue, bone, blood damage and complications including stroke, priapism, splenic sequestration, osteonecrosis, renal failure, pulmonary hypertension, liver disease, bone damage, limited growth, increased susceptibility to infections, fatigue, and progressive cognitive decline, meningitis, skin ulcers, complications in pregnancy functional asplenia, splenic infarction, splenic sequestration, septicaemia; sepsis, avascular necrosis, osteomyelitis, retinopathy, post-hyphema glaucoma, retinal infarction (tissue death), avascular necrosis, cardiomegaly, diastolic heart failure, ACS, Pulmonary hypertension, oedema, pulmonary embolisms, hyperbilirubinanaemia, gallstones, sickle hepatopathy, erectile dysfunction, albuminuria, isosthenuria, substantial kidney injury, acute renal failure, clinically extremely vulnerable susceptible to virus's and infections). We experience stigma, misogynoir, and behaviours that arise out of racism and prejudice in plain sight, its an oft written about phenomenon yet patients and their families are reporting things are getting worse. In addition, there is poor mental health generated

by all these triggers. Poor pain management services causing Drug dependency risks. This is compounded by the deprivation, vulnerability, discrimination, and the economic and social disadvantage people with SCD experience in both the health ecosystem, and wider societal ecosystems. These issues result in greater illness and hospitalisation for those living with SCD. NICE seem, as usual to ignore Principle 9 of NICE's Charter for health inequalities. Having a cure reduces and removes the clinical, social, and economic burdens of living with an invisible fluctuating illness that no one; including patients and medical practitioners, understand. Nobody should have to live with all these chronic and acute burdens, as well as constant and acute pain!

There appears no consideration that in many countries including Sub-Saharan Africa 4 in five children die before the age of five years old. According to the WHO between 50% and 80% of SC Warriors die by the age of 18. This is germane to the NICE QALY calculations.

Page 24 of NICE company evidence Committee Papers, ID4016, says 14,200 patients, when the latest used by the NHS is 17,500 patients. It suggests some significant flaws in the reported information!!!!!!

I honestly believe it is a scandal the way the SC community is treated! At every turn despite help being available, we are left to suffer, forced to endure abuses, and can die without any medical staff being held to account for complaints or serious harm and death. This treatment could be a gamechanger, but like my book; 'The Sick Cell Guide', anything good in sickle cell appears to get blocked and denied, as such the plight of people living with the condition will continue to worsen.

I and probably 100% of patients as a goal, would ask for zero hospitalisation and better quality of life. Guess what that is what Casgevy is proposed to deliver!!! And would clearly save the health services huge sums of money as an IRR (Internal Rate of Return), and a huge saving in the social costs of carers, as well as the multi-disciplinary medical teams, ambulance services, GP's, Doctors, Nurses, Consultants, and the 4 Psychologist we have; joke, yes it is a joke; and its one that results in suffering!

If I were given the treatment, Casgevy would also enable me to enjoy, no symptoms of SCD, halt bodily deterioration and enable repair where possible, no VOC's, no chronic or acute pain, longer life expectancy, reduced need for medications and analgesia (pain relief), improved mood, confidence, work productivity, increased family and social participation, time with the children, ability to swim, ski, travel, reduced expenditure on medicines, recover lost education, ability to do day to day tasks including look after the house, be less vulnerable, suffer less stigma, better sleep, better emotional regulation, support my partner and children, increase and improve employment options, reduce isolation, less anxiety, stress, and depression, etc etc.

Many of those at NICE and ordinary folk without SC take these things for granted and have no idea people without SC reading this have no idea of the burdens we face, or how other limit our humanity. Doctors and Nurses have no idea, they see us for a fraction of a fraction of their life, are not invested in the condition, and the vast majority have received no training in the condition; have not even read my Lancet reviewed book, where the most prestigious medical journal in the world advocate the book is an essential read for any medical professional or student.

Just a glance at the hundreds of pages that are part of this consultation indicate there is nothing in the pipeline of treatments, guidelines on care, pathways coming down the line, the landscape looks positively barren including the actual recent removal of treatments like Crizanlizumab, and Voxelotor under dubious rational. SC has 3 approved treatments, cystic fibrosis 511, this disparity is in plain sight, I gaslighting and denial that goes on and block progress often leaves me worrying that I appear to be the only person that can see the emperor has no cloths on! And those that do know the emperor is naked, are unwilling to listen to and support basic solutions to level-up.

As a patient I would prefer the option of a Cell and Gene Therapy because this is quicker safer, treatment only involves my own screened stem cell genetic material, less chemotherapy, can avoid GvHD, and higher rates of success. I would encourage patients to store sperms and eggs prior to the treatment.

I, and people living with SCD report and complain that NICE commissioning guideline CG143 is routinely not enforced to the harm and detriment of the SC community, not in A&E, or on the ward; even in HCC's (Specialist Sickle Cell Hospitals – Haemoglobinopathy Coordination Centres), and the NHP, CQC, hospital leaders themselves stand there letting it happen! If these behaviours regularly occurred with, stroke, heart attack patient's; both these, as SCD, are ranked as 'Medical Emergencies', the NHS would not tolerate it! If you consider this scenario bad allow me to expand, I have highlighted many times the existence of the 36 Quality Indicators in section 4.2 pages 10 to 12 Quality Indicators; Standards NHS England Service Specification No 170126S Specialist Haemoglobinopathy Services (All Ages) Specialist Haemoglobinopathy Teams <https://www.england.nhs.uk/wp-content/uploads/2019/07/Specialist-Haemoglobinopathy-Teams-Service-Specification.pdf> The 250 page consultation report does not mention it in its table of national SC guidelines at page 50. This 2019 specification, developed carefully at great expense by the NHS, is all but ignored; and no one listens to those that raise it, epitomising the sentiments and concerns in the Parliamentary report "No One's Listening".

The concern of the SC community is that we keep asking, and keep getting ignored, promises made are reneged on. MHRA Authorised the treatment to great plaudits and adoration for the UK Life Sciences, across mainstream media, in November 2023, only to see it fall apart like a cheap suit within

weeks with this NICE rejection. The studies and trials; CLIMB SD-121 and 131 evidence 'high' clinical safety and efficacy, and 96.6% all participants VOC free, 100% hospitalisation free. In America the FDA have approved the treatment, whilst in the UK we drag our heels.

I sincerely urge NICE to reverse its decision and start to prioritise the health and well-being of those affected by Sickle Cell. NICE should recognise the disparity surrounding SC, Cystic Fibrosis, HIV, Haemophilia, etc and position a plan to level up. The inequality experienced by SC Warriors has persisted far too long.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Please ensure that sickle cell sufferers receive any available medication they will help their condition

To remove access to medication is to say that their suffering does not matter.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

I believe that the cost effectiveness for this treatment has been undervalued with the savings in recurrent blood and exchange transfusions required by patients and also the reduction in hospital admissions and length of stay.

There will be a significant gain for these patients on QALYs with reduction in significant comorbidities such as stroke and renal pathology as well as the contribution that patients will be able to make to society as a whole if they are well. This doesn't even necessarily take into account the impact on mental health that a severe, debilitating and life threatening chronic condition can have on the patients and their families.

I believe that the gain for individuals and families around them, far outweighs the perceived initial cost for the medication and I therefore believe we should follow in the footsteps of other gene therapies for other severe chronic conditions such as Cystic Fibrosis and SMA to allow equity of access for these patients too.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes the lack of concern or urgency against a particular section of society is definitely discriminatory.

Comment on draft guidance consultation:

Living with a brother with sickle cell has been very hard to say the least. When he has a crisis it is always very traumatic for both him and the family, seeing the immense pain that we can not do anything about, the screams, the anguish, the pain. It is unbearable and we have lived with this debilitating condition with no way out or cure/solution since my brother's birth. The fact that any solution available will not be available is hard to consider and take in. This is needed to improve the quality of life of people in the black community and if it was a cancer that affected white people this surely would have been available ages ago on the NHS? Why discriminate and deprive the black community of a needed gene therapy/cure? The community is owed at least that after decades or even centuries of discrimination and racism.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

NO

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I do not believe all the relevant evidence has been taken into account as there was not consultations with sufferers of this disease or better still a disorder as it is a gene alteration condition.
Myself and several sufferers barely exist rather than live as this condition affects our everyday existence and it can be quite unpredictable as well.
This gene therapy treatment is proven to improve out daily life's and I don't believe the cost should come into consideration in approving this treatment as overall the NHS will make massive savings in the long run considering the fact that future treatments will not be needed as they won't need to through crises and possibly organ damage due to sickle cell disease.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No the recommendations are not sound enough as some people do not do well on hydrocarbomide not blood transfusions as one can develop anti genes and thereby not able to get transfusions in the future.
We all know EXchange blood transfusions or normal blood transfusions have it's own negative consequences.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The cost should be an issue at all as the NHS will make massive savings in the entire lifetime of a typical sufferer.

For instance if a baby is given the gene therapy as soon as possible in their life then they will not have to be medications and different treatments for the rest of their lives.

I sickle cell patient in their lifetime will probably have a stroke, organ damage and various issues like eye conditions, hip and different bones replacement etc, however if this Exagamglogene treatment is approved for use by the NHS then all these will not need treatment and different costs in the lifetime of the patient so it's a win win and definitely a money saving strategy for the health service.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Name	
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

No, please also consider the negative impact that severe sickle cell has on the day to day life of people living with the condition
The worsening impact that sickle cell has over time
The impact of sickle cell on life expectancy and the risk of mortality

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, missing factors such as the life changing transformation that this will have.

It's a new lease of life

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, cost effectiveness should be re-evaluated

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Effectiveness criteria should be reconsidered

Name	
Organisation	Solace Sickle Cell and Thalassemia support group
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account? Yes Comment on draft guidance consultation: Dear NICE, As a member of the African and Caribbean community, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom. This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease. Sickle cell disease is a genetic blood disorder that predominantly affects individuals of African and Caribbean heritage. In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of African or African Caribbean heritage. This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years. The impact of sickle cell disorder on the African/Caribbean community is staggering. In England, we are over 80 times more likely to have sickle cell disease compared to White people. Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18. These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community. The health inequalities faced by the African and Caribbean community in the UK are well-documented.	

We are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare.

A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts.

Furthermore, we are more likely to experience poor health outcomes across a range of conditions, including sickle cell disorder.

Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition.

By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease.

This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run.

It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition.

Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future.

Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system.

It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be.

This is unacceptable and goes against the principles of equality and fairness that should underpin our society.

I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible.

The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group.

By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long.

Thank you for your attention to this critical matter.

Yours sincerely,

[REDACTED]

Board member of Solace Sickle Cell and Thalassemia support group -
representing City and Hackney in London

Name	[REDACTED]
Organisation	CAHN
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Yes, as far as I am aware.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes, from my knowledge.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes, from my knowledge.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

not that I aware of.

Name	[REDACTED]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I believe so. I could be wrong though

Are the recommendations sound and a suitable basis for guidance to the NHS?

I live with sickle cell anaemia and I am 45 years old. I cannot explain years of painful crisis, life choice compromises and other sacrifices I have made to be a survivor. I have lost close friends and acquaintances to this ailment

Therefore I plead that any medicine that can possibly cure this disease should be funded by NHS. Even if it can only cure the disease in few people.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes. It makes a lot of sense but what value will you say is too high to make a human being live a life free of pain

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

None that I can think of

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I do not think all the evidences have been taken into consideration.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, the recommendation are not sound and does not sound suitable for guidance to the NHS

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Summaries of the clinical and cost-effectiveness does not represent reasonable interpretation of evidence. The evidence sound like a discrimination against the SCD group because other groups of diseases do have a variety of treatments that are available to them whilst the sickle cell community can barely count the interventions or treatment available to the SCD group

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender

reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I believe the SCD group have been mainly discriminated based on their race and the recommendations of its cost-effectiveness prove that these race groups do not deserve the treatment because of its expense. This is extremely racially discriminatory and continue to prove the inequality to this particular race group.

I believe if the condition affects other race groups, NICE or NHS will not make every attempt to make the treatment available to them.

In the long run, if the treatments are not available to these groups, the NHS will suffer the cost in the long run.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

i don't feel all relevant evidence has been taken into consideration , i have only just heard of this treatment and as a sickle cell patient , aged over 50 i know this is the type of treatment we have been waiting for . I have gone through a lot of Red cell exchange protocol but i had to take time off as this process drains me physically , i dread going to the hospital for my treatment because my it is never easy to cannulate me , and i have to endure this or be exposed to the use of a line which leaves me with scars etc

other treatment options for me is Hydroxyurea which makes me sick all the time i often can't eat for days and have to rely on Supplements like Complain shakes ,

By not including older age group of SCD suffers in your consultation , This consultation would be Biased against our Disability and age , The older age group of SCD Patients should be given the option of treatment with Exa-cel ,

Are the recommendations sound and a suitable basis for guidance to the NHS?

Not in my opinion , This is only a recommendation which has not taken account of the use case for majority of sickle cell patient who are in the older age bracket , this recommendation seems biased

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

it maybe , but then what is the cost of a life to anyone ?

SCD Predominantly affects people of African, Caribbean, Middle Eastern or South Asian family backgrounds , do our lives matter as much every other life ?, why is the question of cost effectiveness even being brought up specifically ?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

yes , The recommendations need to take account of the aging population of sickle cell Patients whose quality if lives may be changed with the use of Exa-cel and not just those in the age 12 -35 age bracket Eradicating SCD burden would significantly increase for this group , But for the older group it will be a case of reducing hospital Admissions ,giving a chance to live a disease free life and improved organ function, such as kidney and liver which are often affected by the use of other treatment options like hydroxycarbamide and Pain management medications Morphine , Tramadol, codeine , Di hydro codeine etc as well as minimising risks to these lives

Name	
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

Please see my comments on the document. There are other sources of data on disease outcomes for SCD treated in the NHS which could be helpful There are detailed single centre or regional studies, including the E London Newborn Sickle Cell cohort study, as well as data from the National Haemoglobinopathy Register, including regular reports on mortality rates (<https://nhr.mdsas.com/>). I was not sure if the paper by Piel et al (NHS HES data) was considered (Piel et Blood Cells, Molecules and Diseases 89 (2021) 102567).

I am CI for the the East London Newborn Cohort study. The analysis up to 2018 includes 152 patients with Hb SS age 12+ (max age 35), 39 had 2 consecutive years with >2 VOC, in 33 cases before the age of 19. Of these 33, only one had evidence of chronic complication (AVN) before the age of 19.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I am concerned that the negative opinion will restrict availability of this innovative, curative therapy for NHS patients. The definitive publication on CLIMB 121 outcomes is about to be published in the New England Journal

of Medicine. The efficacy results are beyond expectation and it is hard to see how any trial could produce more positive results. It is not just the cessation of acute VOC's but also the haematological efficacy in correcting anaemia and haemolysis which demonstrate a reversal of the sickling phenotype. The protocol for engrafting stem cells is more or less the same as for allo-HSCT and I am fully confident that the effects will be as durable as for allo-HSCT.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The negative opinion is influenced by uncertainty about mortality rates and complication rates, but the committee has an acceptable body of evidence to make these estimates. In my opinion, the mortality and chronic morbidity seen with standard care for SCD would be completely prevented if Exa-cel is offered to young patients who have not yet developed irreversible complications.

I have commented in the document on the application of the 3.5% discount rate, which I think is unfair. For this kind of one-off curative treatment, where costs are incurred up front, the discount rate has a particular negative effect. The three criteria for a discount rate of 1.5% are met, and if the discount is to be applied, it should be at this rate.

I also don't understand why SCD would not qualify for the highest severity modifier. The life expectancy is estimated at 50 for the whole population, and lower for severely affected patients. This is at least 20 years less than the general population. This alone would account for >17 QALYS before even considering morbidities associated with reduced QOL

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am concerned that the committee's negative opinion is influenced by uncertainties about disease outcomes with standard care. The deficiencies in data on long-term outcomes in the UK SCD population may be difficult to address where there is inadequate funding and resources to undertake the necessary studies. This was highlighted as an aspect of inequality in the APPG 'No one's Listening' report.

Comment on section 3.2 (Treatment options), "Regular blood transfusions may be required, which also means iron chelation therapy may also be considered":

The committee should also be aware that 10- 20% of patients cannot be transfused because they have developed red cell antibodies which limit the availability of compatible blood or have severe haemolytic reactions when transfused with apparently compatible blood.

Comment on section 3.2 (Treatment options), “Clinical experts noted that exa-cel could offer a chance at disease-free survival, improved organ function, reduced symptoms such as VOCs and reduced healthcare use. But, they noted that people with mild SCD and few VOCs are less likely to derive benefit from exa-cel and the treatment risks may outweigh any benefit”:

I agree with these comments from the clinical experts, but would add that many of the younger patients who would be eligible for exa-cel could be treated before they develop any significant organ dysfunction, and would therefore have normal rather than improved organ function after treatment. Also, it is difficult to predict the long-term health outcome for patients who are apparently mildly affected with few VOC's in adolescence and early adulthood. A significant proportion of patients who do not have frequent VOC's have evidence of severe haemolytic anaemia and may develop chronic complications such as pulmonary hypertension and renal impairment in their 4th or 5th decade, as documented in studies referenced in this guidance document. The natural history of these complications is not yet sufficiently clarified, and require results from long-term cohort studies which are not yet mature.

Comment on section 3.5 (Clinical trial evidence), “It also noted that more data collection to establish the long-term effectiveness of exa-cel would reduce the uncertainties around durability of the treatment effect.”:

The committee should also consider the supportive data on long-term cure from numerous publications on allogeneic stem cell transplantation in children and adults with SCD. Exa-cel treatment is expected to produce the same or better outcomes. It involves the same procedure: use of harvested stem cells which are infused into recipient after myeloablation with chemotherapy. The long-term persistence and safety is expected to be superior, because exa-cel uses autologous rather than allogeneic stem cells, so there is no risk of graft versus host disease and less risk of rejection.

Comment on section 3.14 (Non-reference case discount rate):

I question the application of a reference case discount rate, although apparently standard practice in NICE assessments. My understanding is that this is based on the premise that the public prefers not to pay the full cost of treatment up-front, when the health benefits are achieved over a lifetime. Has this been verified by public consultation in the case of curative therapy for a life - shortening, debilitating disease, affecting a minority population, and where a novel gene therapy technology is concerned? It seems fairer to make a balanced health economic assessment where the full life-time costs of standard care, and the full additional social costs associated with lost productivity and QOL for patient and carers are taken

into account, without discounting. If the discounting is to be done, it seems clear to me that the 1.5% conditions are met for SCD

Comment on section 3.15 (Non-reference case discount rate), “The committee considered the third criterion was not met, concluding that it may be plausible that exa-cel benefits were sustained over a long period. But it noted that this was highly uncertain given the limited follow up of clinical evidence. So it would like to see this explored with further data collection (see section 3.23).”:

The effects of exa-cel are highly likely to be sustained. Evidence from allo-HSCT can be extrapolated. The durability is likely to be improved compared to allo-HSCT given that the risks of rejection are minimal and the risks of GVHD are zero

Comment on section 3.15 (Non-reference case discount rate), “When considering the second criterion, the committee noted considerable uncertainty with the likelihood of exa-cel returning people to full or near-full health. It understood from experts that exa-cel would reduce the risk of complications, but it was not clear whether persistent damage from complications and comorbidities would be reversed. The committee considered the second criterion was not met, concluding that it may be plausible that exa-cel returns people to full or near full-health. But, it noted the uncertainty was compounded by the short-term follow up of the clinical-effectiveness evidence and that further data could allow the committee to consider if this criterion was met”:

As commented above, the evidence on returning people to full or nearly full health can be extrapolated from experience with allogeneic HSCT. It is clear from the CLIMB study data that patients are cured, with reversal of anaemia, haemolysis and absence of true vaso-occlusive events. For subjects meeting criteria for treatment who have not yet developed any significant chronic complications, there would be no risk of subsequently developing chronic complications of SCD. A query of data in the East London Sickle Cohort study (patients with SCD diagnosed at birth from 1983 to the present and followed in NHS hospitals) 39 of 267 patients with HbSS met the inclusion criteria for Exa cel treatment, 33 of them between the age 12 and 18. Of these only one had a chronic complication (AVN hip). This younger population, if treated before age 18 would be cured by Exa-cel without any long-term complication developing

Comment on section 3.15 (Non-reference case discount rate), “The committee concluded that the first criterion for using a 1.5% discount rate was not met because there was insufficient evidence to show that people would otherwise die or have a severely impaired life.”:

I don't understand how the committee can come to this conclusion. Evidence from the literature has been presented that the mean life expectancy for the treated population with standard care is 53 years at the most optimistic estimate. This is more than 20 years less than a normal

population. Furthermore, there can be no question that repeated episodes of pain requiring hospital admission, chronic pain and fatigue, and the increasing risk of morbidities such as renal impairment, pulmonary hypertension, impaired mobility due to avascular necrosis of hips, spine, visual impairment, and other morbidities etc, must severely impair life. The committee has heard testimonies from patients and clinicians and there is a very substantial literature documenting these effects

Comment on section 3.8 (Standard care mortality modelling), “It considered that the company's SMRs were more representative of the severe SCD population, but concluded that further validation is needed about the most accurate life expectancy for people having standard care.”:

These estimates of survival with standard care are reasonable and it is difficult to see what additional evidence can feasibly be provided. The co-operative study of sickle cell disease (CSSD) estimate of survival from a large population in USA followed carefully over >10 years gave an estimated median survival of 42 years for men and 48 for women. VOC was a significant predictor of worse survival. (Platt et al, NEJM 1994). More recent estimates based on less robust data quality do reflect improved care and availability of hydroxycarbamide, both of which have probably improved survival. The committee is aware of the more recent papers, and have selected the paper of Jiao et al (2023) which is based on USA patients covered by state health care schemes. The estimated survival of 53 years would be a most optimistic estimate, and does not account for the negative effect of frequent VOC's which are a feature of the population to be treated with. Exa-cel. I am CI for the E London Newborn Cohort study which is following patients followed from birth in the NHS and treated in E London (Telfer et al, Haematologica 2007 and subsequent abstracts at ASH and EHA). There are currently about 420 patients in the cohort, the oldest 40 years of age. It is not yet possible to estimate median survival, but we have observed a significant increase in mortality rate in young adults between 15 and 25 years of age, and this has also been observed in the Dallas newborn cohort study (Quinn et al, Blood. 2010;115(17):3447-3452).

I think it is unreasonable to make a negative judgement based on the uncertainty of the survival estimate, when the model has a reasonable estimate based on the most optimistic assumptions. In my view, the mean standard-care survival estimate for the eligible population is certainly less than 53 years.

Comment on section 3.9 (Long term treatment effects), “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.”:

The evidence of outcomes after sibling allogeneic stem cell transplantation for SCD is very relevant here. Adults who go into transplantation with a past history of frequent VOC's may continue to have pain episodes for several years after the procedure, but are functionally cured. The reason for the

continued pain is that these patients have developed a complex pain syndrome (chronic pain) which is not directly related to Vaso-occlusion from sickled red cells. It is highly likely that this phenomenon will be observed in adults receiving Exa-cel, but less likely if the therapy is prioritised for teenagers and young adults who are less likely to have developed a chronic pain syndrome.

Comment on section 3.11 (Complication rates), “The committee concluded that directly estimating complications from the Brousse et al. (2023) severe population was most appropriate but that there was uncertainty associated with the estimated frequency of SCD complications.”:

Please see comment about the publication of Piel et al, which may provide more certainty of estimate

Comment on section 3.11 (Complication rates), “. The EAG assessed the effect on the incremental cost-effectiveness ratio (ICER) of using different complication rates, including directly modelling those from the literature (including Brousse et al. 2023, Shah et al. 2019 and the company's BOI study). It found that the ICER was sensitive to how complications were modelled. Clinical experts reviewed the complications from the literature and said that they were plausible. But they noted that there were some significant complications missing from the model, such as priapism and acute multi-organ failure”:

The study of Piel et al (Blood Cells, Molecules and Diseases 89 (2021)) assesses mortality and co-morbidities in a UK population using HES data over the period 2009-2018 and may be more representative than a French or US population

Comment on section 3.16 (Severity), “It noted that the condition disproportionately affects people from areas with higher levels of deprivation and considered how this could bias the estimates.”:

I believe that the absence of sufficiently convincing data, for instance on survival estimates, disease severity and quality of life, are examples of inequity. The All Party Parliamentary Group report 'No one's listening' and other reports highlight the inequality in health care provision for SCD compared to other long-term conditions in the NHS, and also highlight the paucity of research in SCD outcomes and treatments, which is another aspect of inequality. The difficulty for the committee in estimating important outcomes in SCD, including mortality rates and quality of life, reflect the reduced resources and funding available for these studies. As Chief investigator for the East London Sickle Cell Newborn Cohort Study, I can confirm that it is extremely difficult to obtain funding to sustain a long-term study into the natural history of this condition for NHS patients, which would help to answer some of these questions where uncertainty persists. There is a risk of the situation becoming self-fulfilling, where evidence cannot be

produced to satisfy regulatory committees and funders because of scarcity of funding opportunities and resources

Comment on section 3.16 (Severity), “The committee took into account the quantitative estimates and any possible changes to these estimates due to uncaptured benefits and uncertainties. It did not consider that the threshold for a severity modifier was met but noted the uncertainty in modelled mortality and complications.”:

I do not understand how SCD would not be treated as a high level severe condition. The following section is copied and pasted from the NICE reference document on severity modifiers:

Severity is to be calculated as “Absolute Shortfall” (AS) and “Proportional Shortfall” (PS). Both express the difference between Quality Adjusted Life Years (QALYs) over remaining life expectancy for the general population compared to those with the health condition, conditional on age and sex. AS expresses this difference in absolute QALYs. PS expresses this as the ratio of general population QALYs / QALYs for those with the condition. Weights should be applied to incremental QALYs.

The weight that is to apply is specified in Table 6.1 of the manual and reproduced below. The definition that provides the highest weight is the one that should be used.

Table 1: QALY weightings for severity
QALY weight

Absolute QALY shortfall

1 Less than 12

x1.2 12 to 18

x1.7 At least 18

If the committee use a mean survival of 53 years, would this not amount to at least a 20 year loss of life (ie 20 QALY'S) compared to the general population? Within the 53 years of life, would not the reduced quality of life also add to the absolute loss of QALY'S compared to the general population?

Comment on section 3.17 (Identified health inequalities), “The committee asked if the evidence gaps seen in this appraisal are because SCD mainly affects people from ethnic minorities, who are likely to be more socioeconomically disadvantaged and less likely to engage with clinical research.”:

I have extensive experience of conducting investigator-led and commercial trials in this population (Including the CLIMB 121 trial). I have not encountered problems in recruiting patients, indeed there is a lot of

enthusiasm to participate and help in developing more therapies. The committee perhaps should ask the question whether the evidence gaps are related to unequal funding opportunities for research and trials, and to insufficient resources of NHS health care staff and researchers to undertake the work

Name	
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

yes the nice evidence has been reviewed

Are the recommendations sound and a suitable basis for guidance to the NHS?

No as recommendations are based on cost not quality of life. insufficient data/numbers- 29 responses is not sufficient, however 86% of patients in study were voc and 97% were hospitalisation free does warrant further trials of exa-cel.

Long term hospitalisation costs could outweigh the cost of exa-cel

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No the clinical effects look promising and need further long term studies, the recommendations appear to be based purely on cost

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Lack of research/drug therapy and treatments for sickle cell does cause inequalities in health with cystic fibrosis having vast access to new treatments- only hydroxycarbamide and blood transfusion is available for this condition

Name	
Organisation	The UBELE INITIATIVE CIC
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

The decision-making panel need to understand much more deeply the views of people living with Sickle Cell

Are the recommendations sound and a suitable basis for guidance to the NHS?

The NHS needs to value the lives of people, Sickle Cell and their quality of life

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

There is no price that can be placed on human life. It is not being appreciated the life-saving nature of this treatment.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

This disease predominantly affects black and brown communities in the UK. There must be a robust equalities impact assessment to ensure that the right thing is done.

Comment on draft guidance consultation:

I have lived with Sickle Cell for the last 42 years. Since birth, I have suffered the range of complications. This includes priapism which meant that I could only sleep four hours at a time for the last 20 years. This has impacted my physical and mental health. I have had two hip replacements due to avascular necrosis. I have also recently had two serious eye surgeries due to a vitreous haemorrhage in my right eye. In my early 20s, I suffered a and fatal renal failure. All these complications along with many other episodes of extreme pain (Crisis) as well as ongoing chronic pain are as a result of Sickle Cell. I have seen very young people with Sickle Cell die as children, in their teens as well as in their 20s and 30s. In my 40s I feel lucky to have lived this far, but I do live with the constant fear that one day my number will come up. this constant fear of death is extremely challenging mentally and has serious impact on quality of life. I would urge nice to review the decision-making around Funding for gene therapy and, to view Sickle Cell as an extremely life, threatening as well as life altering disease. Gene editing, represents a cure for Sickle Cell and cure could solve cancer or other more mainstream diseases. My feeling is that it would be considered very differently. This is a matter of equity and equality where it is possible to change the life chances and directly save the lives of so many. I am happy to be contacted by NICE and I urge them to reconsider.

Name	

Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account? No. Are the recommendations sound and a suitable basis for guidance to the NHS? No. Patients who suffer from these conditions should also be taken into consideration when making a sound decision. The day to day living with illness has a negative impact on all aspects including family life, work and social balance. As years go by the current treatments available can build up and become difficult to maintain on individuals, and affecting ones life expectancy. Instead of being stuck in the past we should embrace innovative treatments and new technologies available, in the hope they lead to further effective treatments and possibilities for other illnesses and conditions. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? NA	
Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account? Yes Are the recommendations sound and a suitable basis for guidance to the NHS?	

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

Comment on draft guidance consultation:

There are limited effective treatment options for people living with SCD. The negative impact of SCD should not be underestimated, and as someone who lived with SCD I can confidently say the severity of this condition contributes to a very poor quality of life, making everyday tasks difficult, with a constant risk of triggering a crisis. The worsening impact that sickle cell has over time reduces life expectancy.

As allogeneic transplants carry a higher risk of causing harm, are not regularly provided due to cost, can be challenging to find a matching donor, and treatment is limited by age. I believe Exagamglogene autotemcel should be considered for patients suffering the worst kind of symptoms of SCD, and do not qualify for an allogeneic transplant, and are experiencing no adequate improvement in health while undergoing alternative treatments that include, disease modification with hydroxycarbamide and automated red cell exchange transfusion programme.

Name	
Organisation	University Hospital of Bristol Foundation Trust
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No, section 3.15 is interpreting the data incorrectly in my view.

*The benefits are likely to be sustained over a very long period.

Exa-cel is a genetically modified patient's stem cell which is being transplanted into a SCD patient. This is no difference to an autologous transplant. Patients who have undergone the same procedure ie autologous stem cell transplantation, have a long term benefits from this. Nothing in the report is mentioning these benefits.

*It is likely to restore them to full or near-full health.

Genetically patients who have been treated with exa-cel have a sustainable high HbF level, this level will enable them to have a normal life and no/very few symptoms. I agree with the committee that more long-term follow-up is needed, however the results from the CLIMB trial are sound and showing restoration of normal full health.

*The technology is for people who would otherwise die or have a very severely impaired life

SCD patients with severe phenotype die early and mostly unexpectedly. The life expectancy is limited, and I agree that 40yr represent a more accurate number. In addition there is a peak of mortality in the young patients - which is not taken into consideration by NICE. As Exa-cel targets this peak (ie between 12-35yo), this mortality data should be taken into account. All of the severe SCD patients would have a severely impaired life and some would die.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, my patients have been waiting for this treatment for a long time and are excited to undergo this.

For them sickle cell disease is a daily struggle, and the prospect of a cure provides them hope. By not taking Exa-cel into account and proceeding with a NICE appraisal, that hope is taken away. I don't know any the patient population that have had so few new treatments approved or even taken away (Crizanlizumab).

The Exa-cel treatment is for a selected group of patients (ie 12-35yr) and they have the opportunity to live longer and have a better QoL with the treatment. How the QoL measures were done and whether they did not meet the NICE standards is not of importance, however what matters is that there is an improvement, and that should be taken into account !

England is far behind in innovating medicine, and although I agree that costs should be taken into account and treatment should be cost effective, we should still aim to individualise per disease entity and this is not done in the current NICE report.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, as stated above they are not.

As lead of the Haemoglobinopathy coordinating centre, I urge NICE to reconsider their conclusions and recommendation and actually 'listen' to the HCPs and patients advising NICE.

SCD kills patients, this treatment cures SCD for a life-time, meaning more contribution to society and most importantly an improved survival and QoL for the patient and their family.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

There is unfortunately a tone of discrimination against this patient group. It is important to highlight that by not agreeing with the reasoning behind items discussed in section 3.15, we are putting patients on the second place and money on the first.

Kind regards, [REDACTED]
[REDACTED] Haemoglobinopathy Coordinating Centre South-West
Bristol

Name	[REDACTED]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Dear NICE,

As a member of the African and Caribbean community, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom.

This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease.

Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent.

In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage.

This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life

expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years.

The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people.

Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18.

These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community.

The health inequalities faced by the African and Caribbean community in the UK are well-documented.

Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare.

A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts.

Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease.

Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition.

By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease.

This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run.

It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition.

Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future.

Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system.

It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be.

This is unacceptable and goes against the principles of equality and fairness that should underpin our society.

I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible.

The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group.

By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long.

Thank you for your attention to this critical matter.

I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.

Yours sincerely,

[Redacted Signature]

Uk Taxpayer

Name	[Redacted Name]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I would like to highlight a paper by Gardner et al , Blood, Volume 128, Issue 10, 8 September 2016, Pages 1436-1438, which reported on clinical outcome in a London cohort of 712 adult sickle cell patients over 10 years (2004-2013). Here the authors show that hospitalisation frequency was a simple but strong predictor of survival in SCD; the risk of death was more than threefold if patients had high-frequency admissions compared with those with low admission rate. Thus, it could be assumed that VOCs leading to hospitalisation are strongly associated with mortality.

Another paper to highlight is by Aljiburi et al J Public Health (Oxf). 2013 Dec;35(4):510-7. Here the authors show that SCD patients from the most socio-economically deprived areas and with co-morbidities are at highest risk of both SCD readmissions and in-hospital mortality, suggesting that

there are inequalities in healthcare access and health outcomes amongst people with SCD.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I would like to point out that the innovative nature of the technology of exa-cel is why there is the obvious lack of long term outcome data. The technology is new, and hence long term data are lacking. While this may be cause for concern for any authorisation body, in view of the health inequality and historical injustice afforded to this group (as agreed by the committee), it is important that this treatment is approved, and simply lack of long term data is not cited as a reason to not do so. It may be preferable to give a managed access conditional approval, pending availability of 3-5 year follow up data, rather than not approving this at all

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I am not an expert in health economics. However, I disagree with the committee's assessment that the criteria for the 1.5% discount is not met. The burden of illness of sickle cell is considerable, and those who are currently going through curative treatments vouch for their transformative potential. Life of an adult patient over 35 y with 2 or more multi morbid conditions is significantly challenging, only a few people are able to participate in full time economic activity, and the lack fo a curative option results in median age of death of approximately 44 years. For a baby being born today with sickle cell, to imagine that they are likely to live only until 44, even in a high quality health system should be considered by the committee

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I would recommend that the committee pays heed to the significant lack of investment in research in this condition in the past. This has led to marked lack of innovative treatments. This patient population has had a long history of social injustices, and the committee should take that into account when considering any revision of its conclusions

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	

I have concerns that data is incomplete with regards to the impact of sickle cell disease on patients and their families. In particular, I am concerned that this impacts negatively on the plausible cost per QALY gained. I elaborate more in the other responses.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I have concerns in this area. The committee appears to be aware that sickle cell is a very severe and disabling disorder, which has impact on both patients and their families. However, it does not seem to take this sufficiently into consideration in its interpretation and conclusions. In particular, the committee should give more weight to the long history of discrimination and underresourcing of this disease, under representation in research funding, and the impact of the disorder on families as well as patients - which, if correctly considered, would affect the cost per QALY (see other comments)

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I would challenge whether the quoted cost per QALY has considered the cost of not treating patients with a treatment with as high an efficacy as Exa-cel. Patients are not only unable to work, but often use substantial hospital resources when unwell (repeated, prolonged admissions; transfusions; medications), and their family members (even if not themselves unwell) are often themselves unable to work to be care givers. The cost per QALY would be far more favourable if this was accurately considered.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I agree with the current draft that there is a high unmet need for effective treatments that improve outcomes and QOL in SCD.

Exa-cel is clearly effective, and its efficacy is higher than any other treatment option. I agree that the absence of long-term data raises both concerns and uncertainties, but this should not be a reason to withhold an effective medication. Explaining these limitations is the remit of doctors, nurses and patient support groups who should be given the opportunity to offer this treatment to patients and inform them so they can make the best choices for themselves.

I am particularly concerned a comment that the baseline EQ-5D value suggests that people with severe SCR experience a "reasonable QOL relative to the general population". I am unable to account for this interpretation, but certainly there are data to suggest that the EQ-5D has

limited ability to predict QoL accurately in sickle cell disease (e.g. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7839355/>)

In the report, concerns are raised about appropriate modelling. Considering the urgent need for effective treatment for sickle cell disease, I entreat the committee and the Decision support unit to act proactively in this area - if need be, by supporting the company with developing modelling that the committee would regard as more accurate, so this is not a barrier to correct interpretation of the data.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

In England, Black people are over 80 times more likely to have Sickle Cell Disease compared to white people. The African and Caribbean community in the UK deserve the same opportunities for improved health outcomes.

Comment on draft guidance consultation:

Dear NICE,

As a member of the African and Caribbean community, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom.

This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease.

Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent.

In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage.

This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life

expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years.

The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people.

Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18.

These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community.

The health inequalities faced by the African and Caribbean community in the UK are well-documented.

Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare.

A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts.

Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease.

Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition.

By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease.

This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run.

It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition.

Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future.

Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system.

It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be.

This is unacceptable and goes against the principles of equality and fairness that should underpin our society.

I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible.

The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group.

By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long.

Thank you for your attention to this critical matter.

I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No. There is much more about sickle cell disease that needs to be considered in relation to casgevy. Also I think that if the The fact that there was a conditional approval while waiting for NICE to approve, shows that a lot of evidence must have been studied first. The Crispr technology has shown a lot of promise and the one of the differences between crispr and bone marrow transplant is that it uses the patients own stem cells which erases the chance of rejection. If bone marrow transplant works as a permanent cure, there is no reason why casgevy will not be permanent.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, I don't believe so. The cost issue will definitely go down the more people are given the treatment. Also the present cost to the NHS is huge i terms of treatments for life, hospital appointments and admissions, and the strain on the human, medical and financial resources that are needed as of now.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. It is more costly in the long run to continue to treat sickle cell patients as is the case now, than a one off cure.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes. Sickle cell is a minority illness, so the vast majority of people will see it as discrimination against the minority groups who suffer the disease.

Comment on draft guidance consultation:

Sickle cell has limited options of treatment and it is only in the last few years that a change is occurring. As a carer to sickle cell adults, it is a consistent cycle of pain, hospital admissions and low quality of life. The options available do not give a cure and are laden with side effects that not every one with sickle cell can tolerate. A one time cure will save the constant uncertainty, multiple hospital visits and admissions, costly medicament regimes, and a lack of ability to work that plagues those living with sickle cell. This new treatment brings hope to many who are unable to get a donor for bone marrow transplant. There is no fear of rejection as it is the persons own stem cells unlike bone marrow transplant. Also, lifelong drug regimes are difficult to keep to, and over time becomes ineffective. When more people are given a drug regime that cures, it naturally brings the cost down as more people are subscribed to it. Gene therapy has been used in cancer treatments and some other diseases and it has been found to be effective. I have no doubt in my mind that sickle cell cannot be an exception to effectiveness as a cure. It is pertinent to note that this particular CRISPR technology is directed first for treatment of sickle cell because it is easier to implement as there is only one gene responsible for the disorder unlike other diseases.

Name	
Organisation	National Haemoglobinopathy Panel Stem Cell Transplant/Cellular Therapy Operational Group
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

We agree with that the relevant evidence in relation to the trial data for Exacel has been taken into account, however the evidence in relation to clinical consequences and mortality for sickle cell disease has been too broad. The committee discussion references the effects of sickle cell disease but does not focus adequately on the effects of severe sickle cell

disease which is the group of patients this therapy would be used for, and indeed was the population included in the trials to date. This is as opposed to living with pain that may occur in milder forms of the disease, which although significant may not result in hospitalisation for vaso-occlusive crisis (VOC). For example a recent large French study (Arlet et al, Landet Reg Health Eur Apr 2024) focussing on the population of sickle cell patients hospitalised for VOC showed an increased hazard ration for death of up to 3.7 in patients with VOC compared to non-VOC patients. The median age of death on patients who died was 49.8 which is significantly lower than the normal population. Of the 8018 patients in the study the overall VOC rate was 30%. We are concerned that the committee discussion did not adequately focus on the relative small proportion of patients with severe sickle cell disease and the relevant clinical and cost effectiveness modelling has therefore not been taken into account.

In considering the impact of gene therapy it is particularly important to consider gains in quality of life (QoL). A number of transplant studies (most recently Aljaafri et al Onc Stem Cell Ther 2023, Bawdawy et al Blood Advances 2021) demonstrate improved quality of life post-transplant in the context of cure. It is likely these QoL gains would be even greater in the context of gene therapy as unlike stem cell transplant there is no risk of GVHD which is a major factor adversely impacting QoL.

Are the recommendations sound and a suitable basis for guidance to the NHS?

We do not believe the recommendations are sound given the wrong assumptions have been used in relation to sickle cell severity as noted above.

Additionally concerns in relation to the ability to extrapolate a 12 month effect size were thought speculative by the EAG. We note that the committee considered results to be potentially life-changing and our clinical experience would be consistent with this as detailed below.

A key issue in the assessment of efficacy and cost effectiveness is whether a month 12 assessment is an appropriate and representative time-point to assess the long-term effects of a myeloablative therapy. To address this, Dania El Tabeach & Josu de la Fuente audited the relationship of allogeneic transplantation for sickle cell disease to long-term outcomes in 65 consecutive transplants at St Mary's Hospital, Imperial College Healthcare. This can be treated as a representative cohort, not only because over two thirds of all allogeneic transplant in the UK have been conducted in this centre, but also because approximately 50% of the allogeneic transplants with complete data in the European Society for Blood & Marrow Transplantation (EBMT) come from this centre. Six transplants were excluded due to not having reached a minimum 12 months follow-up and five due to transplant related mortality. The transplant procedures included a combination of related, unrelated and haploidentical stem cell sources, and both myeloablative and reduced intensity approaches, avoiding the outcomes to be eschewed by a particular approach.

With a median follow up of 3 years (range 1-8 years) 54 consecutive transplants with a minimum 12 months follow-up were audited with a median age of 15.24 years. No patient with successful engraftment had sickle related complications at 12 months. One patient had a subsequent secondary graft failure at 3 years. None of the 54 patients without sickle related events at 12 months went on to develop a sickle related event at subsequent follow up indicating that the 12 months assessment is an appropriate and sufficient time point to assess efficacy.

A potential way to address committee uncertainties would be via a managed access programme and we would be supportive of this approach to allow access to potentially curative therapy for sickle cell disease.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Again as the data taken by the committee were at the level of the whole sickle patient population rather than the group studied for this therapy- i.e those with a severe phenotype we do not believe this interpretation is adequately balanced. The threshold of returning patients to full health is incredibly high, and above that of a generally accepted gold standard of curative treatment in most disease therapies.

The discussion notes that a cure is usually assumed after five years in other disease areas. This is normally the case for malignant disease but this concept should not be applied to a non-malignant disorder such as sickle cell disease. In the absence of any known biological mechanism that would reverse gene editing it would not be expected that a non-malignant disease would not recur/relapse. This is in contrast to cancer where evolution of the malignant clone, tumour escape and other immunological mechanisms contribute to relapse.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We note that the committee has discussed the disproportionate health inequality experience in the ethnic population that suffer from sickle cell disease. We think it is critical to note that this population has suffered from a significant lack of investment in relation to research and approved effective therapy available on the NHS. As noted by Lee et al (Pub Health Rep, Dec 2019) this is in significant contrast to patients who are affected by cystic fibrosis, also a genetically inherited disorder but one that is present in white/Caucasian individuals. A decision to fund Exacel would be a major advance in addressing inequities in care that have occurred across decades as noted in the the Sickle Cell and Thalassaemia All-Party Parliamentary Group's 'No one's listening' report.

Adults with sickle cell disease also suffer from age inequity in that haploidentical transplant which may offer a potential cure is also not funded by the NHS where it is funded in children. There is limited scientific rationale for this decision. This population is also more likely to have related donors that disadvantaged making their ability to donate less certain, increasing further still the attractiveness of an autologous therapy.

Name

Organisation

Wessex and Thames Valley Hemoglobinopathy Coordinating Centre

Conflict

N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

1. There is a failure to appreciate the severity and quality of life of patients with SCD, which is akin to dialysis dependent renal failure.

2. Although no head to head studies, we can extrapolate the long term effects of gene therapy from allogeneic BMT.

Are the recommendations sound and a suitable basis for guidance to the NHS?

NO

SCD is a disease with significant unmet therapeutic needs. The cost effectiveness model that NICE uses is not fit for SCD, and needs to be reviewed.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

NO

Pain as an end-point of outcomes will always be a challenge, as it is so subjective. Consideration should be long term outcome on QOL, chronic multi-organ disease and reduced survival in SCD.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

1 This group of patients is almost exclusively of African and afro-Caribbean origin that have been subjected to racial prejudice in access to care and

health inequalities which are well documented. This interim recommendation would appear to perpetuate the historical discrimination.

Name

Organisation

N/A

Conflict

N/A

Comments on the DG:

Sickle cell disease is a chronic relapsing condition that often result in multi organ morbidity affecting the individual's physical health, mental health, capacity to work and contribute to society. Most treatments available are mainly reactive. Treatment under consultation if tolerated has shown very good results in reducing morbidity, improving general health of individual, reducing constant hospital admissions and allowing individuals to carry on with their daily lives and contribute to society.

Name

Organisation

N/A

Conflict

N/A

Comments on the DG:

It is wholly unfair that a decision such as this, that affects the black and Asian communities, specifically, is allowed to go ahead.

Name

Organisation

All-Party Parliamentary Group on Sickle Cell and Thalassaemia

Conflict

N/A

Comments on the DG:

Dear Celia,

I am writing in my capacity as an officer of the All Party Parliamentary Group on Sickle Cell and Thalassaemia, in response to the NICE consultation into exagamglogene autotemcel (exa-cel) for sickle cell treatment.

For people living with Sickle Cell disease, everyday life is a struggle. People with Sickle Cell disease suffer from a wide range of problems including gallstones, strokes, serious lung conditions, eyesight problems, high blood pressure and anaemia. The most common symptom of Sickle Cell disease is a sickle cell crises, which some people may have one of every week. These painful episodes are caused when blood vessels become blocked resulting in severe pain affecting any part of the body, but is most common in the limbs or back.

A person living with Sickle Cell disease in the UK lives, on average, to 67 years of age, over a decade less than the national average for those without the disease.

Exa-cel is a new treatment which is licensed by the MHRA to treat severe sickle cell in people aged 12 and over who do not have a matched sibling donor for stem cell transplant, but who would have been well enough to tolerate a transplant. If successful, treatment with exa-cel effectively provides a cure for sickle cell, meaning no more suffering for those who have the disease. It would be the first gene therapy available to treat sickle cell in the UK.

Whilst I understand NICE draft recommendation that exa-cel should not receive NHS funding as it is not considered cost-effective, I would urge the board to seriously consider the quality of life benefits, as well as extension to life, that this treatment will have for those who suffer from this disease.

Best wishes

██████

Name	████████████████████
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Hi please help me I need this treatment my life is very difficult.
Thanks, ██████

Name	████████████████████
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Dear NICE,

As a member of the African and Caribbean community, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of gene therapy for sickle cell patients in the United Kingdom.

This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell disease.

Sickle cell disease is a genetic blood disease that predominantly affects individuals of African and Caribbean descent.

In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage.

This chronic condition causes immense pain, organ damage, and a significantly reduced life expectancy. Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years.

The impact of sickle cell disease on the Black community is staggering. In England, Black people are over 80 times more likely to have sickle cell disease compared to White people.

Furthermore, the mortality rate for sickle cell patients in the UK is alarmingly high, with an estimated 1 in 16 individuals with sickle cell disease dying before the age of 18.

These statistics highlight the urgent need for effective treatments like the CRISPR gene editing therapy to be made available to the African and Caribbean community.

The health inequalities faced by the African and Caribbean community in the UK are well-documented.

Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare.

A report by the NHS Race and Health Observatory found that Black people in the UK have a life expectancy that is up to four years shorter than their White counterparts.

Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease.

Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition.

By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease.

This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run.

It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK, particularly those from the African and Caribbean community who are disproportionately affected by this condition.

Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future.

Moreover, the decision to stop the availability of gene editing therapy for sickle cell patients sends a troubling message about the priorities of our healthcare system.

It suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be.

This is unacceptable and goes against the principles of equality and fairness that should underpin our society.

I urge NICE to reverse its decision and work towards making gene therapy for sickle cell disease more widely accessible.

The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group.

By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long.

Thank you for your attention to this critical matter.

I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.

Yours sincerely,

[Redacted Signature]

Civil Servant

Name	[Redacted Name]
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Dear NICE, As a black British Woman, I am writing to express my deep concern and disappointment regarding the recent decision by the National Institute for Health and Care Excellence (NICE) to potentially stop the availability of this Cell and Gene Therapy for British Sickle Cell (SC) patients. This decision is a devastating blow to our community, which has long faced significant health inequalities, especially when it comes to sickle cell	

disease. Research shows misogynoir and racism results in black women being 4 times more likely to die in childbirth than our white counterparts.

In the UK, it is estimated that 1 in every 2,000 babies born are affected by sickle cell disease, with the majority being of Black African or Black Caribbean heritage. A shocking WHO fact; is 4 in 5 people born with SC in Sub-Saharan Africa die before the age of 5, these highlight the vulnerabilities that we face at every age of our existence.

This chronic condition causes me immense pain, I have children, but get regularly hospitalised. The pain come on fast for me and leaves me screaming in agony. Pain relief often fails, this is exacerbated by delays in complying with pain relief commissioning requirements, poor care, conflict and confrontation Sickle Cell Warriors experience at the hands of the NHS. We so wish we had access to a cure, removing us from the pain we suffer, the abuse of poor care, the stigma foisted upon us by medical professionals refusing us medication, accusing us of pretending to be ill, drug addiction, fecklessness, needing too much NHS resources. SC is a medical Emergency like a stroke and heart attack, yet people with these conditions are treated perfectly well and receive great healthcare at the point of need. Despite our widely reported burdens as a SC community as stated in your 250 page long Committee report, the associated aspects of anaemia, organ damage, bone and tissue damage, a significantly reduced life expectancy, medical practitioners and Society at large accuse us of faking illness. We so wish there was a cure available to us. The Lancet acclaimed book The Sickle Cell Guide, is meticulously referenced and has an encyclopaedic knowledge of SC. The understanding of the condition that the book delivers would greatly enable NICE decision makers to appreciate the scope, scale, issues and impacts of the condition across the whole SC medico-social ecosystem.

Shockingly, the average life expectancy for someone with sickle cell disease in the UK is just 40-60 years, compared to the national average of 81 years. For the time we live, many of us experience constant chronic pain, fatigue, anxiety, stress, and a difficult relationship with mental health. Relationships with benefit departments, and indeed social services can also be traumatic and triggering, plus our deprivation can results in difficulty paying for prescription drugs; and the rationing and going without that results becomes a huge detriment to patient safety. Peer conditions get their treatments and prescriptions free.

We have seen people cured of sickle cell relieved of the burdens and saving health services millions per person as US studies have found. In America Casgevy is approved as a treatment, but as usual NICE seek to reject any opportunity to relieve the Sickle cell community of its burdens to the point where Cystic Fibrosis has 511 treatments and SC just 3. This disparity is a disgrace anywhere on the planet and it happens despite NICE having clear policies on equality and tackling inequality. Being frank the way we are treated in all parts of the sickle cell ecosystem, the failure to enforce makes such policies a waste of time.

Black people are more likely to experience poverty, discrimination, and barriers to accessing quality healthcare. Furthermore, Black people are more likely to experience poor health outcomes across a range of conditions, including sickle cell disease.

Gene therapy offers a revolutionary approach to treating sickle cell disease by addressing the root cause of the condition.

By modifying the patient's own stem cells to produce healthy red blood cells, gene therapy has the potential to alleviate the painful symptoms and complications associated with sickle cell disease.

This innovative treatment can greatly improve the quality of life for those affected and reduce the burden on the healthcare system in the long run. The signal NICE send out in rejecting Crizanlizumab, Voxelotor, Casgevy, etc treatments and cures, is that Britain does not really care, so investing in the UK on sickle cell patients will never receive support. This results in a spiral of no funding, no research, no trials, and no treatments for generations to come, whilst other conditions continue to progress widening gaps in care and health. This is a very troubling message about the priorities of our healthcare system.

It is crucial that NICE reconsiders its decision and ensures that gene editing therapy remains available to sickle cell patients in the UK. Denying access to this potentially transformative treatment would be a significant setback in the fight against health inequalities and would leave our community without hope for a better future.

Moreover, the decision to stop the availability of gene editing therapy suggests that the lives and well-being of those affected by this condition, who are predominantly from the African and Caribbean community, are not valued as highly as they should be. This is unacceptable and goes against the principles of equality and fairness that should underpin our society.

The African and Caribbean community in the UK deserves the same opportunities for improved health outcomes as any other group.

By investing in and supporting this innovative treatment, we can take a significant step towards addressing the glaring health inequalities that have persisted for far too long.

Thank you for your attention to this critical matter.

I sincerely hope that NICE will reconsider its position and prioritise the health and well-being of the African and Caribbean community in the UK, especially those affected by sickle cell disease.

Yours sincerely,

[Redacted Signature]

Name	
Organisation	N/A
Conflict	N/A
Comments on the DG:	
For Whomever This May Concern, Allow me to introduce myself. My name is Joshua Kwamya, a 21 year old law studernt and although I'm not a sufferer of sickle cell myself, being a member of the BME community I've had a lot of exposure to the terrors of sickle cell and the impact it not only places unto individuals with the sickle trait but the extension of the terror unto their families. Sickle cell disease is a complex genetic disorder that affects millions of people worldwide, particularly those of African descent. The debilitating symptoms, frequent hospitalizations, and reduced life expectancy associated with sickle cell disease underscore the urgent need for effective treatments. Traditional treatments such as pain management and blood transfusions offer temporary relief but do not address the underlying genetic cause of the disease. The recent advancements in gene editing technologies, such as CRISPR-Cas9, have significantly improved the feasibility and efficacy of gene therapy for sickle cell disease. Clinical trials have demonstrated promising results, with patients experiencing a reduction in the frequency and severity of vaso-occlusive crises, improved quality of life, and, in some cases, complete remission of symptoms. However, despite these encouraging developments, access to gene therapy remains limited, and many patients are unable to benefit from this life-changing treatment option. The decision to discontinue or scale back gene therapy programs for sickle cell patients would be a devastating setback for those who are eagerly awaiting access to this innovative therapy. I urge the NHS to prioritize the continued funding and expansion of gene therapy programs for sickle cell patients. By investing in research, infrastructure, and patient access initiatives, the NHS can ensure that individuals living with sickle cell disease have equitable access to cutting-edge treatments that have the potential to transform their lives. In conclusion, gene therapy holds immense promise for the treatment of sickle cell disease and represents a critical step towards achieving better outcomes and improved quality of life for affected individuals. It is imperative that we prioritize the continued development and implementation of gene therapy programs within the NHS to ensure that all sickle cell patients have access to the care and treatments they desperately need. Thank you for considering my perspective on this important issue. I look forward to your response and to continued collaboration towards improving the lives of sickle cell patients.	

Sincerely,

[REDACTED]

Name	[REDACTED]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Hello,

It has come to my attention that the NHS was considering gene therapy treatment for Sickle Cell disease, but this was abandoned. I wanted to express urgent interest in this for my community. This is a disease that affects many black families, but it is something not adequately looked into. I have relatives with the disease, and it is disheartening to know that there is not much help for them should they need it.

Many lives could be saved and much pain avoided with this treatment, so I urge you to reconsider the case for dismissal. Look into these communities where this issue is rampant and work with them to find a way forward.

I, and many others, greatly appreciate the work that you do. Please do not allow a community to go unseen and uncatered for when there is an opportunity to make meaningful change.

Thank you for your time,

[REDACTED].

Name	[REDACTED]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Good Afternoon,

I hope I am not too late to submit my thoughts to the consultation, as this is a matter of the utmost importance to me. I have multiple members within my family who have sickle cell, having lost my Aunt to the condition in 2013 after a very serious crises which left her hospital bound.

Alongside the ongoing unawareness around the impacts of the disease within the medical community, effective treatment remains one of the greatest hinderances to Sicklers having a good quality of life and ensuring their continued wellbeing.

Given that there a so few black people in the UK who donate blood, there is already a higher likelihood that there will not be viable donors it is crucial

that there are other forms of treatment available such as the Exa-cel gene therapy.

Although I am not privy to know how much the treatment would cost exactly, if there was any sort of treatment which could have prevented the death of my Aunt I believe it would be worth it just to see her laugh again. Not a day goes by without my family grieving the loss of someone so dear to us. I wish that no other family in the UK would ever have to experience such pain.

I hope that in this consultation the intrinsic human value of life is considered, rather than simply treating human beings simply as statistics which need to be balanced against other monetary pressures.

I look forward to hearing the consultations final decision.

Kind Regards,

[REDACTED]

Name	[REDACTED]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Dear Team

I trust you are well. Thanks for all that you do to support people who live with sickle cell anaemia.

Just taking this opportunity to express my support for gene therapy in treating sickle cell disease and to express my concern that this vital treatment could be be stopped.

Please reconsider. My two children and I have the sickle cell trait as do a significant proportion of people who originally from the African continent. While I have advised my children to be carefully consider their partners, because of the trait, I would be reassured that this option is open to them and any other young people in the unlikely event that they have a child with the full-blown disease.

Thanks for your consideration of my opinion.

Yours sincerely

[REDACTED]

Name	[REDACTED]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

DoI – [REDACTED] was part of the MHRA marketing authorisation

Dear NICE,

I live with **Sickle Cell Disorder (SCD)**, [REDACTED] **the award-winning UK Sickle Cell Society for a decade**, and have been a member of multiple NICE steering Committees, as well as NHS Boards and Groups evaluating and approving medicines, pathways, specifications, assurance etc, across different medical conditions, but including SCD, and other rare diseases. I have written articles published from the **Guardian** to **Elsevier**. Please note rejecting treatments with great efficacy for any condition de-incentivises funders, pharmaceutical companies, researchers, and the whole medical ecosystem from investing.

I am the longest serving member of the SC and Thalassaemia All Party Parliamentary Group and Chaired the same when needed. Please accept my deep concern and disappointment regarding NICE's decision on the 14th March 2024, to reject Exagamglogene (Casgevy). This is a devastating blow to my community of fellow sickle cell Warriors and their families across the UK, **a community that remains long suffering, and continues to face extreme health inequality.**

[REDACTED] **'The Sickle Cell Guide'** which was reviewed and highly acclaimed by the **Lancet Medical Journal** who say it is **essential reading for medical professionals, I wonder how many on the NICE Committee have read this book?** ('The Sickle Cell Guide' is available at Amazon <https://www.amazon.co.uk/dp/B0BJ84YHGY> Lancet Review April edition of the Lancet Medical Journal Hematology <https://www.sciencedirect.com/science/article/abs/pii/S2352302623000704>). In December 2023 the FDA Approved the world's first CRISPR gene editing drug.

[REDACTED]

In the UK **structural and systemic inequality** has contributed to little, to no change in sickle cell care, because no one in the NHS with any power cares, resulting in the utter stagnation we see today. Of course, we would welcome the opportunity to debate this, but even that offer gets rejected and dismissed with impunity.

My reports highlighting the **testimonies of many patients and their complaints are ignored**. Government and other reports on sickle cell disorder (SC) are ignored, **Black, Achison, Marmot**, etc are ignored. Other peer conditions race miles ahead in the care and treatments they receive.

The disparity occurs in plain sight, complaints are ignored, and patients are abused with impunity. Nearly **50% of patients, fearing to go to hospital**, because of the abuse and harm they experience, ref **SWAY** and 'The Sickle Cell Guide'! In their Vaso-Occlusive Crisis; which is a **'Medical**

Emergency', the majority of patients say, they prefer to suffer at home, than suffer conflict with white authority!!!!

The above is important, there is so much I could do to save the NHS money, but it just does not care! People living with the condition know it, have voiced it for decades, and have little trust in the NHS and its clinical professionals at every level. This breaks my heart, and I think it would break anyone's heart if they really cared. They would understand that human beings in a civilised country should not be having totally avoidable, harmful, unsafe, distressing experiences, at a greater rate, and higher severity than their white counterparts.

As a public for good I have tirelessly encourage my SC community to engage in the consultation <https://www.youtube.com/watch?v=E20-z3qOeio> if only the NHS and its associates demonstrated such leadership, ethics, and sincerity. This at the time of the Hilary Cass Report, where puberty blockers untested, that reportedly do not work, have unethically been prescribed on the NHS to vulnerable children.

The link sets out the flaws on the decision including the abject lack of choice and failure to develop healthcare, decade upon decade for people living with SC. The pain of a VOC likened to being repeatedly hammered or axed, indeed mothers from around the world report child-birth hurts less than a sickle cell crisis.

I and the majority of people living with this life limiting, unpredictable, multi-system disorder; experience accumulative organ, tissue, bone, blood damage and complications including stroke, priapism, splenic sequestration, osteonecrosis, renal failure, pulmonary hypertension, liver disease, bone damage, limited growth, increased susceptibility to infections, fatigue, and progressive cognitive decline, meningitis, skin ulcers, complications in pregnancy functional asplenia, splenic infarction, splenic sequestration, septicaemia; sepsis, avascular necrosis, osteomyelitis, retinopathy, post-hyphema glaucoma, retinal infarction (tissue death), avascular necrosis, cardiomegaly, diastolic heart failure, ACS, Pulmonary hypertension, oedema, pulmonary embolisms, hyperbilirubinanaemia, gallstones, sickle hepatopathy, erectile dysfunction, albuminuria, isosthenuria, substantial kidney injury, acute renal failure, clinically extremely vulnerable susceptible to virus's and infections). We experience **stigma, misogynoir**, and behaviours that arise out of racism and prejudice in plain sight, its an oft written about phenomenon yet patients and their families are reporting **things are getting worse**. In addition, there is poor **mental health** generated by all these triggers. Poor pain management services causing Drug dependency risks. This is compounded by the **deprivation**, vulnerability, discrimination, and the economic and social disadvantage people with SCD experience in both the **health ecosystem**, and wider societal ecosystems. These issues result in greater illness and hospitalisation for those living with SCD. **NICE seem, as usual to ignore Principle 9 of NICE's Charter for health inequalities**. Having a cure reduces and removes the clinical, social, and economic **burdens** of living with an invisible fluctuating illness that no one; including patients and

medical practitioners, understand. Nobody should have to live with all these chronic and acute burdens, as well as constant and acute pain!

There appears no consideration that in many countries including Sub-Saharan Africa 4 in five children die before the age of five years old. According to the WHO between **50% and 80% of SC Warriors die by the age of 18**. This is germane to the NICE **QALY** calculations.

Page 24 of NICE company evidence Committee Papers, ID4016, says 14,200 patients, when the latest used by the NHS is **17,500 patients**. It suggests some significant flaws in the reported information!!!!!!

I honestly believe it is a scandal the way the SC community is treated! At every turn despite help being available, we are left to suffer, forced to endure abuses, and can die without any medical staff being held to account for complaints or serious harm and death. This treatment could be a gamechanger, but like my book; 'The Sickie Cell Guide', anything good in sickle cell appears to get blocked and denied, as such the plight of people living with the condition will continue to worsen.

I and probably 100% of patients as a goal, would ask for zero hospitalisation and better quality of life. Guess what that is what Casgevy is proposed to deliver!!! And would clearly save the health services huge sums of money as an **IRR (Internal Rate of Return)**, and a huge saving in the social costs of carers, as well as the multi-disciplinary medical teams, ambulance services, GP's, Doctors, Nurses, Consultants, and the 4 Psychologist we have; joke, yes it is a joke; and its one that results in suffering!

If I were given the treatment, Casgevy would also enable me to enjoy, no symptoms of SCD, halt bodily deterioration and enable repair where possible, no VOC's, no chronic or acute pain, longer life expectancy, reduced need for medications and analgesia (pain relief), improved mood, confidence, work productivity, increased family and social participation, time with the children, ability to swim, ski, travel, reduced expenditure on medicines, recover lost education, ability to do day to day tasks including look after the house, be less vulnerable, suffer less **stigma**, better sleep, better emotional regulation, support my partner and children, increase and improve employment options, reduce isolation, less anxiety, stress, and depression, etc etc.

Many of those at NICE and ordinary folk without SC take these things for granted and have no idea people without SC reading this have no idea of the burdens we face, or how other limit our humanity. Doctors and Nurses have no idea, they see us for a fraction of a fraction of their life, are not invested in the condition, and the vast majority have received no training in the condition; have not even read my Lancet reviewed book, where the most prestigious medical journal in the world advocate the book is an essential read for any medical professional or student.

Just a glance at the hundreds of pages that are part of this consultation indicate there is nothing in the pipeline of treatments, guidelines on care, pathways coming down the line, the landscape looks positively barren including the actual recent removal of treatments like Crizanlizumab, and Voxelotor under dubious rational. SC has 3 approved treatments, cystic fibrosis 511, this disparity is in plan sight, I gaslighting and denial that goes on and block progress often leaves me worrying that I appear to be the only person that can see the emperor has no cloths on! And those that do know the emperor is naked, are unwilling to listen to and support basic solutions to level-up.

As a patient I would prefer the option of a Cell and Gene Therapy because this is quicker safer, treatment only involves my own screened stem cell genetic material, less chemotherapy, can avoid GvHD, and higher rates of success. I would encourage patients to store sperms and eggs prior to the treatment.

I, and people living with SCD report and complain that NICE commissioning guideline CG143 is routinely not enforced to the harm and detriment of the SC community, not in A&E, or on the ward; even in HCC's (Specialist Sickle Cell Hospitals – Haemoglobinopathy Coordination Centres), and the NHP, CQC, hospital leaders themselves stand there letting it happen! If these behaviours regularly occurred with, stroke, heart attack patient's; both these, as SCD, are ranked as 'Medical Emergencies', the NHS would not tolerate it! If you consider this scenario bad allow me to expand, I have highlighted many times the existence of the **36 Quality Indicators in section 4.2 pages 10 to 12 Quality Indicators**; Standards NHS England Service Specification No 170126S Specialist Haemoglobinopathy Services (All Ages) Specialist Haemoglobinopathy Teams <https://www.england.nhs.uk/wp-content/uploads/2019/07/Specialist-Haemoglobinopathy-Teams-Service-Specification.pdf> The 250 page consultation report does not mention it in its table of national SC guidelines at page 50. This 2019 specification, developed carefully at great expense by the NHS, is all but ignored; and no one listens to those that raise it, epitomising the sentiments and concerns in the Parliamentary report "No One's Listening".

The concern of the SC community is that we keep asking, and keep getting ignored, promises made are reneged on. MHRA Authorised the treatment to great plaudits and adoration for the UK Life Sciences, across mainstream media, in November 2023, only to see it fall apart like a cheap suit within weeks with this NICE rejection. The studies and trials; **CLIMB SD-121** and 131 evidence 'high' clinical safety and efficacy, and 96.6% all participants VOC free, **100% hospitalisation free**. In America the FDA have approved the treatment, whilst in the UK we drag our heels.

I sincerely urge NICE to reverse its decision and start to prioritise the health and well-being of those affected by Sickle Cell. NICE should recognise the disparity surrounding SC, Cystic Fibrosis, HIV, Haemophilia, etc and

position a plan to level up. The inequality experienced by SC Warriors has persisted far too long.

[REDACTED]

Name	[REDACTED]
Organisation	South East London and South East Haemoglobinopathy Coordinating Centre.
Conflict	N/A

Comments on the DG:

Response to NICE Exagamglogene gene therapy for treatment of sickle cell disease from South East London and South East Haemoglobinopathy Coordinating Centre.

[REDACTED]

*[REDACTED] of South East London and South East Haemoglobinopathy
Coordinating Centre
On behalf of SELSE HCC clinicians*

South East London and South East Haemoglobinopathy Coordinating Centre manages almost 4,000 patients with sickle cell disease. We have experience of both reduced intensity fully matched sibling stem cell transplants and full intensity haploidentical transplants for the treatment of sickle cell disease.

We feel strongly that the NICE appraisees have misjudged the severity of sickle cell disease (SCD).

SCD is a severe condition and patients die prematurely, including many severely affected individuals dying in their 20s, 30s and 40s, even those who have received best currently available treatment such as long-term red cell exchange transfusion and hydroxycarbamide treatment.

The medical literature provides clear evidence for a reduced life expectancy, a severely impaired quality of life, and accumulation of complications and co-morbidities with age.

Exagamglogene gene therapy should be a final option for patients with progressive life-threatening or organ-threatening disease which has failed to respond to standard treatment such as an effective red cell exchange transfusion programme or hydroxycarbamide, in those with no available fully matched or haplo-identical donor.

Exa-cel has the potential to return patients to near normal health and the benefits are likely to be sustained over a very long period.

Fetal haemoglobin is maintained at around 40% in a pancellular distribution. This would be expected to prevent the process of vaso-occlusion and prevent progression of existing organ damage and development of new organ damage. This is evidenced by outcomes in compound hereditary persistence of fetal haemoglobin (HbS+HPFH) in which affected individuals do not suffer the pain and organ complications seen in sickle cell disease and have normal life expectancy.

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Title: Exagamglogene autotemcel for treating sickle cell disease- EAG response to company draft guidance form and additional work post ACM1

Produced by Warwick Evidence

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Rider on responsibility for report

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Contributions of authors

Jo Parsons (Assistant Professor), Martin Connock (Honorary Senior Research Fellow), Xavier Armoiry (Honorary Senior Research Fellow and Professor) and Amy Grove (Professor) reviewed and critiqued the clinical effectiveness evidence. Martin Connock reviewed and critiqued the statistics and undertook any additional statistical analyses. Xavier Armoiry reviewed and critiqued the mixed treatment comparisons. Naila Dracup (Information Specialist) critiqued the company's searches and undertook additional searches. Emanuela Castelnovo reviewed and critiqued the cost-effectiveness evidence and undertook additional economic analyses. Baba Inusa (Paediatric Haematologist) and Elizabeth Rhodes provided expert clinical advice. Peter Auguste (Assistant Professor) reviewed the cost-effectiveness evidence and co-ordinated the project and the report.

Please note that: Sections highlighted in [redacted].
Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

Remaining QALYS	
without the disease:	22.53
with the disease:	11.44
absolute shortfall:	11.09
proportional shortfall:	49.21%
QALY weight [ⓘ] :	x1

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Content of this report

In this document, we provide the EAG responses to Vertex draft guidance comment form, with further details included in the appendices. We then provide a validation or replication of the company's base-case results and scenario analyses. Finally, we present EAG analyses, which considers the company's preferred assumptions/preferences following the first appraisal committee meeting.

Table 1: EAG's responses to company comments

Comment number	Company's comments	EAG response
1	Executive summary Application of the non-reference discount rate - Vertex maintains that exa-cel qualifies for the non-reference discount rate and demonstrates that each of three criteria are firmly met. Severe SCD has a substantial impact on daily living, quality of life over time, and reduces life expectancy by several decades. Exa-cel provides an irreversible genetic edit that directly addresses the underlying cause of SCD, restoring patients to normal or near-normal health. Severity modifier - Following correction of the errors in the model provided to the committee by the EAG, SCD qualifies for the 1.2x severity modifier, by NICE's preferred methodology. Vertex re-affirms the belief that progressive diseases where mortality increases and HRQoL deteriorates substantially over time are unfairly penalised by the discounted QALY approach. A similar approach to HST, where undiscounted QALYs are used in the calculation is more appropriate here. When using this methodology exa-cel qualifies for the 1.7 modifier. Economic model - Vertex has amended its original model structure and is providing the committee with a new version of the model where the committee's concerns are addressed and therefore uncertainty reduced. Furthermore, several of the committee's preferred assumptions are now reflected in an updated base case. Vertex appreciates the attempt made by the EAG to address the committee's concerns in the previous version of the model; however several inaccuracies have been found e.g. the EAG has inappropriately added a calculation of the costs of treatment withdrawal prior to exa-cel infusion and the prevalence of chronic complications. We therefore provide an updated model for decision-making, including the committee preferences that Vertex has accepted. We request that the model submitted with this response be used to run all scenarios in future. Uncaptured benefits - SCD has a substantial detrimental impact on QoL, not just for patients but also for caregivers. SCD impacts caregivers' ability to maintain employment, and results in higher degrees of depression, anxiety and stress relative to those not caring for SCD patients. The committee	We thank the company for providing key discussion points along with their summaries and further details on these points in subsequent sections of this form. The EAGs responses to the company's points are discussed in the relevant sections of this form.

Comment number	Company's comments	EAG response
	should take this into account when considering the most appropriate ICER threshold, beyond the flexibility in the threshold given for health inequalities. Accounting for patients who do not have exa-cel infusion in the model - In the trial, and model, some patients undergo cell collection but do not go on to have exa-cel treatment. The reasons for this are related to the nature of SCD and systemic health inequalities experienced by patients. [REDACTED] Equally, treatment effects for those patients that do not have exa-cel infusion should be removed from the exa-cel arm of the model, to ensure model results accurately represent the effect of treatment with exa-cel. Definition of baseline VOCs - Vertex strongly believes that all VOCs that require healthcare attendance should be accounted for in the model. All VOCs are related to SCD complications, and result in a reduction in QoL. Further, issues with VOCs definitions in baseline vs follow up periods are alleviated by the new model structure. Modelling of chronic SCD complications: choice of source - While Vertex maintains the position that frequency of VOCs is a valid predictor of complications over time in severe SCD patients and therefore a hazard rate approach to model the risk of complications is appropriate, Vertex agrees to a new model structure whereby the risk of complications is derived from the literature e.g. from Brousse et al. Vertex presents two scenarios with data on complications derived from Brousse et al (as per committee's request) and data from Udeze et al. The latter provides a more complete source for the relevant population, based on UK data, and will therefore also be useful for the committee to consider. Utility of SoC patients and evolution over time - As requested by the committee, Vertex provides a longitudinal view of how the net utility of SoC patients in the model changes over time, to ensure it is clear that patients experience a severe impact on their quality of life as they grow older. Vertex has also implemented additional scenarios to evaluate the uncertainty related to baseline utility. Choice of utility value following exa-cel treatment	

Comment number	Company's comments	EAG response
	Vertex acknowledges the committee's uncertainty with utility value following exa-cel treatment. Vertex believes that this value reflects the QoL gain experienced with functionally cured SCD patients. However, based on a post-hoc subgroup analysis, which excludes patients with a baseline score equal to 1, Vertex provides an alternative scenario value of ■■■. We hope the below detail adequately addresses questions raised by committee and supports the case for the value of exa-cel, and the severity of SCD, for patients, who have few other options.	
2	Application of the non-reference discount rate Vertex maintains that exa-cel qualifies for the non-reference discount rate and demonstrates that each of three criteria are firmly met. Severe SCD has a substantial impact on daily living, quality of life over time, and reduces life expectancy by several decades. Exa-cel provides an irreversible genetic edit that directly addresses the underlying cause of SCD, restoring patients to normal or near-normal health. The overall objective of the 1.5% discount rate is to avoid penalising those treatments with high upfront (undiscounted) costs but where the QALY gain and cost savings accrue over a long time period and are subject to discounting. As described in the ACD, the committee queried whether exa-cel qualifies for the non-reference discount rate, with repeated mentions that uncertainty could be addressed by further data collection. Vertex reiterates that exa-cel qualifies for the non-reference discount rate, satisfying the three qualifying criteria as set out below (and further detailed in this section), and is committed to working in partnership with NICE, as we are currently doing in TDT, to agree a managed access agreement that meets the committee's requirements.	Section 4.5.3 of the NICE health technology evaluations: the manual (PMG36) sets out the criteria that should be met for the committee to consider a non-reference case discount of 1.5%: <i>'The technology is for people who would otherwise die or have a very severely impaired life.'</i> <i>'It is likely to restore them to full or near-full health.'</i> <i>'The benefits are likely to be sustained over a very long period.'</i> The EAG re-iterates that given the relatively short duration of follow-up, that there is no certainty that the benefits of treatment are likely to be sustained for a long period. The EAG also believes that whilst exa-cel may halt the progression of SCD, there is no evidence, direct or indirect or based on clinical opinion heard during ACM1, that exa-cel will revert the

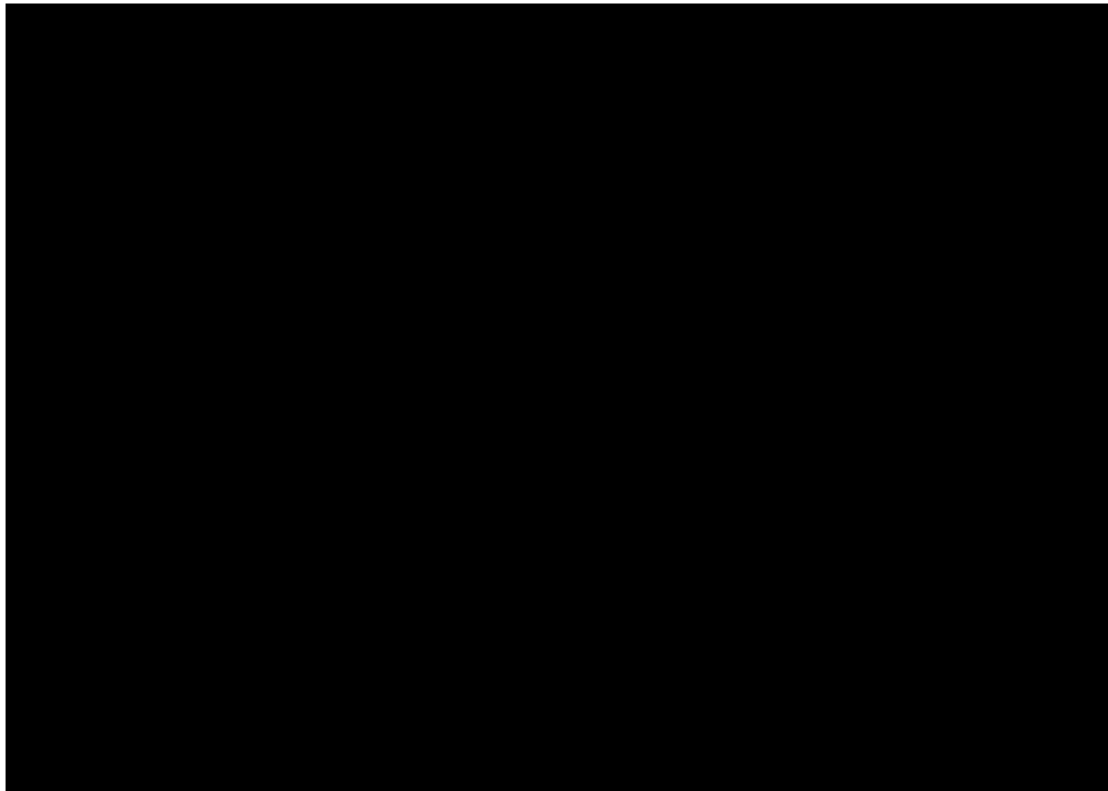
	• SCD has a substantial, daily impact on patients' & caregivers' QoL, and age at death for severe SCD patients is in the 40s, constituting a reduction of several decades relative to the general population. • Treatment with exa-cel has a transformational impact on outcomes, with no new complications related to SCD expected, and current complications likely to be halted or even reversed, as supported by evidence from HSCT in SCD. • Genetic editing with exa-cel results in a permanent and durable effect, supported by stable HbF %, and allelic editing in patients. • Finally, whilst strongly defending that the totality of evidence supports exa-cel's qualification for the non-reference discount rate, Vertex is committed to a managed access agreement to further demonstrate this. 1. <i>Technology is for people who would otherwise die or have very severely impacted life</i> The National Institute of Health defines a severe illness as '<i>a health condition that carries a high risk of mortality AND either negatively impacts a person's daily function or quality of life, OR excessively strains their caregivers.</i>' (1). We provide evidence below that SCD is a severe illness and fulfils all three of these criteria, with further detail on the caregiver burden elaborated in Section 5 'Uncaptured benefits'. SCD is a chronic, life-limiting, and debilitating condition that causes significant morbidity and mortality. In patients with severe SCD (with frequent vaso-occlusive episodes) mortality and morbidity are increased even further. SCD is characterised by haemolytic anaemia, widespread organ damage, unpredictable episodes of severe pain called VOC ('vaso occlusive crisis') and shortened life expectancy (2, 3). SCD has significant negative emotional, social and quality-of-life (QoL) effects on patients, but also their families on a daily basis. As described in the ACD (S3.1), '<i>They [patient experts] noted that they could not remember a day without pain, whether that be mild, moderate, or severe</i>'. The ACD also reports the findings of the 2019 Sickle Cell World Assessment Survey, in which 76% of respondents reported having to reduce their working hours, and 58% having to stop work entirely (4). This daily impact of SCD was characterised by clinical experts in the ACD, who explained that vaso-occlusion happens constantly, even if a patient is not experiencing a crisis. In view of this, the committee concluded that SCD is a debilitating and life-limiting condition. This conclusion is supportive of qualification for non-reference criterion #1. Furthermore, it is stated in Section 3.8 of the ACD that '<i>Clinical experts commented that the life expectancy for people with SCD with recurrent VOCs is in the fifth decade of life</i>'. When exploring how best to define 'severe' SCD during an advisory board conducted in the UK, advisers were in	health of all patients to full health. Specifically, it is highly uncertain whether exa-cel will restore full health in people who have a history of SCD complications. Mortality The EAG believes that these rates are obtained from studies with a more severe population than the one in the model decision problem. Specifically with reference to the absence of data for older people, the company's argument that there are no data because there are no deaths is disproven by Jiao, who include Medicare datasets, covering people with SCD in the age groups with mean age equal to 70 and 50. The absence of records for older people with SCD is not because there are none, but because the databases where these cases are recorded have not been included. However, given that the company has accepted the committee's preferred model structure, using mortality rates selected by the company, there are no material implications regarding mortality rates. The EAG has added specific study details (in appendix) to provide the evidence regarding 50 years being

Comment number	Company's comments	EAG response																																						
	agreement that any other disease with a median life expectancy in the 40s would be classed as severe as a whole (5). The severity of SCD, seen in both the substantial reduction in life expectancy, and impact on quality of life, is supported by clinical experts, the body of evidence detailed below, and the committee deliberations, as detailed in the ACD. The committee asked for additional data on mortality and QoL, which we provide below to further demonstrate the severity of SCD, and substantial impact on daily living. Early mortality Patients with SCD are affected by a myriad of complications and associated chronic multi-organ comorbidities, which results in a reduction in life expectancy by several decades relative to the general population. There is extensive recent literature (including studies from the UK) that consistently demonstrates that SCD patients have a significantly reduced life expectancy which is further reduced for patients with severe SCD/recurrent VOCs. These figures are consistent across cultures and over time with a lack of significant improvement over the last few decades even if optimal treatment is available (6). We summarise this data in Table 1, before providing additional detail. Table 1: Summary of the literature on mortality estimates in SCD <table><tr><th rowspan="2">Lead author (year)</th><th rowspan="2">Sample size</th><th rowspan="2">Mean age, years</th><th rowspan="2">Geography</th><th colspan="2">Mean age at death, years (mean)</th></tr><tr><th>All SCD</th><th>Severe SCD*</th></tr><tr><td>Udeze <i>et al</i> (2023)</td><td>1,117</td><td>24.96</td><td>UK</td><td>NA</td><td>40</td></tr><tr><td>Piel <i>et al</i> (2021)</td><td>9,503 (all) 1,171 (severe)</td><td>22.9 (all) 23.4 (severe)</td><td>UK</td><td>46.7</td><td>39.7</td></tr><tr><td>Di Mauro <i>et al</i> (2023)</td><td>1,069</td><td>35 (HbSS) 45 (HbSC)</td><td>UK</td><td>41.5 yrs (HbSS) 52.5 (HbSC)</td><td>NR</td></tr><tr><td>Brousse <i>et al</i> (2023)</td><td>20,412 (all) 4,270 (severe)</td><td>24.0 (all) 21.8 (severe)</td><td>France</td><td>58 yrs**</td><td>44**</td></tr><tr><td>Jiao <i>et al</i> (2023)</td><td>94,616</td><td>26.6</td><td>US</td><td>52.6 yrs</td><td>NR</td></tr></table> NR, not reported. *severe SCD definitions differ by paper, and are summarised in the below text. **median values.	Lead author (year)	Sample size	Mean age, years	Geography	Mean age at death, years (mean)		All SCD	Severe SCD*	Udeze <i>et al</i> (2023)	1,117	24.96	UK	NA	40	Piel <i>et al</i> (2021)	9,503 (all) 1,171 (severe)	22.9 (all) 23.4 (severe)	UK	46.7	39.7	Di Mauro <i>et al</i> (2023)	1,069	35 (HbSS) 45 (HbSC)	UK	41.5 yrs (HbSS) 52.5 (HbSC)	NR	Brousse <i>et al</i> (2023)	20,412 (all) 4,270 (severe)	24.0 (all) 21.8 (severe)	France	58 yrs**	44**	Jiao <i>et al</i> (2023)	94,616	26.6	US	52.6 yrs	NR	the lower bound for a reasonably justified life expectancy for this decision problem.
Lead author (year)	Sample size					Mean age, years	Geography	Mean age at death, years (mean)																																
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Comment number	Company's comments	EAG response
	<i>Increased mortality in patients with severe SCD/recurrent VOCs</i> Udeze et al (2023) observed a mean age at death of 40 years in a UK severe SCD population (n=1,117), defined as at least 2 VOCs per year for 2 consecutive years, followed retrospectively between 2008 – 2018 (7). In another UK SCD cohort followed from 2009-2018, Piel et al (2021) observed a mean age at death of 39.7 years for those with four or more hospital admissions due to sickle cell crises over the two base years (n=1,171) (8). Notably, in this study the mortality rate for the five-year period of 2014 – 2018 (3.2%) was actually higher than that observed between 2009 – 2013 (2.2%), with the number of deaths increasing over time, from 36 in 2009 to 69 in 2018. Brousse <i>et al.</i> (2023) had similar findings with an observed mean age of death of 44 for severe SCD patients between 2012-2018 in France (n=4,270) (9). In this study, severity was defined by 2 vaso-occlusive events in the year preceding index or 4 VOs in the 2 years preceding index for 3,855 of the 4,270 patients, with the definition for the remainder relating to hydroxyurea and transfusion use. <u><i>Increased mortality in all patients with SCD regardless of severity</i></u> In a recent analysis of data from the southeast London sickle cell gene bank cohort, Di Mauro <i>et al.</i> (2023) observed an average age at death of <u>41.5 years</u> for HbSS (all severities) male SCD patients (n=692) (10). Brousse et al (2023) had an observed median age at death of <u>58 years</u> in the total (unselected for severity) SCD patient cohort (n = 2,619) and Piel et al showed a mean age of death of 46.7 in the total patient cohort (9). Similarly, Jiao et al showed a mean age of death of <u>52.6 years</u> in the total SCD population (11). The SMRs applied in the economic model and accepted by committee were sourced from Desai et al (2020) (12). Between the period of 2000 – 2013, Desai et al observed a cumulative incidence of mortality of 27.3% in 19–35-year-old patients with SCD in a US Medicaid population (n=44,033), (of which 11,064 were 19-35 years), demonstrating the impact of SCD on survival in even young patients. In those >35 years of age, the cumulative incidence of mortality was substantial, at 45.4%. In this study, higher VOC burden in the preceding year was associated with a considerably increased risk of mortality: 2-4 VOC vs <2 VOC HR 1.62.	

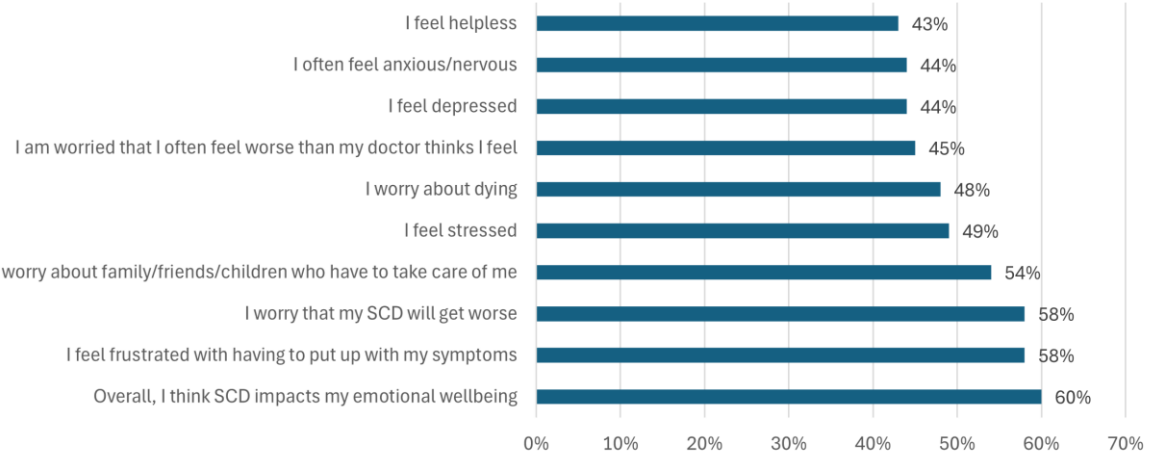
Comment number	Company's comments	EAG response
	In response to the EAG's critique that the Desai mortality rates were obtained from a younger cohort, the SMRs from Desai were stratified by age band. Furthermore, there was no age limit restriction in the eligibility criteria of the Desai study. The reason that there was a lack of older patients in Desai was simply because there were none: the majority had died. The fact that both the US Institute for Clinical and Economic Review (ICER) and the present NICE committee favoured use of the Desai et al. paper to inform mortality estimates for exa-cel provides further support for the Desai mortality estimates and the substantial reduction in life expectancy seen in all patients with SCD (13). In summary, it is clear from the weight of the literature that life expectancy for SCD patients is reduced by many decades compared to the UK general population (median age at death of 81.8 years for males and 85.5 years for females in 2020 (14)), with this reduction even more pronounced in severe SCD patients, as demonstrated by a mean age at death of 40.2 years in a UK population. Severely impacted quality of life <i>'describing the actual pain I feel is a real challenge – I can say that it feels like being stabbed everywhere repeatedly or having all your bones broken, but the words just don't do the pain justice' – Patient expert, ACM1 slides</i> <u>Multi-organ damage, co-morbidities and complications</u> As described consistently in the clinical literature and summarised in the NHS Commissioning Policy, severe SCD is associated with a very significant rate of morbidity and mortality (2, 15-17). The toll of SCD on the patient is considerable. Frequent severe and unpredictable acute pain episodes which often need hospital admission but may be managed at home prevent school and work attendance and cause disruption of normal life for the patient and their family. Patients experience high rates of acute complications including stroke, infection, acute chest syndrome, acute renal failure, respiratory failure. As their disease progresses patients will also experience high rates of chronic organ impairment and reduction in organ function (eg brain, lungs, kidney, heart, spleen, eyes) and high levels of chronic pain. These complications, both acute and chronic, inevitably worsen with age and are not stopped by current therapies (6). For example, in a 10-year cohort analysis of 9,503 patients with SCD in the UK, using Health Episode Statistics (HES) data, Piel <i>et al</i> (2021) examined co-morbidities commonly associated with SCD and 10- year mortality rates compared with the general population (8). The most common acute co-morbidity recorded was acute chest syndrome, which occurred at least once in 53.9% of the most severe SCD patient group. High prevalence of eleven other co-morbidities (including osteonecrosis, sepsis, renal disease, cardiovascular disease and priapism) were also reported in this study. The	

Comment number	Company's comments	EAG response
	mean number of co-morbidities per patient over the 10-year study period was 2.5, for severe patients, with 63.2% of patients having two or more co-morbidities. <u>Substantial impact of SCD on QoL further adds to the severity of the disease</u> There is robust and extensive evidence showing the impact of SCD on QoL confirming the severity of this condition. SCD patients have an inherited condition and have experienced symptoms since early childhood. Whilst it is clear that baseline EQ-5D in CLIMB SCD-121 is well below age-adjusted population norms, the likely adaptation to their condition and associated underestimation of the burden on QoL means that their experience may not be fully captured by EQ-5D. This is further discussed in the section on utility values in the model (Section 9). The ACD states that the committee expected the QoL difference between the SCD population and the general population to be greater than stated by the company 'if a condition caused people to have a severely impaired life'. We refute the committee's perspective that the data from the trial indicates the population is not severe. <u>CLIMB SCD-121 EQ-5D data</u> We believe that first, the difference in QoL between patients at baseline in the trial and the age adjusted general population norm is significant and <u>does</u> show a severely impaired quality of life. The baseline EQ-5D value in the trial is 0.81, which compares with the UK population norm for an adult aged 18-24 of 0.93, providing us with a difference of 0.12 (18). The minimal clinically important difference (MCID) for EQ-5D is 0.08, so a reduction of 0.12 relative to general population is significant and clinically meaningful. However, the reduction of 0.12 is not representative of the majority of SCD patients and we agree with the committee that this may be because the EQ-5D only partially captures the impairment of QoL in SCD, as evidenced through a more granular view of the CLIMB SCD-121 EQ-5D data: Figure depicts the distribution of EQ-5D scores in the d120 FAS. Two contrasting observations can be made from the histogram: Firstly, while 0.81 represents the mean of the CLIMB SCD-121 cohort, a proportion of patients had extremely low EQ-5D index scores; the minimum EQ-5D value at baseline at d120 in the FAS (n=31) was ■ and approximately ■ of patients had scores less than ■. Secondly, the mean of 0.81 represents a value highly skewed by a significant proportion of patients with an EQ-5D utility at full health (over ■ of patients in the PES and over ■ of patients in the FAS). When estimating the baseline value for those patients in the FAS and PES not reporting perfect health the mean EQ-5D was ■ and ■, respectively. These two contrasting observations support the evidence that patients with SCD have a severely reduced QoL compared with the UK general population, but also that the EQ-5D may not adequately capture the impact of SCD in a significant	

Comment number	Company's comments	EAG response
	proportion of patients: the idea that people with perfect health would be willing to trade that for a burdensome transplantation with an experimental therapy clearly lacks face validity.  Figure 1: Histogram of EQ-5D-5L UK Index Scores for all patients at baseline in CLIMB SCD-121 FAS (N=30) The severity of SCD is further evident when one considers that this lower utility value of 0.81, relative to the age-adjusted general population at baseline, is captured at the point at which exa-cel would be administered before patients go on to develop additional significant complications that characterise their	

Comment number	Company's comments	EAG response																
	condition. The applicability of this value is evident based on the results presented in Table 8. When using a baseline value of 0.81, the predicted baseline net health state utility (■) in the model aligns with the observed baseline utility value (■) reported by patients ≥18 and ≤35 with baseline utility < 1. It is also clear that their QoL would continue to deteriorate as they grow older and live with multiple co-morbidities. This effect on QoL has been accurately captured in the updated Vertex economic model (see Table 8, discussion in Point 9). This is supported by the significant body of evidence on this, which looks at QoL of patients of all ages with SCD disease, detailed in 'summary of QoL data in SCD'. Further support for this comes from the literature, where lower EQ-5D values have been reported in comparable patient populations (Table 2) Table 2: Alternative SCD utility values reported in the literature <table><tr><th>Source</th><th>Sample size</th><th>Population</th><th>EQ-5D value</th></tr><tr><td>Anie <i>et al</i> (2012) (19)</td><td>510</td><td>SCD patients admitted to hospital, followed to 7 days post-discharge</td><td>0.39 - 0.75</td></tr><tr><td>O'Brien <i>et al</i> (2009) (20)</td><td>N/A</td><td>Severe paediatric SCD patients</td><td>0.7</td></tr><tr><td>Drahos <i>et al</i> (2023) (21)</td><td>139</td><td>Adults with SCD, including subgroup with a recent VOC</td><td>0.48 – 0.59</td></tr></table> <u>Summary of QoL data in SCD</u> It is evidently clear from published literature and from patients' experiences (as illustrated in the APPG No One's Listening report) that SCD severely affects patients' life (22). Multiple studies in various populations all consistently show a reduction of QoL in SCD, and patients with severe SCD (characterised by frequent VOCs) have a more marked reduction in QoL, which, as already demonstrated, is also associated with a further reduction in life expectancy. A systematic review in 2012 by Panepinto and Bonner found 39 studies of HRQoL in SCD and concluded that adults and children have significantly impaired HRQoL that is comparable to or worse than other chronic diseases (23). The included studies looked at a variety of QoL measures, most commonly SF-36 or PedsQL. Most studies showed that pain has a negative impact on QoL. For example, a large study based on the US Co-operative Study of SCD (Dampier <i>et al</i> 2011) looked at	Source	Sample size	Population	EQ-5D value	Anie <i>et al</i> (2012) (19)	510	SCD patients admitted to hospital, followed to 7 days post-discharge	0.39 - 0.75	O'Brien <i>et al</i> (2009) (20)	N/A	Severe paediatric SCD patients	0.7	Drahos <i>et al</i> (2023) (21)	139	Adults with SCD, including subgroup with a recent VOC	0.48 – 0.59	
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	1180 patients (median age 28 years) (24). All individual SF-36 scores were significantly decreased compared to the general US population and the occurrence of VOCs progressively decreased SF-36 scores. A 2012 UK study measured HRQoL in 510 patients (mean age 28.9 years) using EQ-5D on admission with VOC to the day unit or hospital and repeating this measurement on discharge and at one week post discharge (19). It showed utility values of 0.39 on admission, increasing to 0.65 at discharge and 0.75 one week later. Health scores derived from EQ-5D showed a negative association with pain, with patients reporting EQ-5D well below general population level even after recovery from VOC. A further study from the same lead author (Anie et al 2002) included 96 patients (mean age 30.1 years) and showed a significant reduction in all domains of SF-36 compared with the general population (25). Similar findings were shown by Shafrin et al (2021), who enrolled a population of 301 patients (average age 30.1 years) performing EQ-5D twice, once when experiencing a VOC and once when not experiencing a VOC. Results showed a reduced HRQoL at baseline (0.738) reducing further to 0.311 during a VOC, with disease severity strongly predicting worse self-reported HRQoL (26). A further study by Drahos <i>et al</i> (2023) looked at 142 adults from US and Europe and compared various PRO measures in patients who had or had not experienced a recent VOC (within one week). The overall mean EQ-5D-5L health utility US index score among participants with SCD (0.59 [SD: 0.27]) was much lower than the US general population mean score (0.85 [SD: 0.21]) and even lower (by -0.11) among participants with SCD who experienced a recent VOC (0.48 [SD: 0.25]). Similar reductions were seen in overall mean FACT-G score and EQ-5D-5L VAS (21). Further evidence of the impact of SCD on patient reported outcomes has been shown by the SWAY survey (2,145 patients), where a substantial proportion of patients reported that SCD caused a high negative impact on emotions (60%) and school achievement (51%) and a reduction in work hours (53%) (4). Fatigue was the most commonly reported symptom (65%), graded "high severity" by 67% of patients, and this is poorly captured by EQ-5D. Even among the minority of patients able to work, a separate study found that participants reported missing approximately 9.8 hours in the past week due to SCD (27).	

Comment number	Company's comments	EAG response
	 Figure 2: Proportion of patients reporting a high impact of SCD per statement Source: Figure 1b, Osunkwo <i>et al</i> (2021) (4). The significant burden of complications patients experience has a huge impact on overall health, which translates into a reduction of many decades in life expectancy, as already detailed. Severity of SCD is also demonstrated by considering the resource use associated with severe SCD and the complications patients experience (7, 9). For example, patients with severe SCD in the UK require 22.17 hospital visits per year compared with 2.63 visits per year in matched controls, and receive 31.06 outpatient prescriptions compared with 7.58 in the matched population (28). In summary, SCD has a substantial, daily impact on QoL, with worries about their condition worsening, lack of understanding from doctors, and fear of dying all posing a substantial burden on patients (Figure 2). This burden is particularly pronounced for patients experiencing recurrent VOCs, the patient population that would be eligible for treatment with exa-cel. <i>2. Technology is likely to restore them to full or near-full health</i> Before going into detail on the transformational benefit achieved with exa-cel, and supporting literature, we include testimony from the first ever patient to receive exa-cel as part of CLIMB SCD-121, provided as part of the FDA advisory committee meeting held in October 2023:	

Comment number	Company's comments	EAG response
	<i>“After receiving this treatment, I no longer have pains, I no longer have to take opioids, I no longer have hospital stays or receive blood transfusions. I get to participate with my kids and join them in their activities when they play sports, cheer them on at their dances and just be here just to play with them, knowing I no longer have to leave them to go to the hospital. I now work full time and I contribute to my household and my community. “</i> <u>Clear long-term benefits of exa-cel demonstrated in CLIMB SCD-121</u> The data from CLIMB SCD-121 demonstrates the substantial, transformational and consistent benefit of exa-cel for SCD patients. At baseline, these patients (PES, d120, n=29) were experiencing a mean 3.9 VOCs per year, 2.7 hospitalisations per year, and a mean of 17.4 inpatient hospitalisation days for severe VOCs per year. Following treatment with exa-cel, 96.6% of patients achieved 12 months free of VOCs, with 100% achieving 12 months free of hospitalisation, with patients VOC-free for up to 43.6 months at the time of the d120 data cut (29). Furthermore, we note that 27/29 patients in the PES, (follow-up of 17.8 - 48.1 months after exa-cel infusion) remain VOC free, a substantially clinically meaningful improvement from the rates reported at baseline. <u>Pain</u> As discussed at the previous committee meeting, a small number of patients do experience acute pain after exa-cel infusion. As discussed, these events are not VOCs, and do not represent treatment failure or lack of response to exa-cel. It is important to remember that the VOC definition as per CLIMB SCD-121 protocol was ‘acute pain needing attendance at hospital for opiates/iv NSAIDs, ACS, splenic sequestration or priapism’ (29). This broad definition of acute pain will inevitably include patients who are experiencing acute pain not related to vaso-occlusion. Post-transplant acute pain events (which would be classified as VOCs if trial criteria were used) are observed in the post allo-transplant context, even in patients with 100% chimerism (i.e. only non-sickle red cells). This is more marked in patients with a history of chronic pain and hyperalgesia. Among patients with SCD who undergo HSCT, 1 in 5 patients continue to experience acute pain events during the 12 months post-HSCT period (30). We go into further detail on post-HSCT findings in the relevant sub-section. Of the small number of patients who experienced these acute pain events after exa-cel, none needed hospitalisation (29). There were no episodes of ACS (which is the leading cause of death, responsible for up to 25% of SCD-related deaths) and no priapism or splenic sequestration. When the clinical details of the patients who experienced acute pain post exa-cel are reviewed in detail, it becomes apparent	

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	that they all had chronic pain and had reasons other than vaso-occlusion for their pain. This point is substantiated in the section relating to benefits being sustained over a very long period. <u>Other benefits of exa-cel</u> While VOCs have been used as a primary endpoint in the study, they do not capture the systemic impact that exa-cel mechanism of action has on the pathophysiology of SCD. The rapid and consistent increase in fetal haemoglobin (HbF) not only prevents vaso-occlusion but also reduces haemolysis and resolves anaemia and consequently will remove the risk of acute and long-term complications of haemolysis. This is substantiated by the CLIMB SCD-121 clinical results showing a rapid and persistent resolution of anaemia (mean Hb >13.0g/dl from month 12) and reduction in haemolysis: Results presented at ASH 2023 showed that: 1. Lactate dehydrogenase: mean levels normalised by Month 9 and were sustained at normal levels thereafter. Elevated LDH as a haemolytic marker has been independently associated with increased morbidity and mortality in SCD (31, 32) 2. Haptoglobin: all patients had increases in haptoglobin to detectable levels after Month 6, which sustained over time, consistent with resolution of intravascular haemolysis. 3. Absolute reticulocyte count: mean improvement from elevated levels at baseline, with reduction maintained over time, consistent with improvement in haemolysis post exa-cel All of these improvements were durable, with data for 30 patients at month 24, and range of follow-up in the PES from 17.8 months to 48.1 months (29). This normalisation of haemolysis, while shown via surrogate markers, demonstrate the profound effect of exa-cel on addressing the underlying pathophysiology of SCD. <u>Development of new complications is prevented. Existing complications will be halted or reversed by prevention of vaso-occlusion and maintenance of high HbF.</u> As described in the CS, exa-cel's mechanism of action results in an increase in HbF levels. Increases in HbF level ameliorate the clinical manifestation of SCD. Support for this comes from the experience of patients with hereditary persistence of fetal haemoglobin (HPFH), a naturally occurring variation that causes continued persistence of HbF into adulthood (33, 34). Patients with compound heterozygosity for SCD and HPFH experience little or no SCD symptoms, leading to a normal life expectancy, and this is particularly true for those who maintain HbF levels above 20% (34-36). In CLIMB SCD-121, a mean HbF % of 40% was achieved by Month 6, and maintained at this level thereafter, well above the level shown to result in little or no SCD symptoms. Exa-cel therefore has a positive impact on all aspects of	

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	SCD: reversing anaemia, haemolysis and vaso-occlusion and stopping crisis due to vaso-occlusion (VOCs). A key factor in eligibility for treatment with exa-cel is the individual patients' fitness to safely undergo myeloablative conditioning with busulfan. As such, while patients treated with exa-cel in CLIMB SCD-121 had severe SCD (i.e. were experiencing recurrent VOCs at baseline), they will not have developed significant, irreversible, complications as this would render them ineligible for myeloablative conditioning. In the real-world patients will be treated in the 'clinical window' after they have developed severe, recurrent VOC but before they have developed severe organ damage, ensuring they are able to return to near-normality after exa-cel treatment. Furthermore, all cases will require approval by the National Haemoglobinopathy Panel which will confirm that all patients meet the eligibility criteria set out in the SmPC including fitness to undergo conditioning. Furthermore, there is evidence from treatment with hydroxycarbamide and transfusion that increasing the HbF and reducing the red cells ability to sickle reduces the development of complications and reverses the severity of complications (37, 38). In addition the contrast between asymptomatic patients with co-inheritance of HbS and genes that cause pancellular increases in HbF (HPFH) and symptomatic patients suggest that, if it were possible to induce high HbF levels in most sickle erythrocytes and if this could be done before organ damage occurs, one might expect the disease to be cured (36). Therefore, the literature supports the view that the sustained high levels of HbF will prevent the development of any new disease-related complications, and halt or reverse the progression of any existing disease-related complications. <u>Post-HSCT outcomes in SCD support the return to full or near-full health</u> The substantial body of evidence gathered in HSCT, the other curative therapy for SCD, indicates that once the sickle phenotype is reversed, there is no recurrent haemolysis, and therefore no further disease-related complications occur. Detailed below are a selection of these studies: 1. Inam <i>et al</i> (2023) (39): Outcomes and long-term effects of hematopoietic stem cell transplant in sickle cell disease Expert opinion provided as part of this article states the following: <i>'HSCT, both allogeneic and autologous gene therapy, in the SCD population reverses the sickle phenotype, prevents further organ damage, can resolve prior organ dysfunction in both pediatric and adult patients.'</i>	

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	Specific outcomes detailed in Inam <i>et al</i>: • Neurologic outcomes: TCD velocities normalise post-HSCT. By 5 years post-HSCT, evidence of improvement in white matter changes and stable or improved cerebral vessel abnormalities. In general, patients with SCD and prior stroke history are protected from subsequent clinical strokes following successful engraftment and can safely stop secondary prevention with chronic RBC transfusion therapy following HSCT • Cardiac Function and Pulmonary Hypertension: Following successful HSCT, there are significant improvements in cardiac size and function • Pulmonary Function: The majority of studies report stabilisation and/or improvement of lung function as measured by pulmonary function testing following transplantation • Renal Function: Evidence of stable kidney function • Bone Health: published studies comment on stability of avascular necrosis up to 3-5 years post-HSCT in those with pre-HSCT avascular necrosis 2. Walters et al (2010) (40): Pulmonary, gonadal, and central nervous system status after bone marrow transplantation for sickle cell disease Prospective study with a median follow-up of 6.5 years (range: 3.0-12.4 years) after transplant in patients <16 years of age to receive a stem cell transplant between 1991 – 2000. 1. After BMT, patients with stroke who had stable engraftment of donor cells experienced no subsequent stroke events after BMT, and brain MRI exams demonstrated stable or improved appearance. 2. After transplantation, most patients also had unchanged or improved pulmonary function. Among the 11 patients who had restrictive lung changes at baseline, 5 were improved and 6 had persistent restrictive disease after BMT. 3. Mahesri et al (2023) (30): VOC-Free Status Among Patients with Sickle Cell Disease Following Allogeneic Hematopoietic Stem Cell Transplant: A Cohort Study of Medicaid Enrollees Retrospective cohort study of 44,685 patients with SCD in the US, of which 103 had undergone HSCT between 2000 – 2014 and had ≥24 months of follow-up. • Among patients with SCD who undergo HSCT, 1 in 5 patients continue to experience acute pain events during the 12 months Post-HSCT period. This population-based study provides	

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	valuable information regarding long-term acute pain event-free status among patients with SCD who have undergone allogeneic HSCT in routine clinical care. In summary, the substantial body of evidence for outcomes post-HSCT in SCD demonstrates that patients post-transplant are restored to full or near-full health. Importantly, this benefit is expected to be even more pronounced for exa-cel, because as an autologous therapy there is no risk of graft rejection, or graft-versus-host disease. <u>Exa-cel will restore QoL to population norms</u> Review of the full breadth of QoL measurements in CLIMB SCD-121 confirms the impact of SCD on trial participants. For example, the baseline of EQ-VAS (where 100 is best imaginable health and 0 is worst imaginable health) was 69 compared with a population norm of 85. A similar reduction at baseline was seen in the other measures used. In CLIMB SCD-121, exa-cel resulted in a substantial, clinically meaningful increase in QoL as measured by five different tools, including the disease-specific Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me). As shown in Table 3, exa-cel resulted in improvements above the minimal clinically important difference, across all QoL measures, irrespective of whether these measured general QoL (EQ-5D), pain (NRS Pain Scale), or SCD-specific QoL (ASCQ-Me) (29). Table 3: QoL measures tracked in CLIMB SCD-121 <table><tr><th>QoL tool</th><th>Baseline (popⁿ norm)</th><th>Improvement, M24</th><th>MCID</th></tr><tr><td>EQ-5D (UK)</td><td>0.81 (0.93*)</td><td>0.11</td><td>0.08</td></tr><tr><td>EQVAS</td><td>69 (85*)</td><td>20</td><td>7-10</td></tr><tr><td>FACT</td><td>73 (80)</td><td>22.5</td><td>3-7</td></tr><tr><td>FACT-BMT</td><td>101</td><td>26</td><td>2-3</td></tr><tr><td>NRS Pain Scale</td><td>2.5</td><td>Reduction of 1.7</td><td>Reduction of >1</td></tr><tr><td>ASCQ-Me</td><td>Various domains</td><td>6.6-17.5**</td><td>>5</td></tr></table> *Age-adjusted population norm. **improvement in all domains except sleep. Source; D120 report (29). <u>Precedent supports exa-cel qualifying for this criterion</u> We also note precedent from HST15, where <i>‘the committee was uncertain about whether most of the people who would have onasemonogene abeparvovec would be considered to have a ‘normal or near</i>	QoL tool	Baseline (pop ⁿ norm)	Improvement, M24	MCID	EQ-5D (UK)	0.81 (0.93*)	0.11	0.08	EQVAS	69 (85*)	20	7-10	FACT	73 (80)	22.5	3-7	FACT-BMT	101	26	2-3	NRS Pain Scale	2.5	Reduction of 1.7	Reduction of >1	ASCQ-Me	Various domains	6.6-17.5**	>5	
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ASCQ-Me	Various domains	6.6-17.5**	>5																											

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	<i>normal-health'. But believed that a proportion might', with this consideration supporting an ultimate decision to apply the non-reference discount rate in HST15.</i> <i>3. The benefits are likely to be sustained over a very long period</i> As a CRISPR technology, there is no biological plausibility that exa-cel's genetic edit will not be permanent. There is no known mechanism by which an edited haematopoietic stem cell (HSC) could convert back to a wild-type sequence. Edits to HSCs are permanent and durable. Support for this comes from the latest data from CLIMB SCD-121. The stable proportion of alleles with the intended genetic modification (allelic editing) in peripheral blood and in the CD34+ cells of the bone marrow over time are indicative of the durable engraftment of edited long-term HSCs and reflect the permanent nature of the intended edit (29). Acute pain events may occur infrequently after allo-SCT and have been reported at low event rates even in subjects with high donor chimerism, who have no cells capable of sickling as all haematopoiesis has been replaced by donor cells (41-43). The interpretation of pain events after HSCT for SCD is complicated, because post-HSCT pain in patients with SCD can be related to factors that may not represent VOC events. Pain events can be due to consequences of pre-existing disease such as exacerbation of chronic pain (e.g., related to pre-existing avascular necrosis), allodynia (pain elicited by normally innocuous, low threshold stimuli) and hyperalgesia (enhanced pain response to noxious stimuli) exacerbated by chronic opiate use. Clinical experts have stated the reasons for the acute pain events seen after exa-cel in a small number of patients is likely to be similar (5). These events were predominantly in the first year following treatment with exa-cel. Pain, and acute pain events are complex, multifactorial issues in SCD. There is no evidence of microvascular occlusion-related VOC. All the VOCs observed are in patients with chronic pain, and so are not expected to be related to additional VOC complications. As explained by the clinical expert at committee <i>'if fetal haemoglobin is maintained at around 40% across every red blood cell, 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 VOC'</i>. The expert went on to attribute this to the problem associated with measuring SCD using countable VOC episodes. Support for the use of HbF % as a measure of long-term durability comes from the clinical course of the two patients in the PES to experience acute pain events (adjudicated as VOCs) during CLIMB SCD-121.	

	It is clear from this that despite experiencing acute pain events, exa-cel is providing a durable, stable, benefit, that allow rapid recovery from complications relating to co-morbidities, that would otherwise not be possible in patients with SCD. Clinical expert feedback obtained as part of this appraisal further supports the expected long-term benefits of exa-cel. It was agreed that clinical experts would like to observe stable HbF levels for at least another 12 months (24 months in total) with at least 10 patients to be confident that exa-cel is providing a sustained treatment effect (5). With additional data available since those discussions, at the D120 data cut there are a total of 15 patients with 24 months of data, with a mean HbF % of 42.2% in those patients, satisfying the required threshold for clinical experts to believe that exa-cel is providing a sustained benefit. Vertex robustly defend the duration of follow-up in CLIMB SCD-121 as suitable for decision-making - supported by the aforementioned regulatory approvals - and note the overwhelming efficacy of exa-cel, with 29 of 30 patients in the PES achieving VF12. However, to address remaining uncertainty, Vertex re-iterates a commitment to working in partnership with NICE, as we are currently doing in TDT, to agree a managed access agreement that meets the committee's requirements. <u>Conclusion – non-reference discount rate</u> In conclusion, • SCD has a substantial, daily impact on patients' & caregivers' QoL, and age at death for severe SCD patients is in the 40s, constituting a reduction of several decades relative to the general population. • Treatment with exa-cel has a transformational impact on outcomes, with no new complications related to SCD expected, and current complications likely to be halted or even reversed, as supported by evidence from HSCT in SCD. • Genetic editing with exa-cel results in a permanent and durable effect, supported by stable HbF %, and allelic editing in patients.	

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	Finally, whilst strongly defending that the totality of evidence supports exa-cel's qualification for the non-reference discount rate, Vertex is committed to a managed access agreement to better characterise this.	
3	Severity modifier Following correction of the errors in the model provided to the committee by the EAG, severe SCD qualifies for the 1.2x severity modifier, by NICE's preferred methodology. Vertex re-affirms the belief that progressive diseases where mortality increases and HRQoL deteriorates substantially over time are unfairly penalised by the discounted QALY approach. A similar approach to HST, where undiscounted QALYs are used in the calculation is more appropriate here. As discussed by committee, shared by patient and clinical experts, and outlined in the Vertex evidence submission to NICE, and in the response above, SCD has a severe impact on patients, reducing life expectancy by many decades. While the committee did not directly conclude whether the severity modifier applied, there was consensus on the fact that SCD is a severe and debilitating disease. Following correction of the errors in the model provided to the committee by the EAG, by NICE's stated methodology, SCD qualifies for the 1.2 severity modifier. Proportional and absolute short fall calculations are provided below. Notwithstanding this, we strongly disagree that the QALYs should be discounted, and this particularly applies where the non-reference case discount rate is used. This is because, the severity modifier calculation performs extremely well in situations where near-term mortality risk is high and/or HRQoL is extremely low at baseline. However, progressive diseases in which mortality increases or HRQoL deteriorates substantially over time, such as SCD, are penalised by the discounted QALY approach and the only way that these diseases would be eligible for a modifier is by decreasing the QALY discount rate. Furthermore, it is notable how, in this respect, the modifier differs between STA and HST. Modifiers in the HST appraisal route are underpinned by undiscounted QALYs. Indeed, it is evident that a number of HSTs would never have been awarded a modifier had it been reliant on discounted QALYs (26). Therefore, from a methodological and consistency perspective, it is clear that either no discount rate, or a lower discount rate of 1.5% should apply in the QALY shortfall calculation where there is a case for the non-reference case discount rate. When this is the case, the severity of severe SCD is appropriately recognised, and severity weighting of 1.7 applies (see Table 4).	The EAG reiterates NICE's position on applying absolute and proportional shortfall calculations should include discounting at the reference case rate of 3.5% per annum. The claim of appropriateness of the 1.7 modifier is based on 1.5% discount rate, a deviation from currently accepted methodology. The EAG accepted all changes by the Company; however, these changes do not resolve the fundamental incorrect conceptualisation of non-conditional complication rates. The model remains structurally affected by double count of events and mortality, resulting in inflated complication rates. It is not surprising that when pushing event rates to extremes, the model returns illogical results. The EAG has taken the view to not attempt to correct the errors, because any possible rectifications would not materially change the magnitude of ICERs in all scenarios, regardless of severity modification and discount

Table 4:Severity modifier calculations based on updated model

Severity Modifier	Value	Weight
General population QALYs (1.5% discount)	34.5	-
Proportional shortfall (1.5% discount)	65.3%	1
Absolute shortfall (1.5% discount)	22.52	1.7
General population QALYs (3.5% discount)	22.52	-
Proportional shortfall (3.5% discount)	56.0%	1
Absolute shortfall (3.5% discount)	12.61	1.2

rate; ICERs remain well above thresholds used to assess cost-effectiveness. Whilst misconceptions in the model have no impact in all current scenarios, should the ICER decrease such that it would be borderline close to acceptable thresholds, model estimates would certainly be unreliable. The EAG reiterates the original recommendation, that the model should be rebuilt using correct health economics methodology.

To our knowledge, the committee's set of preferred assumptions states that the severity weight should be x1.0

Using the shortfall online calculator (<https://shiny.york.ac.uk/shortfall/>) and model data resulting from the EAG's base case (11.4 QALY remaining in the SOC arm, population: 44% female, model baseline age:21) the severity weight returned is 1.

Remaining QALYS

without the disease:

22.53

with the disease:

11.44

absolute shortfall:

11.09

proportional shortfall:

49.21%

QALY weight [?]:

x 1

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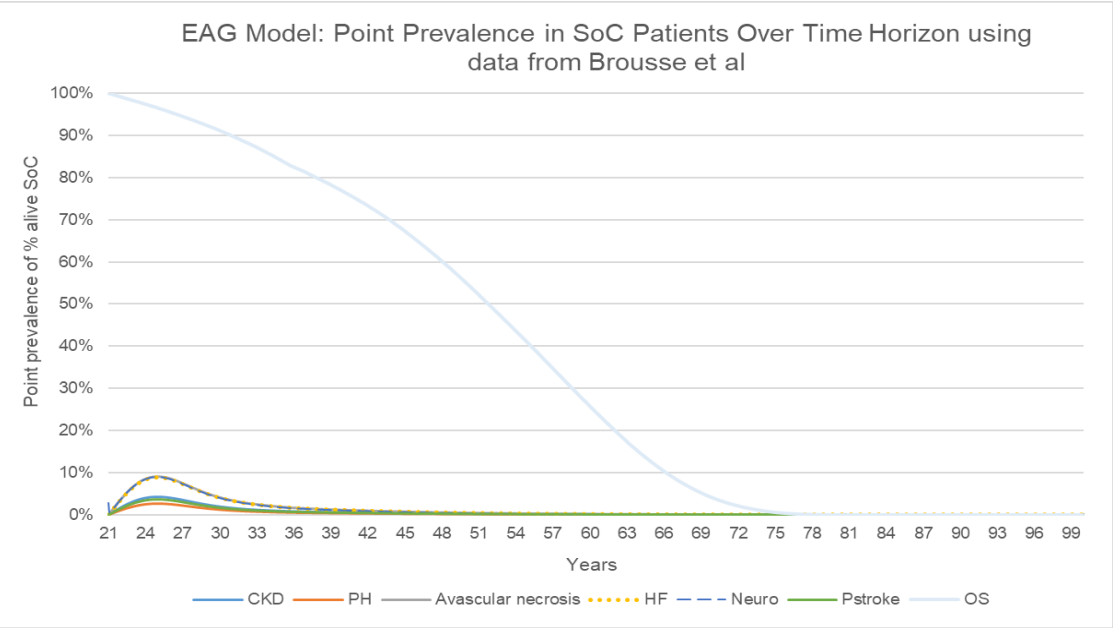
[code](#)

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Comment number	Company's comments	EAG response
4	Economic model – updated base case incorporating the committees preferred assumptions Vertex has amended its original model structure and is providing the committee with a new version of the model where the committee's concerns are addressed and therefore uncertainty reduced. Furthermore, several of the committee's preferred assumptions are now reflected in an updated base case. Vertex appreciates the attempt made by the EAG to address the committee's concerns in the previous version of Vertex's model; however several inaccuracies have been found e.g. the EAG has inappropriately added a calculation of the costs of treatment withdrawal prior to exa-cel infusion and the prevalence of chronic complications. We therefore provide an updated model for decision-making, including the committee preferences that Vertex has accepted. We request that the model submitted with this response be used to run all scenarios in future. Vertex has provided an updated economic model incorporating an updated model structure and a selection of the committees' preferred assumptions. The following amendments and assumptions have been accepted and incorporated into the base case: - the company's updated model structure which addresses two important issues: - mortality in ACD point 3.6, whereby mortality is addressed by a standardized mortality rate (SMR), and, - link between VOCs and risk of developing SCD-related complication replaced by fixed risks/rates of complications derived from the literature - the company's preferred model input on standardised mortality ratio - model inputs on the risk of complications derived from the literature; different scenarios are provided: - data from Brousse et al. (2023) (9) severe population, - data from Udeze et al. (2023) (7) considered a more complete data set avoiding the need for strong assumptions to estimate cumulative incidence. - Exclusion of adverse events for exa-cel Economic model – corrections and comments	The company's base-case did not include all Committee's preferred assumptions; correctly, the company states that the model has been rerun with a selection of Committee's preferred assumptions. Specifically, - The company did include functionality to add costs and outcomes of people who start apheresis (the first study drug) and who did not receive exa-cel. However, the functionality did not, and the rate of dropout was changed to a rate that did not correspond to intention-to-treat (ITT) data from CLIMB SCD-121 with no justification. To our knowledge, [REDACTED] to relieve exa-cel dose costs when the patients does not receive the manufactured dose. The inclusion of costs and outcomes for all that start the therapeutic pathway is a fundamental requirement in health economics. - The company's base-case did not include the Committee's preferred utility value after exa-cel.

	Vertex has corrected an issue with the model's age- and sex-matched general population utility values. The error resulted in an inflation of utility values within the exa-cel and SoC cohorts, as noted by the EAG during ACM. The difference between utilities for patients with severe SCD and functionally cured from SCD was incorrectly subtracted from the general population utility values. Vertex has therefore corrected the age- and sex-matched utility adjustment in the model, using the multiplicative method. This therefore resolves the inflated utility value issue raised by the EAG during ACM. Vertex has also corrected the potential issue of double counting Acute Chest Syndrome (ACS) in the model. In point 3.11 of the ACD, the EAG noted that ACS is also included within the Vertex's definition of a VOC. To address this issue, Vertex have reweighted the rate of ACS reported in Udeze et al (2023) to account for the proportion of patients in CLIMB SCD-121 who experienced an ACD event that was then preceded by a VOC event. Note that this correction only applies when Udeze et al (2023) is used as the source for complications data. The rate of ACS is reweighted based on the following assumptions: • 14 of the 43 subjects (32.6%) in CLIMB SCD-121 had an ACS event that was preceded by a VOC event. • Based on this proportion, Vertex reweight the proportion of simulated patients who experience ACS per model cycle by the proportion of patients who experienced an ACS even that was not preceded by a VOC event (i.e., 67.4%) in CLIMB SCD-121. We present this approach as a scenario in Table 11. Since we omit the proportion of patients who experienced an ACS preceded by a VOC event, this addresses the issue raised in point 3.11 of the ACD. Vertex has also identified both major and minor issues with the latest amendments incorporated by the EAG in Vertex's original model and has thus spent significant resources reviewing and correcting such adaptations. Vertex would like to make clear that the EAG did not provide a change log of their initial adaptations. A change log was provided on request; however, Vertex found the change log lacked necessary detail to clearly document the adaptations implemented by the EAG. We have thus endeavoured to update our original model structure to capture flagged modelling issues, including the changes attempted by the EAG, to reflect Vertex's updated base case including committee's preferences. As requested in the draft guidance document, we accept the use of the committee's preferred assumptions regarding modelling of comorbidities and mortality, also supported by the DSU, which addresses point 3.6 and 3.7 in the ACD. The updated base case at the end of this document has been run with an updated version of the company model with a selection of the committee's preferred assumptions. Vertex requests that this version of the model be used for any future analysis.	3. The company's base-case used all-VOCs rate at baseline, not the hospitalisation-VOCs rate as preferred by the committee. 4. The Committee's preference was to use complication rates from the literature. The company's base-case used an alternative base of evidence (Udeze, Vertex BOI) that is new to the appraisal and that has not been presented to the committee before. Whilst the company stated that this source constitutes a 'co-base case', in reality all company's base-case ICERs are based on the Vertex BOI study. The corresponding scenarios have not been presented before. 5. In addition, the company's base-case did not exclude ACSs. All sources of evidence (CLIMB SCD-121, Udeze et al, Brousse et al) clearly state that the definition of VOCs does indeed include ACSs. 6. The errors attributed by the company to the EAG cannot be reconstructed in the EAG model used in the ACM1 data. There are many

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	We have identified issues with the way the EAG has programmed their adjustments in their version of the updated model While the EAG has added functionality to include their preferred scenarios, the overall programming used by the EAG limits the flexibility of the model and thus the ability of the user to explore different scenarios. Generally, the approach taken by the EAG to implement their preferred scenarios has made the model harder to investigate and review and added greater potential for unintentional user errors to occur. Critically, the EAG has incorrectly calculated chronic complications The EAG has applied incorrect calculations to chronic complications in the model. The approach taken by the EAG yields invalid results in the predicted prevalence of each chronic complication. Testing these calculations by means of standard internal and external validation exercises indicates a lack of validity in the estimation of chronic complications throughout the modelled time horizon. The specific calculation issues with the EAG's approach, and the corrected calculations proposed by Vertex, are technically detailed in the Appendix. However, the issues with the EAG's approach to calculating chronic complications are apparent when considering the following: • In Table 6 found in the <i>ID4016 exa-cel EAG TE additional works updated 30012024CM [CON]</i> document (44), the EAG state that "<i>For chronic complications, cumulative lifetime incidence was calculated for Brousse over the life-years estimated for SOC in the model (22.36) using probability from Brousse et al (median follow up of 7 years) converted to rate, scaled up to 22.36 years and reconverted to probability.</i>" The EAG has only provided a table with hard coded percentage values in their model, which it claims estimates the "<i>cumulative lifetime incidence [i.e., prevalence]</i>" of "<i>chronic complications over the course of the model or equivalent.</i>" To follow the logic of the EAG's argument, this suggests that peak point prevalence in the modelled SoC population is expected at roughly 43.5 years of age (i.e., mean survival, calculated as baseline age plus the predicted mean additional life years of SoC patients, which is 22.36 based on the EAG's statements). However, in the EAG's model, peak point prevalence of chronic complications in the SoC cohort occurs at roughly 25-27 years of age (see Figure 3– note the OS line in the graph is the overall survival of the SoC cohort over time). This contrasts with Brousse et al., who demonstrated that the rate of development of chronic complications continued to increase past age 40 (see Table 3 in Brousse et al.). The predicted peak point prevalence of chronic complications in the EAG's model is thus clinically unrealistic. The peak prevalences	scenarios in the ACM1 model that are invalid as a result of the mathematically incorrect structure submitted by the company. For the scenario corresponding to the EAG's base-case (approximately [REDACTED]) the cumulative rate of CKD is 52%, as per the (company's calculated) cumulative rates pre-set in the model; rates peak at about 44 years old in ACM1. The model also had pre-set cumulative state occupancy; these states are indeed over 100% for each event; as the EAG stated in the previous critique, these states provide overestimations because all company's chronic complications calculations are not calculated conditionally to deaths in the same cycle. The incorrectly calculated state occupancy leads to double counts, that, over the course of the model, cause the state to report proportions higher than one. Nonetheless, the error is likely to be small when rates are set in the ranges shown in the literature. The EAG

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	are, furthermore, several orders of magnitude smaller than those observed in cohorts of severe SCD patients e.g. the prevalences at baseline recorded in Udeze et al., (2023) (7). Figure 3: EAG model – predicted point prevalence of chronic comorbidities in the modelled SoC cohort over time  • The EAG does not appropriately incorporate baseline prevalence into their point prevalence calculations. This is especially noticeable when inspecting the modelled point prevalence of neurocognitive impairment over time (see dashed blue line in Figure 3). At model entry, prevalence sharply drops in neurocognitive impairment, indicating that baseline prevalence is not appropriately incorporated into the point prevalence calculation. This is similarly true for all other chronic complications in the model, whereby baseline prevalence is not correctly counted. Please also see Figure 7 in the Appendix, which provides a magnified visualisation of this issue. • If you set the per cycle probability of developing chronic kidney disease (CKD) in the EAG's model to 100%, the maximum point prevalence of CKD is 2802.9%, occurring in cycle 47 of	has not implemented corrections. The company's point around incorporating baseline values all set to zero (as from CLIMB SCD-121- exception made for cognitive impairment and retinopathy). Baseline prevalence (i.e., event rates prior to the start of the study) should not be incorporated in the forward rates estimation. Because the company has stripped this functionality out of the model, it is not possible for the EAG to reproduce the values stated by the company.

Comment number	Company's comments	EAG response
	the EAG's model. Whilst the sum of the point prevalence across all model cycles can exceed 100%, a cycle-specific point prevalence should never exceed 100%. For all other chronic complications altered by the EAG, the issue is similar. Correction of this approach leads to more valid predictions that follow clinical reality We have corrected the EAG's calculations in line with Equation 2 (see Appendix). These amended calculations lead to more realistic predictions. Predicted peak point prevalence in the updated Vertex model's SoC cohort occurs approximately between 42-45 years of age (see Figure 4- note the OS line in the graph is the overall survival of the SoC cohort over time). This aligns more closely with the evidence presented in Brousse et al (9). Moreover, the predicted point prevalence of chronic complications generally follows the proportions that, according to the EAG, are to be expected at roughly the point of mean survival (i.e., expected additional LYs from model baseline) in the SoC arm. A tabulated comparison of these proportions, based on the arguments presented by the EAG in Table 6 of the <i>ID4016 exa-cel EAG TE additional works updated 30012024CM [CON]</i> document, is presented in Table 5.	

Figure 4: Vertex model – predicted point prevalence of chronic comorbidities in the modelled SoC cohort over time

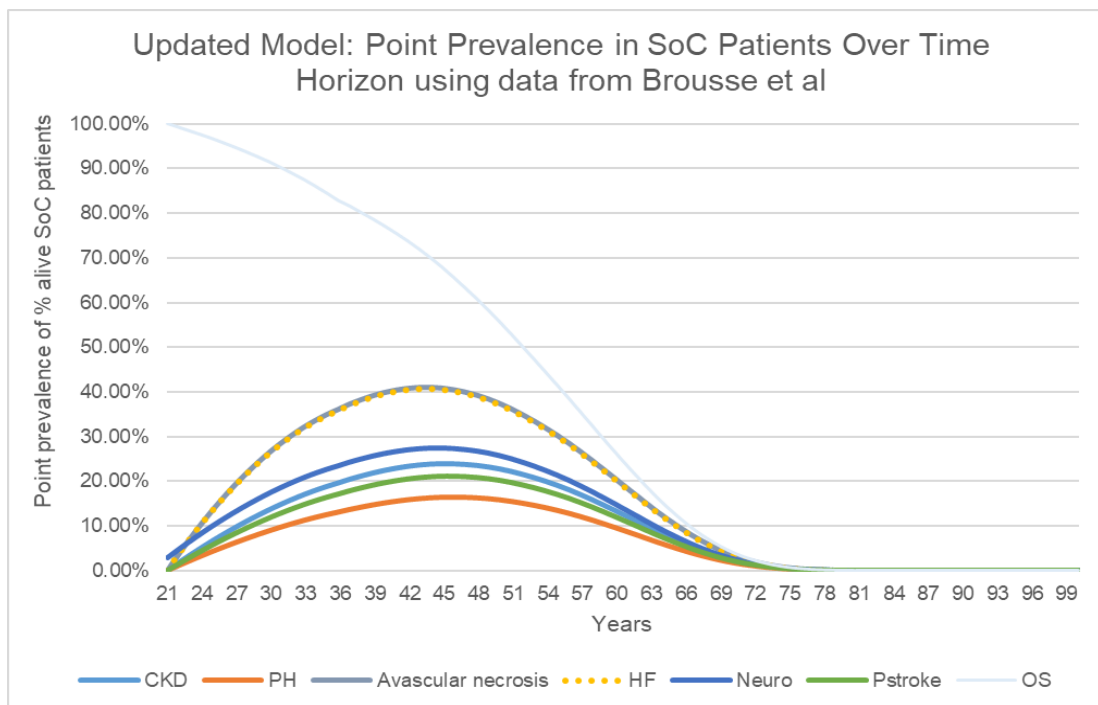
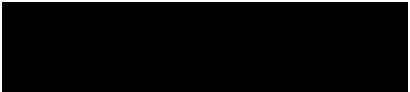


Table 5: Expected prevalence after 22.36 years based on the Brousse et al (2023) severe population compared to the point prevalence predicted by the EAG and Vertex models in the SoC Cohort

Chronic complication	EAG's calculation for expected prevalence for severe patients after 22.36 years based on Brousse et al (Table 6 of EAG TE critique)	EAG model amendments predicted point prevalence after 22.36 years into model time horizon	Vertex model - as per Equation 2 - predicted point prevalence after 22.36 years into model time horizon

Comment number	Company's comments				EAG response
	Chronic Kidney Disease	23%	0.38%	23.87%	
	Pulmonary Hypertension	15%	0.24%	16.16%	
	Avascular necrosis	42%	0.80%	40.93%	
	Heart Failure	41%	0.79%	40.66%	
	Neurocognitive impairment	N/A	0.79%	41.52%	
	Post-stroke	20%	0.32%	20.80%	
	The EAG's approach to calculating withdrawal prior to treatment with exa-cel is overly complex and double-counts the costs and outcomes of withdrawal prior to treatment with exa-cel Vertex maintains its position [REDACTED] and, therefore, that the cost uplift applied by Vertex appropriately captures the expected risks of withdrawal within the UK target population. Nonetheless, Vertex recognises the committee's preferred assumption regarding this issue and has thus maintained model functionality to consider the additional costs and health outcomes of treatment withdrawal by means of a scenario. The scenario is implemented using the same approach used by the York EAG for the TDT model, with costs and outcomes weighted in a secondary table of results. Vertex does however note concern with the EAG's approach to calculating the economic outcomes associated with patients who do not go on to receive exa-cel. The approach taken by the EAG seems to imply that patients only withdraw from the procedure for two reasons: inadequate apheresis or low manufacturing yield. The proportions of these patients are then used to inflate the costs of exa-cel and reduce its efficacy. Withdrawal prior to receiving exa-cel and exa-cel's actual efficacy ought to be modelled as separate issues. This is discussed in in detail in Point 6 of this document. In addition to the fact that the methodology used by the EAG to estimate these proportions is highly ambiguous, Vertex considers the EAG's interpretation of the reasons for treatment withdrawal as most critical.				

Comment number	Company's comments	EAG response
	Of the 11 subjects who underwent apheresis but did not receive exa-cel infusion during the mobilisation period, the EAG's calculations imply that 6 of these patients did so due to low manufacturing yield. However, this is incorrect. The reasons for withdrawal of these 6 patients comprise various reasons: [REDACTED] [REDACTED] The EAG's calculations for withdrawal also imply that the other 5 patients did so due to apheresis failure. Again, the reasons are broad, and none are directly linked to apheresis failure: [REDACTED] [REDACTED] Given the myriad causes for withdrawal of patients within CLIMB SCD-121, the approach taken by the EAG, to separate withdrawal patients into two distinct groups, relies on very strong assumptions. Vertex has therefore added an alternative approach to including the costs and outcomes of exa-cel patient withdrawal in the model. Please see the Appendix for further details on Vertex's approach to including costs and outcomes of treatment withdrawal. The EAG model errors identified by Vertex significantly bias against exa-cel and may lead to decision making not reflective of the true cost-effectiveness of exa-cel The errors and issues identified in the EAG's model amendments, particularly regarding treatment withdrawal and chronic complications, have a substantial impact on the ICER and significantly bias against exa-cel. For chronic complications alone, switching from using the EAG's method shown in Figure 3 to Vertex's method using Equation 2, which generates the point prevalences shown in Figure 4, reduces the committee's preferred ICER from [REDACTED] (roughly, a [REDACTED] decrease). Overall, Vertex raise significant concern with the EAG's approach to best practice modelling. Vertex would like to emphasise that the programming and some of the calculations used by the EAG are not in line with general good practices expected in health economic modelling. Both the issues with treatment withdrawal and chronic complications have significant impact on the cost-effectiveness of exa-cel. Moreover, using the EAG's calculations for chronic complications simply leads to flawed extrapolation. Again, we expand on this issue with greater technical detail in the Appendix. We therefore provide a corrected version of the model, based on the version submitted by Vertex at technical engagement as a starting point, incorporating the committee preferences which Vertex has chosen to accept (as summarised at the beginning of Point 4).	
5	Uncaptured benefits	

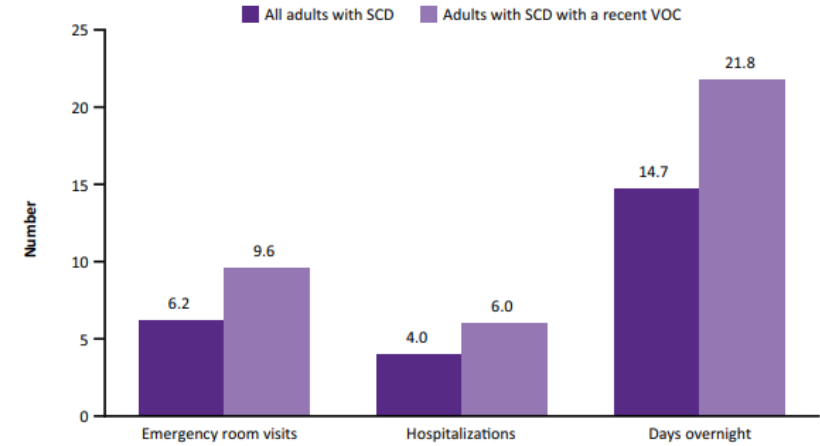
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	SCD has a substantial impact on QoL, not just for patients but also for caregivers. SCD impacts caregivers' ability to maintain employment, and results in higher degrees of depression, anxiety and stress relative to those not caring for SCD patients. The committee should take this into account when considering the most appropriate ICER threshold, beyond the flexibility in the threshold given for health inequalities. As described in Section 3.16 of the ACD, there are benefits to the treatment of exa-cel in SCD that are not captured in the economic modelling. The committee acknowledges some uncaptured benefits, such as the health inequalities that exist in SCD, but this has not been extended to the substantial burden SCD imposes on caregivers. These aspects contribute to the severity of SCD, and the potential benefit that exa-cel might bring in delivering a functional cure. SCD has a significant impact on caregivers' QoL and mental health, and treatment with exa-cel stands to alleviate these burdens for caregivers and family members. D'Amico Gordon <i>et al</i> (2024) surveyed caregivers of children with SCD in 5 US centres between 2014 – 2021 (45). Of the 244 caregivers in this study, 10.3% reported employment loss in the last 5 years due to having to attend the hospital, and 17.5% reported missing 10 or more days of work for the same reason. This study found that unemployment rates are much higher for families impacted by SCD than the general population, with rates of 20.7% and 4.7% respectively. The authors explained that SCD has many impacts that may make maintaining employment significantly challenging for caregivers, including the need for frequent appointments, home management of vaso-occlusive pain episodes, cognitive deficits, and chronic disability. Ebeid <i>et al</i> (2024) noted that parents of children with SCD had higher degrees of depression, anxiety, and stress and a significantly lower HRQoL compared to parents of healthy controls (46). This is further supported by Barcelos <i>et al</i> 2022, who observed a mean EQ-5D-5L score for caregivers in the UK was 0.62 and mean CarerQoL-7D score was 78 (47). A majority of caregivers reported mental health problems: 72% and 64% by EQ-5D-5L and CarerQoL-7D, respectively; 68% reported financial problems due to their caring responsibilities. The mean percentages of impairment due to caregiving (n=37) were absenteeism (22%), presenteeism (46%), overall work impairment (34%). Among all caregivers (N=69), the mean for activity impairment was 53% (24%). Mean missed work hours per year was 442 in the UK.	
6	Accounting for patients who do not have exa-cel infusion in the model In the trial, and model, some patients undergo cell collection but do not go on to have exa-cel treatment. The reasons for this are related to the nature of SCD and systemic health inequalities experienced by patients.	As far as the EAG is aware, 

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	***** ***** *****. Equally, treatment effects for those patients that do not have exa-cel infusion should be removed from the exa-cel arm of the model, to ensure model results accurately represent the effect of treatment with exa-cel. A number of patients who underwent apheresis in CLIMB SCD-121 did not receive exa-cel treatment (~19%), and the committee expressed a preference that the costs and outcomes of these patients should be included in the exa-cel arm of the model. This essentially has the effect of capturing outcomes of patients who did not receive therapy, and will go on to be treated with SoC, and have poor outcomes, as though they received exa-cel, generating less QALYs overall for the exa-cel arm of the model. We strongly believe it is unreasonable for these patients to be modelled as having received exa-cel treatment, where no infusion was given. We acknowledge that in other appraisals for ATMPs where cell collection is involved, companies have accepted this way of modelling, however it is important that the committee reconsiders this approach due to some specifics of SCD. <u>Modelling outcomes of patients who do not receive exa-cel infusion</u> The reasons that a patient may proceed to cell collection but not to exa-cel infusion are related to the nature of SCD rather than the treatment they received. Many were clinical trial related, and all are likely to be seen less outside of the clinical trial context. The proportion of patients not proceeding to treatment following their initial apheresis is higher in this patient population, compared to others, such as those patients undergoing CAR-T. This is partly due to the nature of their condition, as patients with SCD have challenges with collecting adequate stem cells during apheresis, and experience discrimination in the healthcare system. Depriving patients of treatment with exa-cel because of the characteristics of their disease would be adding to the already significant and systemic health inequalities experienced by this patient group (48). Some of the reasons for withdrawal were clinical trial related due to the experimental nature of the treatment such as withdrawing consent, and this is unlikely to be the case now that exa-cel is no longer an investigational therapy and is approved by regulators. In CLIMB SCD-121, 6 patients discontinued due to inadequate cell collection following apheresis (not adverse event related) which is related to the nature of sickle-cell disease (29). Several SCD related problems make collecting adequate cells more challenging, due to factors including chronic haemolysis, inflammation and hydroxyurea use which is myelosuppressive and toxic to stem cells. In addition, granulocyte colony stimulating factor (G-CSF), the most commonly used mobilising agent can induce severe SCD	– for any reason – after it has been manufactured. The company states incorrectly that the scenarios using treatment failures use outcomes from exa-cel. To implement the scenario when people fail to receive exa-cel, the EAG has used the functionality built in by the company that assigns a probability for a patient to be cured, assigning the benefits of cure (from sheet Tx1_cure1) or not to be cured (Tx1_nobenefit) as a weighted average in the exa-cel cohort. The EAG acknowledged that using the company inbuilt functionality is non-viable, not because of the outcomes (the 'no benefit sheet replicates SOC closely) but because the model does not impute the cost of exa-cel in one sheet only, rather in several sheets separately. As a result, the 'no benefit' functionality adds the cost of exel to the cost of dropouts, which is incorrect. On the other hand, using a weighted average of costs and outcomes of exa-cel and SOC does not account for the costs of

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	complications and is therefore not used in SCD patients making cell-collection even more challenging (49). It is therefore not equitable or reasonable to include the outcomes of the patients who do not receive exa-cel infusion in the exa-cel arm of the model, as this artificially dilutes the demonstrated efficacy of the therapy and may result in preventing approval of a much-needed therapy for this underserved population. <u>Modelling costs of patients who do not receive exa-cel infusion</u> Via the commercial discussions with NHS England and the treatment centres, [REDACTED] It would be unreasonable for the committee not to take a pragmatic approach to considering the exclusion of treatment effects for those patients that withdraw before infusion, thereby widening health inequity in this population. The pre-treatment cost of patients who withdraw during pre-transplant is accounted for via a cost uplift in the model. Specifically, the pre-transplant costs of patients who withdraw are added to the pre-transplant costs in the first cycle of the model. This cost uplift adds an additional £[REDACTED] to the pre-transplant costs in the exa-cel arm of the model. We strongly believe that our proposed approach of removing the outcomes of patients who do not receive exa-cel infusion from the exa-cel arm of the model, as well as the steps we have taken to reduce financial risk for the NHS, should be considered and accepted by committee. In addition, there is considerable uncertainty about whether the proportion of patients who have cell collection, but do not go on to exa-cel treatment would be the same in clinical practice as in CLIMB SCD-121 (29). Along with increasing knowledge and expertise in apheresis, and support that will be provided to centres the risk of withdrawal prior to receiving exa-cel will be reduced in clinical practice. In recognition of this uncertainty, we present a scenario where [REDACTED] of patients withdraw during the mobilisation period (i.e. do not incur exa-cel treatment costs for patients who do not receive infusion, but outcomes are included). This scenario accounts for the patients that do not go on to receive exa-cel due to inability to manufacture drug product. Our expectation is that in clinical practice, the other reasons for not receiving exa-cel listed in section 4 would not occur. This scenario is presented in Table 11.	apheresis and pre-transplant in all people who drop-out. The EAG scenario does add in the model the cost of producing exa-cel for people who do not proceed to have it; because of the nature of the therapy, the dose produced has to be entirely discarded. The principle applied here is that people who have their biological cells collected are part of the efficacy set, as per ITT analysis. In any cost-effectiveness problem, outcomes for people who do not remain compliant to the assigned treatment always remain part of the ITT, regardless of the reason for non-compliance. The reasons why people withdraw their consent or are non-compliant are not documented, as per CLIMB SCD-121 data; In clinical practice, the EAG believes that it is impossible to predict which patients will remain compliant and which people will have their samples returned in insufficient quantities. These factors are part of genuine uncertainty regarding outcomes for all those that undergo apheresis. The outcomes of those who engage to receive treatment – and undergo

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		apheresis, a procedure with a positive (albeit small) risk of death - and finally are not in a position to receive it, should not be considered in the decision problem.
7	Definition of baseline VOCs Vertex strongly believes that all VOCs that require healthcare attendance should be accounted for in the model. All VOCs are related to SCD complications, and result in a reduction in QoL. Further, issues with VOCs definitions in baseline vs follow up periods are alleviated by the new model structure. VOCs cause ischaemic tissue damage and inflammation, resulting in debilitating pain often requiring healthcare resource utilisation, and are directly linked to end-organ damage, direct healthcare costs and early mortality. There is no biological difference between a VOC requiring in-patient hospitalisation, and a VOC requiring attendance in a day unit or emergency department. The decision to admit to hospital will depend on local resources (e.g. whether a day unit is available), patient factors (social support, caregiver responsibilities), patient prior experience and patient and clinician preference. Therefore, the impact of VOCs on complications, mortality, quality of life and disease burden applies to all hospital attendances. VOCs requiring hospital attendance, not just those related to in-patient hospitalisation have an impact on quality of life, healthcare resource utilisation and long-term outcomes and should be included in the economic model. As described in our response to the non-reference discount rate issue, SCD has a substantial, and daily, impact on patients, with patient experts struggling to remember a day without pain. <u>Hospitalisation is related to multiple factors</u> Whether a patient is admitted to hospital is due to many factors, for example if day units are available patients will prefer to use these to avoid hospital in-patient stays and where specialist services are not available, patients may be admitted to hospital unnecessarily. The “No-One’s Listening” report highlighted that many patients avoid being admitted to hospital due to fear of substandard care, and prefer not to be admitted to hospital following attendance at an accident and emergency department (22). Further support for this comes from Drahos <i>et al</i> (2022), which found that amongst a cohort of 142 adults with SCD in the UK, France, and US, 68% of patients	The effect is not limited to death rates, but more importantly, to the entire set of complications extrapolated in the model. Most literature studies use a definition of VOCs based on hospitalisations or hospitalisation codes. On the other hand, the impact of VOCs that do not lead to hospitalisations, i.e., pain episodes, are captured in the EQ-5D, because one of the 5 dimensions in the EQ-5D is pain. Whilst it can be argued that the EQ-5D may not be very sensitive to some components of quality of life, this is certainly not the case of pain which is directly, explicitly, included in the score. Therefore, the addition of a correction for pain would result in double count. Second, when assessing heterogeneity, inclusion / exclusion criteria in a study are nor a sufficient or a necessary factor to judge the match between a decision problem and the data

Comment number	Company's comments	EAG response
	reported being treated unfairly while seeking care, typically due to race (67%) and/or requesting more pain medicine (65%) (27). <u>All VOCs are related to complications of SCD and mortality</u> As highlighted in a recent study by Brousse <i>et al</i> (2023) looking at the burden of sickle cell disease in a severe cohort of patients with a similar severity to those enrolled in CLIMB SCD-121, patients during follow-up had high rates of acute and chronic complications and had a median of 2 ambulatory medical visits per year and 2.9 in-patient hospitalisations per year (9). This study highlights that both hospitalisation and non-hospitalisation VOCs are similar in prevalence and contribute to the overall disease burden of patients with sickle-cell disease, and the associated reduction in life expectancy. <u>All VOCs are linked to reduced HRQoL</u> A recent global, longitudinal survey, focused specifically on the population with recurrent VOCs, including both in-patient hospitalisation and non-in-patient –hospital visits. The study defined SCD patients (as per the CLIMB SCD-121 study) with recurrent VOCs as having ≥ 2 VOCs/year, in each of the 2 years before study enrolment, that required interaction with a healthcare provider and administration of pain medication or an RBC transfusion. The survey showed the substantial humanistic burden of patients living with SCD, and the additional impairment posed by recurrent VOCs (21) (Figure 5). Figure 1: Relationship between VOCs and requirement for hospitalisation	incorporated in the model. The match should be assessed based on actual observed number of VOCs at baseline applied in model and that reported in study populations used for extrapolation. Model population rates at baseline (i.e., from CLIMB SCD-121) should be in line with baseline rates observed in external studies, so that extrapolation of outcomes throughout the model time horizon is free from biases. The company's argument confuses a priori inclusion – exclusion criteria with effective data observed in a study. For example, data showing an average of 10 VOCs obviously fulfil the a priori ≥ 2 criterion, but 10 VOCs does not equal 2 VOCs. Whilst some of the studies included in the 'literature' scenario do not provide data on the observed baseline number of VOCs as inclusion criteria, the majority does provide the mean number of VOCs observed in their study population at baseline (i.e. in the one or two years before study index date). Most studies used for extrapolation of outcomes have a population with much higher rates of baseline VOCs (except perhaps

Comment number	Company's comments	EAG response												
	Emergency Room Visits and Hospitalizations Compared to the overall cohort with SCD, participants with SCD with a recent VOC had a greater mean number of emergency room visits (9.6 [SD: 12.6] vs 6.2 [SD: 8.8]), hospitalizations with overnight stays (6.0 [SD: 5.7] vs 4.0 [SD: 4.5]), and days overnight in the hospital (21.8 [SD: 32.9] vs 14.7 [SD: 24.7]) in the past 12 months (Figure 3) Figure 3. Emergency Room Visits, Hospitalizations, and Days Overnight in the Hospital in the Past 12 Months  <table border="1" data-bbox="459 469 1276 916"> <thead> <tr> <th>Category</th> <th>All adults with SCD</th> <th>Adults with SCD with a recent VOC</th> </tr> </thead> <tbody> <tr> <td>Emergency room visits</td> <td>6.2</td> <td>9.6</td> </tr> <tr> <td>Hospitalizations</td> <td>4.0</td> <td>6.0</td> </tr> <tr> <td>Days overnight</td> <td>14.7</td> <td>21.8</td> </tr> </tbody> </table> SCD, sickle cell disease; VOC, vaso-occlusive crisis. The SWAY study found that patients reporting a higher number of VOCs (irrespective of whether these required hospitalisation) in the 12 months prior to survey completion were significantly more likely to report a high impact of SCD on all aspects of daily life, schooling, and emotional wellbeing (4). In summary patients with severe SCD suffer from VOCs, that often do not end up with in-patient hospitalisation, for a number of reasons including distrust of the healthcare system., All VOCs that require healthcare attendance impact a patient in terms of both QoL and disease-related complications and impose a significant disease burden. Therefore, all VOCs should be accounted for in the economic model. The updated model estimates mortality and complications independent of VOC rate	Category	All adults with SCD	Adults with SCD with a recent VOC	Emergency room visits	6.2	9.6	Hospitalizations	4.0	6.0	Days overnight	14.7	21.8	that by Brousse et al) and regardless of inclusion criteria. When considering the vertex BOI study, the company uses complication rates for the 'severe' population, defined based on the a priori rate of VOCs, observed in the previous two years being equal or higher than 2. However, there are two issues for this group: 1. The 'severe' population includes a large proportion of people younger or older than the model population; age at entry is correlated with frequency of VOCs; 2. The actual number of VOCs reported in the relevant age group (13-35) when people younger than 13 and older than 35 are excluded is in excess of 6 per year, higher than the actual observed baseline rate of VOCs in CLIMB 121, about 2.6 hospitalisations per year, i.e., much higher than the model population. This means that the 'severe' population is more severe than the model population; the a priori inclusion criterium of ≥ 2 does not guarantee the match of the
Category	All adults with SCD	Adults with SCD with a recent VOC												
Emergency room visits	6.2	9.6												
Hospitalizations	4.0	6.0												
Days overnight	14.7	21.8												

Comment number	Company's comments	EAG response
	The committee noted inconsistencies in the baseline definition of VOCs. Vertex believe that these issues are now addressed based on several changes in the model and from perusing the sources of the data used to estimate mortality and complications. The discrepancy between the definition of the model baseline VOC and the calculation of mortality and complications is alleviated since mortality and complications are modelled independently of VOC rate in the updated model. Moreover, all data used to model mortality and complications aligns with the VOC definition applied in the model and CLIMB SCD-121. Definition of VOCs used in CLIMB SCD-121 and data for mortality and complications used in the model generally align due to several reasons Since mortality and complications are now modelled independently of VOCs, the issue of inconstancy in the definition of VOCs for the data used in the model is negligible. Most data used to model mortality and complications are derived from unselected study populations. For mortality, Desai et al included patients with non-hospitalised and hospitalised VOCs (12). The majority of literature sources used to model complications, specifically Cahill et al (2019) (50), Shah et al (2019) (51), Shah et al (2024) (52), Singh et al (2016) (53), and Yeruva et al (2016) (54), did not have VOC-related inclusion criteria. Hence, the data from these studies are more representative of unselected, less severe populations than CLIMB SCD-121. Moreover, the study criteria of Udeze et al (2023) fully aligns with criteria of CLIMB SCD-121. These populations are thus highly comparable, and it is another reason why Vertex prefers using Udeze et al (2023) for complications input data. For Brousse et al (2023), these data are derived from the severe cohort. The VOC rates for non-hospitalised and hospitalised patients in Brousse et al (2023) are much lower than the rates reported in CLIMB SCD-121. For instance, Brousse et al report a rate of 1.67 per person year for hospitalised VOCs (compared to a rate of 2.6 per person year in CLIMB SCD-121). All these data therefore align with the general definition used in CLIMB SCD-121 and thus the model. In response to the EAG's suggestion that excluding non-hospitalised VOC reduced the need to model a relapse rate, we have already explained in Point 2 section 3 "<i>The benefits are likely to be sustained over a very long period</i>" that the non-hospitalised VOCs experienced by the patients post-exa-cel do not constitute a relapse, with underlying parameters such as HbF %, Hb concentration, and allelic editing remaining stable.	population to CLIMB SCD-121. In people older than 35, VOCs rates are much higher (about 13 per year) therefore, extrapolating the BOD severe population rates with no age restriction is a source of overestimation of treatment effects. The BOD population also has a higher burden of complications at baseline compared with CLIMB SCD-121. The model population has zero complications at baseline (bar cognition and retinopathy). Efficacy from a trial with a population with 4 (or 2.6 hospitalisations) VOCs per year may not be representative of efficacy for people with a three-fold VOC rate; applying efficacy observed in CLIMB SCD-121 to a population with much higher baseline VOC rates and baseline comorbidity rates may bias the model results and may increase uncertainty in the cost-effectiveness. See appendix for detailed data from all extrapolated parameters in the model. The EAG concluded that there is a potentially large mismatch between CLIMB SCD-121 patient

Comment number	Company's comments	EAG response
		population and complication rates used to extrapolate burden of disease in the model.
8	Modelling of SCD complications: choice of source While Vertex maintains the position that frequency of VOCs is a valid predictor of complications over time in severe SCD patients and therefore a hazard rate approach to model the risk of complications is appropriate, Vertex agrees to a new model structure whereby the risk of complications is derived from the literature e.g. from Brousse et al. Vertex presents two scenarios with data on complications derived from Brousse et al (as per committee's request) and data from Udeze et al. The latter provides a more complete source for the relevant population, based on UK data, and will therefore also be useful for the committee to consider. Vertex maintains its position that VOC frequency is a predictor of severe disease and risk of developing complications in SCD. In addition to the clinical evidence presented by Vertex throughout this submission substantiating this argument, Brousse et al. 2023 (9) carved out a more severe subgroup of patients based on the frequency of VOCs and the frequency of treatments for VOC (hydroxycarbamide prescriptions and/or blood transfusions). Brousse et al. demonstrates that the incidence of multiple comorbidities is higher in this severe cohort of SCD patients, supporting the argument that VOCs are a predictor of incidence of multiple comorbidities (9). Furthermore, when employing the Brousse publication comorbidity incidences, the EAG makes the strong assumption that all incidence rates were observed following 7 years of follow up, whereas this figure represents the median length of follow-up of patients within Brousse (interquartile range 4.2-7 years). In contrast, the Shah publication used by Vertex expresses complication rates as an incidence per 100 person-years (6), which requires no such strong assumption, having already been converted to a format suitable for implementation in an economic model by the authors. Finally, the EAG made adjustments to the patient denominators in Brousse to adjust for presence of patients who had received curative therapies. Again, this incorporates strong assumptions regarding the relative follow-up times of patients in the Brousse cohort who did versus did not receive curative treatment. The impact of these adjustments is unclear. Despite these limitations, Vertex presents the committee's preferred approach as a co-base case, using Brousse, for calculating chronic complications in our updated. This is primarily because the rate of complications is derived from the more severe cohort in Brousse and thus should generate similar	

Comment number	Company's comments	EAG response
	results to those when using VOCs as a predictor. However, Vertex present data on complications from Udeze et al (2023) as a preferred co-base case. These data provide an alternative and more complete source for the relevant population, based on UK data, and should therefore be considered by committee. Vertex acknowledges the committee's preference to model complications unconditional on VOC rates Notwithstanding the aforementioned reservations, Vertex understands that the committee would prefer to model complication rates independent of VOC frequency. Therefore, Vertex has adapted the version of the model submitted at technical engagement to calculate complication rates unconditional on VOC frequency. Vertex has implemented these changes using a different approach to the EAG, due to the calculation issues identified by Vertex in the model version shared by the EAG previously (discussed in detail in Point 4 of this response document and the Appendix). We have tabulated the point prevalence of chronic complications at 22.36 follow-up years based on the rates predicted by Brousse et al. compared to the EAG model and the updated Vertex model, as per Equation 2, in Table 5. We discuss the strengths of preferring Udeze et al (2023) and present a comparison of the expected chronic complications over time, between the updated Vertex model and the amended EAG model. Vertex present Udeze et al (2023) as a preferred co-base case As noted above, Vertex has added an additional co-base case as our preferred source for modelling complications, using complication data from Udeze et al (2023) (7). Vertex believes that this source is more robust than Brousse for several reasons. Firstly, Brousse et al. does not report data for six of the complications applied in the model. In contrast, Udeze et al (2023) report data for all complications applied in the model. Secondly, incidence of complications in Udeze et al. is reported as an incidence rate per 100 person-years, and it is thus not reliant on strong assumptions regarding duration of follow-up. However, this is required when using data from Brousse et al. because average duration of follow-up is not reported. Lastly, the definition and study criteria of a patient's VOC rate in Udeze et al (2023) aligns with CLIMB SCD-121, thus alleviating point 3.10 in ACD. In Table 6 we compare the prevalence observed in patients from Udeze et al (2023) at baseline, indexed according to ages 12-35 and >36, with the predicted period prevalence of our updated model and the EAG model. The predicted period prevalence is calculated in each model as an average within two age groups. For the predicted period prevalence in ages 12-35, we take the average prevalence in the model from baseline age to age 35. For the predicted period prevalence in ages	

Comment number	Company's comments	EAG response																																							
	>36, we take the average prevalence in the model from ages >35 to age 86. We use a maximum age of 86 to align with the maximum age observed in the severe SCD cohort from Udeze et al (2023). Vertex reiterates that, given the evidence presented in Table 6, the corrections, applied by Vertex in the updated model, lead to more valid predictions that follow clinical reality more closely. Table 6: External model validation of predicted model prevalence in SoC cohort compared to Udeze et al. <table> <tr> <th>Chronic complication</th><th>Prevalence: Ages 12-35</th><th>Prevalence: Ages > 36</th></tr> <tr> <td colspan="3"><i>Baseline prevalence based on Udeze et al</i></td></tr> <tr> <td>Chronic Kidney Disease</td><td>2.00%</td><td>7.63%</td></tr> <tr> <td>Pulmonary hypertension</td><td>2.62%</td><td>18.88%</td></tr> <tr> <td>Avascular necrosis</td><td>13.71%</td><td>33.33%</td></tr> <tr> <td>Heart Failure</td><td>Not available</td><td>9.64%</td></tr> <tr> <td>Neurocognitive impairment</td><td>1.69%</td><td>4.02%</td></tr> <tr> <td>Post Stroke</td><td>Not available</td><td>Not available</td></tr> <tr> <td>Retinopathy</td><td>8.17%</td><td>26.51%</td></tr> <tr> <td>Liver complications</td><td>5.08%</td><td>5.22%</td></tr> <tr> <td colspan="3"><i>Predicted period prevalence based on updated Vertex Model</i></td></tr> <tr> <td>Chronic Kidney Disease</td><td>4.66%</td><td>5.76%</td></tr> <tr> <td>Pulmonary hypertension</td><td>7.79%</td><td>9.18%</td></tr> </table>	Chronic complication	Prevalence: Ages 12-35	Prevalence: Ages > 36	<i>Baseline prevalence based on Udeze et al</i>			Chronic Kidney Disease	2.00%	7.63%	Pulmonary hypertension	2.62%	18.88%	Avascular necrosis	13.71%	33.33%	Heart Failure	Not available	9.64%	Neurocognitive impairment	1.69%	4.02%	Post Stroke	Not available	Not available	Retinopathy	8.17%	26.51%	Liver complications	5.08%	5.22%	<i>Predicted period prevalence based on updated Vertex Model</i>			Chronic Kidney Disease	4.66%	5.76%	Pulmonary hypertension	7.79%	9.18%	
Chronic complication	Prevalence: Ages 12-35	Prevalence: Ages > 36																																							
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Comment number	Company's comments			EAG response
	Avascular necrosis	18.81%	18.61%	
	Heart Failure	6.67%	8.00%	
	Neurocognitive impairment	7.24%	6.58%	
	Post Stroke	2.04%	2.27%	
	Retinopathy	25.10%	17.22%	
	Liver complications	6.22%	7.50%	
	<i>Predicted period prevalence based on EAG Model amendments</i>			
	Chronic Kidney Disease	1.01%	0.07%	
	Pulmonary hypertension	1.73%	0.11%	
	Avascular necrosis	4.59%	0.30%	
	Heart Failure	5.01%	0.33%	
	Neurocognitive impairment	4.63%	0.31%	
	Post Stroke	0.42%	0.02%	
	Retinopathy	19.07%*	37.90%*	
	Liver complications	5.46%*	27.06%*	
	*In the EAG's model, please note that these chronic complications still use risk equations to estimate point prevalence.			

Comment number	Company's comments	EAG response
9	Utility of SoC patients at baseline and evolution over time As requested by the committee, Vertex provides a longitudinal view of how the net utility of SoC patients in the model changes over time, to ensure it is clear that patients experience a severe impact on their quality of life, especially as they grow older. Vertex has also implemented additional scenarios to evaluate the uncertainty related to baseline utility. We also include additional post-hoc analysis of the trial utility data, indicating significant ceiling effects in the baseline HRQoL trial data. At the point when patients receive exa-cel they will have relatively fewer complications; however, it is clear from the literature that without treatment, their QoL would continue to deteriorate as they grow older and accumulate further co-morbidities. The overwhelming body of evidence looking at all PROs from multiple studies in SCD including EQ-5D shows that SCD has a significant negative impact on quality of life. Therefore, the committee requested additional information on utility values over time in the SoC arm in the model. As patients in the SoC arm age in the model, they develop comorbidities which results in added disutility to the baseline SoC utility value. Vertex provides a longitudinal view of how the net utility of SoC patients evolves over time in Table 7. Although the baseline utility starts at 0.81 for the cohort of CLIMB SCD-121 patients (29), this decreases substantially over time because of the comorbidities incurred and the associated utility decrements. Vertex emphasises that the predicted utility values are	As shown for the case of efficacy, the cost-effectiveness case relies on heterogeneous data (CLIMB SCD-121 versus Udeze and literature) which causes misalignment between efficacy and long-term complication data. The company suggests an analysis excluding a set of patients from CLIMB SCD-121. This is a very risky approach as it implies arbitrary selection of data from the clinical trial to fit the decision problem at hand. Such approach violates established methodology.

within the range of those reported in CLIMB SCD-121 when patients with a utility score of 1 are removed (see post-hoc subgroup analysis, Figure 5).

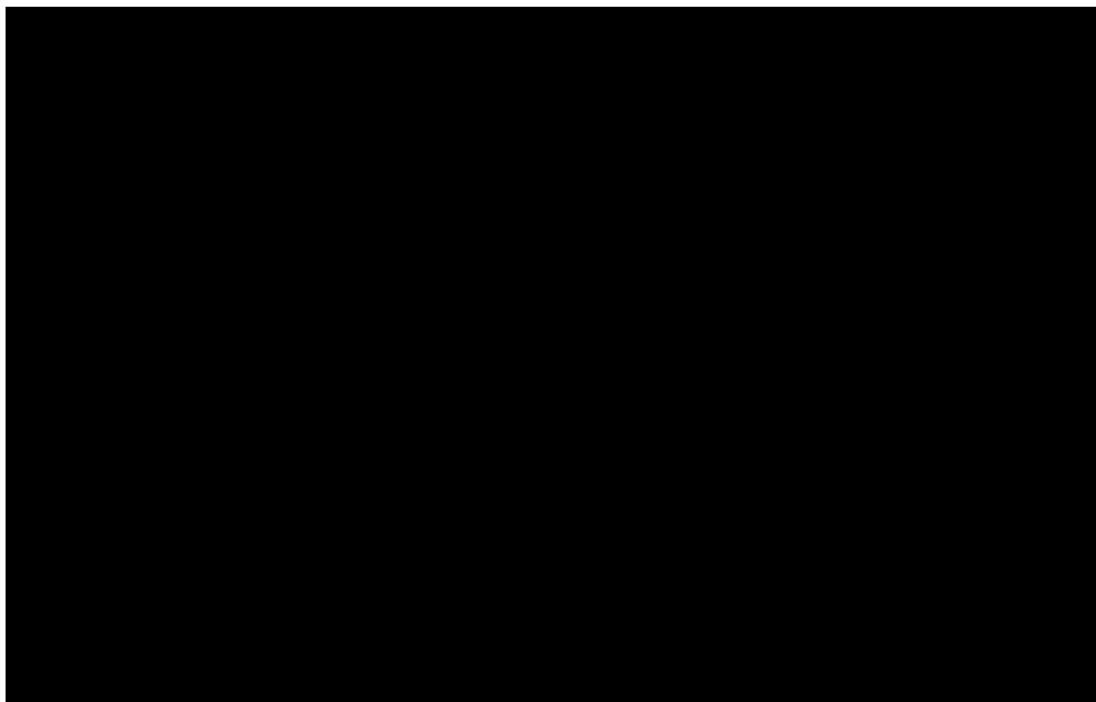


Figure 6: Histogram of EQ-5D-5L UK Index Scores for patients with utility < 1 at baseline in CLIMB SCD-121 FAS (N=21)

As shown in Table 7 and Table 8, the predicted values closely align with the very low utility values observed in the post-hoc CLIMB SCD-121 utility analysis. In fact, when using a baseline utility value of 0.81, the predicted net utility at baseline is more closely aligned with the mean post-hoc subgroup baseline value when all disutilities are included compared to when acute complication disutilities are excluded (see 'Net health state utility' vs 'Net health state excl. acute disutilities' columns). Hence, there is a strong rationale for preferring a baseline value of 0.81. Likewise, the net utility predicted by the model between the ages of 21 and 35 comfortably lies within the realistic range of the values observed in the subgroup of patients aged ≥ 18 and ≤ 35 with a utility score of <1 at baseline (Figure 6). As discussed in Point 2 of this document, the range of values observed in CLIMB SCD-121 are

well supported by values documented in the literature. Please see a comparison of using an alternative baseline value of ■ in Table 8.

Table 7: Evolution of SoC SCD utility value in the economic model using data from Brousse et al. for complications

Age	Core health state utility including age decrement	All Comorbidity disutilities	Net health state utility	Chronic Comorbidity disutilities	Net health state utility excl. acute disutilities
21.2	0.81	-0.10	0.71	-0.02	0.79
30	0.80	-0.20	0.70	-0.13	0.67
40	0.77	-0.29	0.48	-0.22	0.55
50	0.75	-0.38	0.37	-0.30	0.45
60	0.71	-0.45	0.26	-0.37	0.34
70	0.67	-0.53	0.14	-0.45	0.22

Table 8: Evolution of SoC SCD utility value in the economic model using data from Brousse et al. for complications but with a baseline utility value derived from the post-hoc subgroup analysis

Age	Core health state utility including age decrement	All Comorbidity disutilities	Net health state utility	Chronic Comorbidity disutilities	Net health state utility excl. acute disutilities
21.2	■	-0.10	■	-0.02	■
30	■	-0.20	■	-0.13	■

40	■	-0.30	■	-0.22	■
50	■	-0.38	■	-0.30	■
60	■	-0.45	■	-0.37	■
70	■	-0.53	■	-0.45	■

Since we incorporate data from Udeze et al (2023) for calculating complications as our preferred co-base case, we illustrate utility over time in the SoC cohort for this co-base case too (see Table 9). Please see a comparison of using an alternative baseline value of ■ when using data from Udeze et al (2023) in Table 10.

Table 9: Evolution of SoC SCD utility value in the economic model using data from Udeze et al (2023) for complications

Age	Core health state utility including age decrement	All Comorbidity disutilities	Net health state utility	Chronic Comorbidity disutilities	Net health state utility excl. acute disutilities
21.2	0.81	-0.13	0.68	-0.02	0.79
30	0.80	-0.19	0.60	-0.09	0.71
40	0.77	-0.26	0.51	-0.15	0.62
50	0.75	-0.32	0.43	-0.21	0.54
60	0.71	-0.37	0.34	-0.26	0.45
70	0.67	-0.43	0.24	-0.32	0.35

Comment number	Company's comments	EAG response																																										
	Table 10: Evolution of SoC SCD utility value in the economic model using data from Udeze et al (2023) for complications but with a baseline utility value derived from the post-hoc subgroup analysis <table><tr><th>Age</th><th>Core health state utility including age decrement</th><th>All Comorbidity disutilities</th><th>Net health state utility</th><th>Chronic Comorbidity disutilities</th><th>Net health state utility excl. acute disutilities</th></tr><tr><td>21.2</td><td>■</td><td>-0.13</td><td>■</td><td>-0.02</td><td>■</td></tr><tr><td>30</td><td>■</td><td>-0.19</td><td>■</td><td>-0.09</td><td>■</td></tr><tr><td>40</td><td>■</td><td>-0.26</td><td>■</td><td>-0.15</td><td>■</td></tr><tr><td>50</td><td>■</td><td>-0.32</td><td>■</td><td>-0.21</td><td>■</td></tr><tr><td>60</td><td>■</td><td>-0.37</td><td>■</td><td>-0.26</td><td>■</td></tr><tr><td>70</td><td>■</td><td>-0.43</td><td>■</td><td>-0.32</td><td>■</td></tr></table> To address the committee's uncertainty regarding the baseline utility scenario for severe SCD patients, Vertex have implemented additional scenarios To further aid the committee's assessment of the uncertainty in the baseline utility value, Vertex has implemented an alternative baseline utility scenario derived from the post-hoc utility analysis, which excludes patients with a baseline utility score of 1. When these patients are excluded, the cohort has an average baseline utility of ■. We tabulate the impact of this scenario in Table 11, utilising the post-hoc subgroup utility analysis baseline value of ■ and a utility gain value of ■ (see Point 10 of this document for further discussion).	Age	Core health state utility including age decrement	All Comorbidity disutilities	Net health state utility	Chronic Comorbidity disutilities	Net health state utility excl. acute disutilities	21.2	■	-0.13	■	-0.02	■	30	■	-0.19	■	-0.09	■	40	■	-0.26	■	-0.15	■	50	■	-0.32	■	-0.21	■	60	■	-0.37	■	-0.26	■	70	■	-0.43	■	-0.32	■	
Age	Core health state utility including age decrement	All Comorbidity disutilities	Net health state utility	Chronic Comorbidity disutilities	Net health state utility excl. acute disutilities																																							
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40	■	-0.26	■	-0.15	■																																							
50	■	-0.32	■	-0.21	■																																							
60	■	-0.37	■	-0.26	■																																							
70	■	-0.43	■	-0.32	■																																							
10	Choice of utility value following exa-cel treatment Vertex notes the committee's uncertainty with utility value following exa-cel treatment. Vertex believes that this value reflects the gain in QoL patients experience with functionally cured	The EAG's base-case retains the utility value preferred by the Committee, 0.88.																																										

Comment number	Company's comments	EAG response
	SCD patients. However, Vertex provides an alternative scenario value of 0.14, based on a post-hoc subgroup analysis, (only includes patients with utility <1). The committee has raised concerns about using the 0.11 mean change from baseline value and the resulting 0.92 utility value following exa-cel treatment in the model. The committee prefers using a health state utility value of 0.88 in the model for the exa-cel 'functionally cured' population. The committee's preferred utility value following exa-cel treatment does not reflect the QoL gains associated with functional cure in severe SCD populations As shown in Table 3, exa-cel resulted in improvements above the minimal clinically important difference, across all QoL measures, irrespective of whether these measured general QoL (EQ-5D), pain (NRS Pain Scale), or SCD-specific QoL (ASCQ-Me). The magnitude of post-treatment gains in QoL observed in the 24-month follow-up period for patients treated with exa-cel is supported by similar observations in several studies, presented in Jiao et al (2022) (56). For instance, in patients who received HSCT, Jiao et al. (2022) report significant gains in utility, especially when patients do not experience post-treatment related complications, such as graft failure or GVHD (56). O'Brien et al (2009) reports a baseline utility of 0.70 for severe SCD patients pre-HSCT (20). Post-HSCT, these patients without graft-failure report an average utility value of 0.95. Vertex would like to highlight that, similarly, no patients in CLIMB SCD-121 experienced graft failure or GVHD (29). Due to the evidence found in the supporting literature, and the utility gain of █████ reported in the post-hoc subgroup utility analysis, Vertex believe that using a utility gain value 0.11 is, in fact, conservative. However, because the committee has noted uncertainty in the model's baseline utility value for severe SCD patients (already addressed in Point 9) and the utility value following treatment with exa-cel, we provide additional scenarios to address these concerns. Post-hoc analysis of trial utility data indicates a significant ceiling effect present in CLIMB SCD-121 baseline utility values Post-hoc analysis of the utility data also shows that there are significant ceiling effects in the baseline utility values of several patients, with █████ of patients in the PES having EQ-5D scores greater than one at baseline. As explained in Point 2, we believe that this is because the EQ-5D fails to fully capture the QoL impact of SCD, as it is unrealistic for someone to be willing to trade off perfect health for a burdensome transplant with an experimental treatment. To alleviate these ceiling effects, Vertex has conducted a post-hoc subgroup analysis of the CLIMB SCD-121 utility data (55), to derive an alternative utility gain value post-treatment with exa-cel. This analysis excludes patients with a utility score of 1 at baseline, aged ≥18 and ≤35 years at screening. A comparison of the base case and the post-hoc utility value scenario are shown in Table 9. Given	

Comment number	Company's comments	EAG response						
	the results of the post-hoc analysis, Vertex believes that using a utility gain of 0.11 post-treatment with exa-cel is, in fact, conversative. Again, Vertex strongly emphasise that the committee's preferred utility value following exa-cel treatment does not reflect the QoL gains associated with functional cure in severe SCD populations. The post-hoc subgroup analysis shows a consistent gain of [REDACTED], at month 24 in the subgroup of patients who did not have a perfect utility score of 1 at baseline. This gain is largely consistent throughout the follow-up period. From baseline (n = 15), at month 12 (n = 15), patients reported an average utility gain of [REDACTED] without any patients lost to follow-up. Patients only ever experience a lower utility gain ([REDACTED]) at month 3 of follow-up. The utility gain reported at month 24 is also not affected by sample bias, since only 2 patients are lost to follow-up throughout the follow-up period. The scenario results, using the alternative post-hoc utility value of [REDACTED], are provided in Table 11. Table 11: CLIMB SCD-121 utility gain over time <table><tr><th>Source</th><th>Utility gain</th></tr><tr><td>Base case: CLIMB SCD-121</td><td>0.11 (24 months post-treatment with exa-cel)</td></tr><tr><td>Scenario: CLIMB SCD-121 post-hoc</td><td>[REDACTED] (24 months post-treatment with exa-cel)</td></tr></table>	Source	Utility gain	Base case: CLIMB SCD-121	0.11 (24 months post-treatment with exa-cel)	Scenario: CLIMB SCD-121 post-hoc	[REDACTED] (24 months post-treatment with exa-cel)	
Source	Utility gain							
Base case: CLIMB SCD-121	0.11 (24 months post-treatment with exa-cel)							
Scenario: CLIMB SCD-121 post-hoc	[REDACTED] (24 months post-treatment with exa-cel)							

Comment number	Company's comments					EAG response
11	Updated base case					
	Table 12: Base case at 1.5% discount rate with severity modifier, using Vertex's accepted committee's preferred assumptions					
	Base case	Incremental costs (£)	Incremental QALYs with 1.7 severity modifier	ICER with 1.7 severity modifier	Incremental QALYs with 1.2 severity modifier	
	Co-base case: Udeze et al	██████	30.34	██████	21.42	
	Co-base case: Brousse et al	██████	30.96	██████	21.86	
	Table 13: Scenarios at 1.5% discount with severity modifier					
Scenarios	Incremental costs (£)	Incremental QALYs with 1.7 severity modifier	ICER with 1.7 severity modifier	Incremental QALYs with 1.2 severity modifier	ICER with 1.2 severity modifier	
Scenario: Udeze et al and reweighting ACS rate by % of patients who did not experience ACS preceded by VOC	██████	30.00	██████	21.18	██████	
Scenario: Udeze et al, including outcomes of 7% withdrawal	██████	28.25	██████	19.94	██████	

Comment number	Company's comments						EAG response
	(based on Vertex's approach)						
	Scenario: Udeze et al, post-hoc baseline utility (0.72) and utility gain value (0.14).	██████	30.09	██████	21.24	██████	
	Scenario: Udeze et al, alternative utility gain based on post-hoc analysis (0.14)	██████	32.03	██████	22.61	██████	

When presenting the new set of revised results, the company appears to have incorporated only a selected subset of committee's preferences.

Base case ICER before ACM1: [REDACTED], using discount rate at 1.5% per annum.

Company's base case after ACM1: [REDACTED], using discount rate at 1.5% and severity modifier of 1.7.

Because the company stripped or overwrote some EAG's functionality and data out of the model and because some EAG's base case data were deleted, it is not possible for the EAG to reconstruct or appraise the changes between the previous base case ICER and the base case ICER submitted by the company after ACM1.

The company's base-case is described as the ICER reflecting the Committee's preferences. However, there are several preferences that have not been incorporated in the company's base case.

1. The company's base case ICER uses a 1.5% discount and a severity modifier of 1.7.
2. The base-case does not reflect the utility value after exa-cel preferred by the Committee.
3. VOC rates are not reflecting hospitalisations VOCs (2.6 annualised rate).
4. The company added unusable functionality to incorporate the costs and outcomes for people who fail apheresis and for people who did not receive exa-cel because of insufficient doses, substantially reduced drop-out rates and assumed no costs for exa-cel;
5. The base-case uses two sets of evidence for acute and chronic complications, rather than the one preferred by the Committee. The company introduces a 'co-base-case' using rates from the Vertex BOI study (UK, unpublished) and various data retrieved from the literature, including data from Brousse, called 'Literature'.

Issue 1: The EAG generated results based on the 3.5% reference case discount and using no severity modifier.

Issue 2: The utility value has been updated to reflect the preferred utility value

Issue 3: The EAG updated the results to reflect the preferred rate of VOCs at baseline

Issue 4: For the costs and outcomes of treatment failures after apheresis, the EAG reinstated the functionality overwritten by the company to return the corresponding ICER.

However, the company also changed the number of people who drop out from the process in their base case, assigning a probability of drop out of [REDACTED], instead that that calculated from the CLIMB SCD-121 patient flow. The company provides no justification why the rate is reduced. The company's rate is locked, in that any change in the rate does not seem to propagate through the model.

[REDACTED] – regardless of the reason why the manufactured biological materials not reimplanted. The key is that exa-cel cannot be given to another patient, it has to be discarded entirely and as such, it is wasted, regardless of the reason why implantation does not occur, including insufficient yield or patient preferences. The EAG proceed to reinstate the overwritten functionality, as per Committee's preferences.

Issue 5: The company proposed two co-base-cases, reflecting two sets of complications; the rates of complications applied in the model may reflect outcomes from a more severe population than that used in the decision model, derived from CLIMB SCD-121.

1.1 *Company's results*

Table 2: Company's deterministic results

	Preference	Company base-case, Vertex BOI (Udeze et al)	Company base-case, literature-derived
	Company's base case, 1.5% discount, 1.7 severity modifier		
1	No severity modifier		
2	Discount rate 3.5%		
3	Committee's preferred utility values		
4	VOC rates reflecting hospitalisations, set at 2.6		
5	Adding outcomes for people who undergo apheresis but receive no exa-cel and adding the costs of exa-cel for people who fail to be implanted		

1.2 *Company's deterministic results base-case results*

The company presents a co-base-case, which considers 'Veterx's accepted committee's preferred assumptions', using a 1.5% discount rate and 1.7 severity modifier. The co-base-cases use data obtained from Udeze et al. and literature-derived, respectively. These results are presented in Table 3 and Table 4.

Table 3: Company's deterministic base-case results, using 1.5% discount rate with a 1.7 severity modifier (Udeze et al)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	12.54	-	-	-	-	-	-
Exa-cel	████	████	30.39	████	████	17.85	30.34	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

Table 4: Company's deterministic base-case results, using 1.5% discount rate with a 1.7 severity modifier (literature)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	11.98	-	-	-	-	-	-
Exa-cel	████	████	30.19	████	████	18.21	30.96	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

1.3 *Company's deterministic results applying 1.5% discount rate and 1.2 severity modifier*

In Table 5 and Table 6, we present the results based on the company model, using a 1.5% discount rate and 1.2 severity modifier.

Table 5: Company deterministic results, using 1.5% discount rate and 1.2 severity modifier (Udeze et al)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier

Standard of care	████	████	12.54	-	-	-	-	-	-
Exa-cel	████	████	30.39	████	████	17.85	21.42	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

Table 6: Company deterministic base-case results, using 1.5% discount rate and 1.2 severity modifier (literature)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	11.98	-	-	-	-	-	-
Exa-cel	████	████	30.19	████	████	18.21	21.86	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

1.4 *Company deterministic results, using 3.5% discount rate and 1.7 severity weighting (Udeze et al)*

Table 7: Company deterministic base-case results, using 3.5% discount rate and 1.7 severity weighting

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	9.91	-	-	-	-	-	-
Exa-cel	████	████	20.10	████	████	10.19	17.32	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

Table 8: Company deterministic base-case results, using 3.5% discount rate and 1.7 severity weighting

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	9.91	-	-	-	-	-	-
Exa-cel	████	████	20.10	████	████	10.19	17.32	████	████
ACM1 preferences for utilities									
Standard of care	████	████	9.91	-	-	-	-	-	-
Exa-cel	████	████	19.23	████	████	9.32	15.844	████	████
ACM1 preferences VOC as hospitalisations									
Standard of care	████	████	10.29	-	-	-	-	-	-
Exa-cel	████	████	19.27	████	████	8.98	15.263	████	████
ACM1 preferences including outcomes for dropouts and exa-cel dropouts									
Standard of care	████	████	10.29	-	-	-	-	-	-
Exa-cel	████	████	17.57	████	████	7.28	12.370	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

1.5 Company deterministic results, using 3.5% discount rate and no severity weighting and 1.2 severity weighting, respectively (Udeze et al)

Table 9: Company deterministic base-case results, using 3.5% discount rate and 1.2 severity weighting

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	9.91	-	-	-	-	-	-
Exa-cel	████	████	20.10	████	████	10.19	12.22	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

Table 10: Company deterministic base-case results, using 3.5% discount rate and 1.7 severity weighting

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	9.91	-	-	-	-	-	-
Exa-cel	████	████	20.10	████	████	10.19	12.22	████	████
ACM1 preferences for utilities									
Standard of care	████	████	9.91	-	-	-	-	-	-
Exa-cel	████	████	19.23	████	████	9.32	11.18	████	████
ACM1 preferences VOC as hospitalisations									
Standard of care	████	████	10.29	-	-	-	-	-	-
Exa-cel	████	████	19.27	████	████	8.98	10.77	████	████
ACM1 preferences including outcomes for dropouts and exa-cel dropouts									
Standard of care	████	████	10.29	-	-	-	-	-	-

Exa-cel			17.56			7.28	12.370		
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

1.6 Company deterministic results, using 3.5% discount rate and 1.7 severity modifier (literature)

Table 11: Company deterministic base-case results, using 3.5% discount rate and 1.7 severity weighting

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care			9.59	-	-	-	-	-	-
Exa-cel			19.98			10.39	17.66		
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

Table 12: Company deterministic base-case results, using 3.5% discount rate and 1.7 severity weighting

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care			9.59	-	-	-	-	-	-
Exa-cel			19.98			10.39	17.66		

ACM1 preferences for utilities									
Standard of care	████	████	9.59	-	-	-	-	-	-
Exa-cel	████	████	19.12	████	████	9.52	16.190	████	████
ACM1 preferences VOC as hospitalisations									
Standard of care	████	████	9.97	-	-	-	-	-	-
Exa-cel	████	████	19.15	████	████	9.19	15.617	████	████
ACM1 preferences including outcomes for dropouts									
Standard of care	████	████	9.97	-	-	-	-	-	-
Exa-cel	████	████	17.41	████	████	7.44	12.656	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

1.7 Company deterministic results, using 3.5% discount rate and no severity weighting and 1.2 severity weighting, respectively (literature)

Table 13: Company deterministic base-case results, using 3.5% discount rate and 1.2 severity weighting

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	9.59	-	-	-	-	-	-
Exa-cel	████	████	19.98	████	████	10.39	12.47	████	████

ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years

Table 14: Company deterministic base-case results, using 3.5% discount rate and 1.2 severity weighting

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	9.59	-	-	-	-	-	-
Exa-cel	████	████	19.98	████	████	10.39	12.47	████	████
ACM1 preferences for utilities									
Standard of care	████	████	9.59	-	-	-	-	-	-
Exa-cel	████	████	19.12	████	████	9.52	11.43	████	████
ACM1 preferences VOC as hospitalisations									
Standard of care	████	████	9.97	-	-	-	-	-	-
Exa-cel	████	████	19.15	████	████	9.19	11.02	████	████
ACM1 preferences including outcomes for dropouts and exa-cel dropouts									
Standard of care	████	████	9.97	-	-	-	-	-	-
Exa-cel	████	████	17.41	████	████	5.67	8.934	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

1.8 *EAG's critique of company's analyses and results*

Issue 1: Costs and outcomes associated with ACS should be excluded from the model as they constitute to double counting.

Issue 2: In the opinion of the EAG, the Committee's preference is to apply a utility value of 0.88 for cured SCD.

Issue 3: The EAG believes that complication rates extrapolated in the model are obtained from studies with a more severe population than the one in the model decision problem. Specifically with reference to the absence of mortality data for older people, the company's argument that there are no data because there are no deaths is disproven by Jiao et al., who include Medicare datasets, which include people with SCD in the age groups with mean age equal to 70 and 50. The absence of records for older people with SCD is not because there are none, but because the databases where these cases are recorded have not been included.

However, given that the company has accepted the Committee's preferred model structure, using mortality rates selected by the company, there are no material implications regarding mortality rates.

The EAG has added specific study details to provide the evidence regarding 50 years being the lower bound for a reasonably justified life expectancy for this decision problem.

Issue 4: The company base-case complication rates from Udeze et al 2023 should be replaced by the Udeze 2023 rates for the subgroup aged 12-35, more in line with the population of the decision problem. The EAG believes that the complication rates in the company base-case may be from a more severe population than that in the decision problem population and that in the CLIMB SCD-121 study.

Table 5. Acute Complications by Subgroup

Complication, Mean Rate PPPY (SD)	Age Subgroups			VOC Subgroups		Transfusion Subgroups	
	0–11 Years (n = 219)*	12–35 Years (n = 649)	≥36 Years (n = 249)*	<2 VOCs (n = 421)	≥2 VOCs (n = 696)	Baseline Transfusion (n = 303)	No Baseline Transfusion (n = 814)
Acute renal failure	-	0.06 (0.41)	0.43 (1.81)	0.03 (0.12)	0.20 (1.16)	0.23 (0.83)	0.10 (0.95)
Cerebral vasculopathy ^b	0.02 (0.13)	0.01 (0.07)	-	0.01 (0.08)	0.01 (0.12)	0.01 (0.10)	0.01 (0.11)
Gallstones	0.09 (0.38)	0.33 (1.87)	0.38 (2.07)	0.10 (0.44)	0.41 (2.16)	0.59 (3.09)	0.18 (0.73)
Infections (any)	0.11 (0.45)	0.21 (1.19)	0.26 (1.18)	0.12 (1.22)	0.25 (0.99)	0.24 (1.14)	0.19 (1.06)
Leg ulcers	0	0.23 (1.79)	0.58 (3.63)	0.05 (0.49)	0.39 (2.75)	0.35 (1.51)	0.23 (2.40)
Pulmonary embolism	0	0.03 (0.20)	0.18 (0.82)	0.02 (0.19)	0.08 (0.51)	0.08 (0.62)	0.05 (0.31)
Strokes ^b	-	0.01 (0.09)	0.03 (0.16)	0.01 (0.11)	0.01 (0.12)	0.02 (0.11)	0.01 (0.12)
VOCs (any)	2.36 (1.92)	6.37 (13.05)	7.52 (15.53)	1.27 (0.63)	8.61 (15.18)	7.22 (14.66)	5.32 (11.57)
Acute pain crises	1.90 (1.62)	5.66 (12.52)	6.82 (15.07)	1.05 (0.52)	7.68 (14.69)	6.40 (14.11)	4.73 (11.14)
Priapism	-	0.18 (1.14)	0.13 (0.85)	0.01 (0.08)	0.21 (1.21)	0.23 (1.19)	0.10 (0.86)
Acute chest syndrome	0.46 (0.60)	0.53 (0.91)	0.56 (1.16)	0.21 (0.30)	0.72 (1.10)	0.60 (1.21)	0.50 (0.79)

PPPY, per patient per year; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.

*In all reporting, patient numbers <5 were masked (i.e., reported as "-") to protect patient confidentiality, and secondary masking was applied where required to avoid back-calculation; ^bThe maximum number of strokes/cerebral vasculopathy claims per person was assumed to be 3 based on clinician feedback.

Figure 2 :Acute complications by subgroup

Issue 5: The Udeze all-sample data may lack predictive validity with respect to the decision problem population, as they may come from a sicker population than data used in the decision problem for this appraisal. During ACM1, it was discussed that exa-cel would be used preferentially in people with low rates or no history of SCD complications. In the Udeze study, people with one type of event at baseline contributed data for the calculation of another complication. It is legitimate to assume that the risk of new complications would be higher in people that have a history of other SCD complications, probably conflating the overall risk of complications with respect to the decision problem population. The population group aged 12-35 years old is in line with inclusion criteria from CLIMB SCD-121 although it does have a much higher rate of VOCs at baseline (6.37 vs 2.6 hospitalisations or 4.2 all VOCs).

Issue 6: The company provides a co-base-case using literature-derived data for acute and chronic complications (see Table 29).

Literature studies are far from providing accurate data to allow the EAG to identify best matching rates to the decision population.

Overall, rates from the literature are lower than those reported in the Vertex UK BOI study, despite similar inclusion criteria used for restricting results to severe populations.

The company obtained the majority of complication rates from Brousse et al. This study reports the number of VOCs in the more severe population, 166.9 per 100-person-years, equivalent to 1.7 per year, based on number of hospitalisations. This number is more in line with the decision population of this appraisal. The study by Brousse et al also does not provide a rates breakdown by age for most outcomes; however, the study does provide age subgroups for some outcomes; it is unclear whether the company has adjusted the relevant rates in the study to match the age restrictions in the decision problem in this appraisal.

The 'literature' co-base-case also includes one complication rate (chronic liver disease) derived from Udeze 2023.

1.9 EAG's scenario analyses results

Table 15: Committee's preferred assumptions

Model considerations	Assumption
Model structure	Alternative
SoC SMR	Company - Desai / ICER
Treatment failure	Include cost and outcomes
Baseline VOC rate	Hospitalisation VOC
Complications	Not predicted by VOCs, 1. with company's co-base case based on the 12-35 subgroup analysis of complication rates from Udeze et al 2023 2. with literature severe population rates
Utilities	0.88
Adverse events	Exclude
Severity weight	1
Discount rate	3.5%
ICER, Institute for Clinical and Economic Review; SMR, standardised mortality ratio; SoC, Standard of care; VOC, vaso-occlusive crises	

In Table 16 and Table 31 we present the deterministic results, using the committee's preferred assumptions as listed in Table 15, and the company's two co-base-cases regarding the choice of evidence for extrapolated complication rates.

Table 16: EAG's deterministic results, using 3.5% discount rate, complication rates from Udeze 2023, 12-35 years old

Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
SoC	████	████	11.44	-	-	-	-

Exa-cel	██████	████	17.91	██████	████	6.46	██████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years							

Table 17: EAG's deterministic results, using 3.5% discount rate, complication rates from literature

Strategies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
SoC	██████	████	10.19	-	-	-	-
Exa-cel	██████	████	17.47	██████	████	7.29	██████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years							

In Table 18 and Table 19 we present EAG scenario analysis results that considers the committee's preferred assumptions, as well as no ACS costs and outcomes, using a 3.5% discount rate and 1.7, 1.2 and no severity weighting, respectively.

Table 18: EAG's deterministic results, using 3.5% discount rate and 1.7 severity weighting, complications from Udeze 2023 (age 12-35)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	11.44	-	-	-	-	-	-
Exa-cel	████	████	17.91	████	████	6.46	10.984	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

Table 19: EAG's deterministic results, using 3.5% discount rate and 1.2 severity weighting complications from Udeze 2023 (age 12-35)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	11.44	-	-	-	-	-	-
Exa-cel	████	████	17.91	████	████	6.46	7.754	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

In Table 20 and Table 21, we present EAG scenario analysis results that considers the committee's preferred assumptions as well as no ACS costs and outcomes and literature complication rates obtain from Brousse et al, using a 3.5% discount rate and 1.7, 1.2 and no severity weighting, respectively.

Table 20: EAG's deterministic results, using 3.5% discount rate and 1.7 severity weighting, complication rates from 'literature'

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	10.19	-	-	-	-	-	-
Exa-cel	████	████	17.47	████	████	7.29	12.388	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

Table 21: EAG's deterministic results, using 3.5% discount rate and 1.2 severity weighting, complication rates from 'literature'

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	████	████	10.19	-	-	-	-	-	-
Exa-cel	████	████	17.47	████	████	7.29	8.745	████	████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

Additional analyses requested by NICE

In this section, we report the results on additional analyses requested by NICE, which include:

- EAG deterministic base-case (with 1.2 severity modifier)
- Company base-case- Committee preferred assumptions, deterministic (with 1.2 severity modifier)
- EAG deterministic scenarios- EAG base-case (1.2 severity modifier, assuming ACS already removed in these scenarios)

Table 22: EAG deterministic base-case (with 1.2 severity modifier)

	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	Inc QALY with severity	ICER (£/QALY)	ICER with severity modifier
3.5% discount rate									
SoC	██████	██	11.44	-	-	-	-	-	-
Exa-cel	██████	██	17.91	██████	██	6.461449	7.754	██████	██████
1.5% discount rate									
SoC	██████	██	14.64	-	-	-	-	-	-
Exa-cel	██████	██	26.52	██████	██	11.88951	14.267	██████	██████

Table 23: Company base-case- Committee preferred assumptions, Udeze complication, deterministic (with 1.5% discount, 1.2 severity modifier)

1.5% discount rate	QALYs		Costs		Incremental			ICER (£/QALY)	ICER with severity
	Exa-cel	SoC	Exa-cel	SoC	QALY	Modified	Cost		
Company base-case (Udeze complication) Committee preferred utilities (0.81 and 0.88)	20.1	9.91	██████	██████	10.19	21.42	██████	██████	██████
	29.1	12.5	██████	██████	16.5	19.8	██████	██████	██████
Hospitalisation VOCs	29.1	13.0	██████	██████	16.1	19.3	██████	██████	██████
Include treatment withdrawal outcomes and exa-cel costs and outcomes	26.1	13.2	██████	██████	12.9	15.5	██████	██████	██████
Exclude ACS cost and outcomes	26.2	13.7	██████	██████	12.5	15.0	██████	██████	██████

Table 24: Company base-case- Committee preferred assumptions, literature complication, deterministic (with 1.5% discount, 1.2 severity modifier)

1.5% discount rate	QALYs		Costs		Incremental			ICER (£/QALY)	ICER with severity
	Exa-cel	SoC	Exa-cel	SoC	QALY	Modified	Cost		
Company base-case (Literature complication)	30.2	12.0	██████	██████	18.2	21.9	██████	██████	██████

Committee preferred utilities (0.81 and 0.88)	28.9	12.0	██████	██████	16.9	20.3	██████	██████	██████
Hospitalisation VOCs	28.9	12.5	██████	██████	16.4	19.7	██████	██████	██████
Include treatment withdrawal outcomes and exa-cel costs and outcomes	25.8	12.5	██████	██████	13.3	16.0	██████	██████	██████
Exclude ACS cost and outcomes	25.8	12.7	██████	██████	13.2	15.8	██████	██████	██████

Table 25: EAG deterministic scenarios- EAG base-case, Udeze 12-35 complication (1.5% discount, 1.2 severity only, assuming ACS already removed in these scenarios

1.5% discount rate	QALYs		Costs		Incremental			ICER (£/QALY)	ICER with severity
	Exa-cel	SoC	Exa-cel	SoC	QALY	Modified	Cost		
EAG base-case (Udeze 12-35 complication)	30.6	14.1	██████	██████	16.5	19.8	██████	██████	██████
Committee preferred utilities (0.81 and 0.88)	29.3	14.1	██████	██████	15.2	18.2	██████	██████	██████
Hospitalisation VOCs	29.3	14.6	██████	██████	14.7	17.6	██████	██████	██████

Include treatment withdrawal outcomes and exa-cel costs and outcomes	26.5	14.6	██████	██████	11.9	14.3	██████	██████	██████

Table 26: EAG deterministic scenarios- EAG base-case, literature complication (1.5% discount, 1.2 severity only, assuming ACS already removed in these scenarios

1.5% discount rate	QALYs		Costs		Incremental			ICER (£/QALY)	ICER with severity
	Exa-cel	SoC	Exa-cel	SoC	QALY	Modified	Cost		
EAG base-case (Literature complication)	30.2	12.3	██████	██████	18.0	21.5	██████	██████	██████
Committee preferred utilities (0.81 and 0.88)	28.9	12.3	██████	██████	16.6	20.0	██████	██████	██████
Hospitalisation VOCs	28.9	12.8	██████	██████	16.2	19.4	██████	██████	██████
Include treatment withdrawal outcomes and exa-cel cost and outcomes	25.9	12.8	██████	██████	13.1	15.7	██████	██████	██████

Table 27: EAG deterministic scenarios- EAG base-case, Udeze 12-35 (3.5% discount, 1.2 severity only, assuming ACS already removed in these scenarios

3.5% discount rate	QALYs		Costs		Incremental			ICER (£/QALY)	ICER with severity
	Exa-cel	SoC	Exa-cel	SoC	QALY	Modified	Cost		
EAG base-case (Udeze 12-35 complication)	20.2	11.0	██████	██████	9.2	11.0	██████	██████	██████
Committee preferred utilities (0.81 and 0.88)	19.4	11.0	██████	██████	8.3	10.0	██████	██████	██████
Hospitalisation VOCs	19.4	11.4	██████	██████	8.0	9.6	██████	██████	██████
Include treatment withdrawal outcomes and exa-cel cost and outcomes	17.9	11.4	██████	██████	6.5	7.8	██████	██████	██████

Table 28: EAG deterministic scenarios- EAG base-case, literature (3.5% discount, 1.2 severity only, assuming ACS already removed in these scenarios

3.5% discount rate	QALYs		Costs		Incremental			ICER (£/QALY)	ICER with severity
	Exa-cel	SoC	Exa-cel	SoC	QALY	Modified	Cost		
EAG base-case (Literature complication)	20.0	9.8	██████	██████	10.2	12.2	██████	██████	██████
Committee preferred utilities (0.81 and 0.88)	19.1	9.8	██████	██████	9.3	11.2	██████	██████	██████

Hospitalisation VOCs	19.2	10.2	██████	██████	9.0	10.8	██████	██████	██████
Include treatment withdrawal outcomes with exa- cel cost and outcomes	17.5	10.2	██████	██████	7.3	8.7	██████	██████	██████

2 Appendix

Table 29: Data completeness, regarding baseline rates of complication in the Vertex BOI study (Udeze et al., 2023)

	Cohort size	Severe SCD cohort	
		N	%
		1117	100
Acute complications at baseline			
Renal failure	Any record	48	4.3%
Cerebral vasculopathy	Any record	7	0.63%
Gallstones	Any record	244	21.84%
Infections	Any record	94	8.42%
Leg ulcers	Any record	60	5.37%
Post-hyphaemia glaucoma	Any record	0	0%
Retinal infarction	Any record	0	0%
Splenic infarction	Any record	*	*
Stroke	Any record	12	1.07%
Pulmonary embolism	Any record	26	2.33%
Transient ischemic stroke	Any record	*	*
Vaso-occlusive crises	Any record	1117	100%
	SCD with crisis	1110	99.37%
	Priapism	38	3.4%
	Acute chest syndrome	493	44.14%
Chronic complications at baseline			
Leukocytosis	Any record	*	*
Bone and joint problems	Any record	173	15.49%
Cardiopulmonary complications	Any record	193	17.28%
Chronic pain	Any record	88	7.88%
Pregnancy complications related to SCD	Any record	112	10.03%
Delayed puberty	Any record	10	0.9%
Erectile dysfunction	Any record	7	0.63%
Hyposplenism	Any record	77	6.89%
Hyposthenuria	Any record	0	0%
Infertility	Any record	19	1.7%
Liver complications	Any	48	4.3%
Malignancies	Any	15	1.34%
Mental health problems	Any record	107	9.58%
Myelodysplastic syndrome	Any record	*	*
Neurocognitive impairment	Any record	21	1.88%
Proteinuria	Any record	10	0.9%
Retinal disorders or retinopathy	Any record	119	10.65%
Renal complications	Any record	33	2.95%

2.1 Further details

In this section, we present further details to support our critique of the company's response to the draft consultation document.

Issue 4: For the costs and outcomes of treatment failures after apheresis, the EAG reinstated the functionality overwritten by the company to return the corresponding ICER.

The reasons for dropouts in the CLIMB SCD-121 study do not pertain to access inequalities, as stated by the company, but to technical reasons. All patients in the study did provide quantities of biological material as per the CLIMB SCD-121 protocol. Based on the biological material provided, some patients were not returned with sufficient exa-cel for reimplantation. The relationship between technical production and inequalities is hard to see.

Removing the outcomes would violate a basic principle of health technology assessment (HTA), that of using ITT efficacy in the appraisal.

Whilst the company states that their base-case includes the costs of failed exa-cel implants, the company's base case assumes that no costs are imputed for exa-cel for people whose biological samples are sent for manufacture.

The company added alternative functionality to the model that overwrote the previously active EAG functionality.

Incorporate cost of withdrawn patients	No	Decision Tree sheet. Overwrites EAG.apheresis.dropouts, EAG.cost.exa.dropout, and ctrl_RBC_costuplift, and uplifting of mobilisation/apheresis costs, and sets the withdrawal rate to 0%.
Apply exa-cel cost to withdrawn patients	No	Please switch off when assessing cost uplift only. Applies to Decision Tree sheet

The company's functionality assumes that there are no tangible consequences to people that withdraw from the process, but the costs of care are set to the costs of SoC. When activating the functionality, the selection of the "cost of withdrawn patients" menu decreases the ICER slightly, reflecting lower costs of care and lower QALYs, and setting the cost of exa-cel to zero for all dropouts; the application of exa-cel cost to withdrawn patients' menu as per company's functionality has no effect on the ICER.

The company also changed the number of people who drop out from the process in their base-case, assigning a probability of drop out of ■■■, instead that that calculated from the CLIMB SCD-121 trial as in the ACM1 model (see Table 30)

Table 30: Proportion of safety analysis set that discontinues CLIMB SCD-121

Proportion of Safety Analysis Set that Discontinues Study 121		
	N	
Safety Analysis Set	58	
Discontinue Study 121	11	
at apheresis	5	
before conditioning	6	

The company provides no justification why the rate is reduced. The company's rate is locked, in that any change in the rate does not seem to propagate through the model.

– regardless of the reason why the manufactured biological materials not reimplanted. The key is that exa-cel cannot be given to another patient, it has to be discarded entirely and as such, it is wasted, regardless of the reason why implantation does not occur, including insufficient yield or patient preferences. The EAG proceed to reinstate the overwritten functionality, as per Committee's preferences.

2.1.1 Critique

The original submission suffered from the lack of validation of both mortality and complication rates in the model. Some papers were used as references, however there was no attempt to provide a review (systematic or otherwise) of model input and outputs, neither to justify the use of certain values as inputs, a serious deviation from the process of appraisals using the NICE methodology.

In the response after ACM1, the applied in the model, the company has provided somehow more detailed data to populate the model, for both mortality and complication rates although data from none of the mortality studies, and data from only two complications studies are incorporated in the model for the Committee to be able to see the impact of assumptions.

Issue 1: Costs and outcomes for ACSs should be excluded from the model as they constitute double count

The EAG 's found that the definition of VOCs includes ACS rates in most of the studies included as data sources for this appraisal (Udeze 2023; Brousse 2023) Consequently, the EAG argues that costs and outcomes for this endpoint are already captured in the model. Cost and outcomes of ACSs constitute a double count and should be set to zero in the model.

Table 31 VOCs definitions used in studies reporting SCD complication rates and mortality data

Study	VOC DEFINITION
Udeze 2023	VOCs: including SCD with crisis, Priapism, Acute chest syndrome
Brousse 2023	VOE corresponded to inpatient hospitalizations (excluding day-care hospitalizations) for VOC, hepatic sequestration, splenic sequestration, severe priapism or ACS;
CLIMB SCD-121	Acute pain event that required a visit to a medical facility and administration of pain medications (opioids or IV nonsteroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions · ACS, as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever · Priapism lasting >2 hours and requiring a visit to a medical facility · Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in Hb concentration of ≥ 2 g/dL
Shah 2019	Vaso-occlusive events were defined as an inpatient stay with a primary or secondary clinical claim of SCD with crisis (ICD-9-CM: 282.42, 282.62, 282.64, 282.69)
Piel 2021	VOCs not used as study variable; sample stratification based on diagnosis codes~: one or more primary diagnoses of sickle cell crisis (ICD-10 Code D57.0) or SCD without crisis (ICD-10 Code D57.1) three sub-cohorts defined: ‘crises’ sub-cohort, defined as patients with four or more hospital admissions due to sickle cell crises over the two base years 2009 and 2010; the ‘transfusions’ sub-cohort, defined as patients receiving six or more blood transfusions per year in 2009 and 2010; the remaining patients were categorised as the ‘other SCD’ sub-cohort. ACS rates defined as comorbidity; ACSs based on data reclassification in the study: ” In the case of ACS no specific ICD-10 code exists, therefore we developed a composite measure based on an SCD diagnosis in combination with other relevant diagnoses such as chest pain, shortness of breath or abnormal chest X-rays findings” (Piel et al 2021, page 2)
Brousse 2023	VOE corresponded to inpatient hospitalizations (excluding day-care hospitalizations) for VOC, hepatic sequestration, splenic sequestration, severe priapism or ACS;
Jiao 2023	VOC rates not given; no operational definition

Issue 2: Utilities with exa-cel

The first issue affecting utilities calculation in the company’s model was that general population utilities and utilities with exa-cel were applied in the model in an additive manner

causing a spike in utilities up to ■■■ in the exa-cel model. The EAG is satisfied that the calculation has been corrected using a multiplicative approach, therefore this issue is resolved.

The second issue concerns the Committee's preference for utility with exa-cel after transplant, to use the utility value calculated from CLIMB SCD-121 at 12 months. This was because the increment calculated for people who had data at 24 months suffered from selection bias, in that patients who had not hit the 24 months follow up had higher utility values at baseline compared with those included in the 24 months utility analysis, suggesting missingness not at random.

The company provided a post-hoc analysis of utility values that excludes people with utility of 1 at baseline (perfect health). It is unclear what this data has to offer in terms of evidence, since the bias in the utility gain provided by this new analysis is larger than the original bias it meant to resolve.

Further, the company provides a break-down distribution of utilities at baseline for 31 people in the FAS and argues that a lower baseline value should be applied, with a larger gain after exa-cel.

The problem with this approach is that it creates inconsistency between efficacy rates, that remain those for the entire sample of patients in CLIMB SCD-121, and utility values, selected to reflect the (relatively) most severe people. The rate of VOCs at baseline is also likely to differ between the whole sample and the selected sub-sample.

The company argues that the presence of high utility values at baseline should be interpreted as the evidence of a ceiling effect in the measurement of utility values. However the company does not consider the alternative explanation, pointing to another limitation of the trial, that of selecting a potentially relatively healthier population than the general SCD severe population. There are other indications that suggest a potential misalignment between the clinical trial population and the decision problem population, specifically regarding the prognostic data applied in the model, mortality data and complication data.

The EAG's base-case retains the utility value preferred by the Committee, 0.88.

Issue 3: Mortality

The company argues that the correct life expectancy for the decision problem population is in the range 40-44. The original model, albeit based on mathematically incorrect methods, returned life expectancy of around 44.

The Committee's preferred model structure uses data from Desai et al, estimating an approximate life expectancy of 50 years. This outcome has been validated by clinical opinion heard during ACM1.

Following the critique from the EAG, the company added a limited set of studies to show that life expectancy for this population is indeed in the low forties. The data provided are reported in the Table 32 .

Table 32: Summary of the literature of the mortality estimates in SCD

Lead author (year)	Sample size	Mean age, years	Geography	Mean age at death, years (mean)	
				All SCD	Severe SCD*
Udeze <i>et al</i> (2023)	1,117	24.96	UK	NA	40
Piel <i>et al</i> (2021)	9,503 (all) 1,171 (severe)	22.9 (all) 23.4 (severe)	UK	46.7	39.7
Di Mauro <i>et al</i> (2023)	1,069	35 (HbSS) 45 (HbSC)	UK	41.5 yrs (HbSS) 52.5 (HbSC)	NR
Brousse <i>et al</i> (2023)	20,412 (all) 4,270 (severe)	24.0 (all) 21.8 (severe)	France	58 yrs**	44**
Jiao <i>et al</i> (2023)	94,616	26.6	US	52.6 yrs	NR

NR, not reported.

*severe SCD definitions differ by paper, and are summarised in the below text.

**median values.

The EAG believes that these rates are obtained from studies with a more severe population than the one in the model decision problem. Specifically with reference to the absence of data for older people, the company's argument that there are no data because there are no deaths is disproven by Jiao et al, who include Medicare datasets, which include people with SCD in the age groups with mean age equal to 70 and 50. The absence of records for older people with SCD is not because there are none, but because the databases where these cases are recorded have not been included.

However, given that the company has accepted the Committee's preferred model structure, using mortality rates selected by the company, there are no material implications regarding mortality rates.

The EAG has added specific study details to provide the evidence regarding 50 years being the lower bound for a reasonably justified life expectancy for this decision problem.

Lead author (year)	Data sources	Estimates	N in sample	Follow up	Number of VOCs / admissions - mean	Appraisal
Udeze <i>et al</i> (2023)	Vertex BOI study (UK HES and CPRD data)	age at death: 8-79; median (q1-q3): 41 (29-47)	1,117	4.69 years	5.84 per year	Includes the older and younger population (as detailed in complication rates assessment) not matched with decision problem, lacks predictive validity
Piel <i>et al</i> (2021)	HES APC dataset (UK) sickle cell crisis (ICD-10 Code D57.0) or SCD without crisis (ICD-10 Code D57.1)	39-47 years	1171 – crisis cohort	median 9.85 (interquartile range (IQR) 9.44–9.85)	number of admissions (mean, per year) 2009-2010 = 4.5 2011–2018 – 5.5	• NO definition of VOCs. Uses hospitalisations; reports ACSs separately, and priapism separately • largest age group in our cohort were the 2384 patients aged 0–9 years in 2008 (25.1% of the cohort)
Brousse <i>et al</i> (2023)	SNDS, Système national des données de santé	43.5 (SD 21.0) (95% CI 40.9-46.1)	4270 (severe SCD)	Variable; median 7 years	VOC rates not given; VOC and ACS were the most frequent causes of hospitalization (Table 2), with a rate of 86.29 (95% CI: 85.75-86.83) and 12.90 (95% CI: 12.69-13.11) per 100 person years, Hospitalizations for VOC: 166.9 (95% CI: 165.4-168.4) per 100 person years Most severely affected: 2.9 (range, 1.4-6.4) hospitalizations per year	Includes 31% people younger and in excess of 13% older than decision problem age bands
Jiao <i>et al</i> (2023)	Medicare OASI (N= 4 475) Medicare DIB or ESRD (N = 4 153)		94,616	6 years (mean)	n/a	No VOC data

Lead author (year)	Data sources	Estimates	N in sample	Follow up	Number of VOCs / admissions - mean	Appraisal																
	Medicaid (N = 45 068) Dual eligibles (N = 40 920) Mean age at entry (y) 73.4 (7.5) 50.2 (13.5) 15.4 (14.9) 31.4 (21.2)	<table><thead><tr><th>Age</th><th>All</th></tr></thead><tbody><tr><td colspan="2">Total</td></tr><tr><td>Birth</td><td>52.6 (51.9-53.4)</td></tr><tr><td>18</td><td>35.4 (34.9-36.1)</td></tr><tr><td>35</td><td>24.1 (23.7-24.6)</td></tr><tr><td>45</td><td>19.6 (19.2-20.0)</td></tr><tr><td>65</td><td>13.2 (13.0-13.5)</td></tr><tr><td>85</td><td>5.4 (5.1-5.7)</td></tr></tbody></table>	Age	All	Total		Birth	52.6 (51.9-53.4)	18	35.4 (34.9-36.1)	35	24.1 (23.7-24.6)	45	19.6 (19.2-20.0)	65	13.2 (13.0-13.5)	85	5.4 (5.1-5.7)				
Age	All																					
Total																						
Birth	52.6 (51.9-53.4)																					
18	35.4 (34.9-36.1)																					
35	24.1 (23.7-24.6)																					
45	19.6 (19.2-20.0)																					
65	13.2 (13.0-13.5)																					
85	5.4 (5.1-5.7)																					
DESAI	Merative MarketScan Commercial; Medicare Supplemental; Multi-State Medicaid Databases	15% - 27% for decision problem age bands; Max follow-up: 13 years	2310 (people with $\pm$ 2 VOCs/year		4.7-13.14 ~(depending on age, included~: 13 to 35 years old) 3.19 hospitalisations per year 5.72 VOCs per year	Definition of VOC included ACS All patients with ≥ 1 admission: 2.7 admissions per year Subgroup of people with ≥ 2 VOCs per year = mean number of admissions per year = 3.6																

Issue 4: The company base case complication rates from Udeze et al 2023 should be replaced by the Udeze 2023 rates for the subgroup aged 12-35, in line with the population of the decision problem.

The EAG's solution should be intended as a convenience solution. These complication rates remain a source of uncertainty in the model because this subgroup may still be more severe than people in the CLIMB SCD-121 study. As a result, the burden of disease averted with exa-cel may be overestimated. Complication data from Udeze et al. should be matched by age and average VOC rates at baseline, to the CLIMB SCD-121 study population and to the model population.

Detailed explanation and evidence base

The Vertex burden of disease study (Udeze et al 2023) is an unpublished observational study using administrative data from primary care records (Clinical Research Practice Database [CPRD]) linked with secondary care data sources (Hospital Episode Statistics [HES]) in England. The study population has no age limitations. The data were analysed separately for a cohort of people defined as 'severe SCD population (Udeze, 2023: p.22), i.e., cases that met the following definition:

- Patients must have a primary or secondary diagnosis of SCD on or prior to index date.
- Patients must have ≥ 2 VOCs* per year in at least 2 consecutive years
- Patients must be registered within CPRD at index date.
- Patients must be eligible for HES linkage.
- Patients must have a minimum of 1 year follow-up data available from their index date.

VOCs were defined as any of the following:

- Record of primary or secondary diagnosis of SCD with crisis
- Record of primary or secondary diagnosis of priapism

Record of acute chest syndrome [text highlighted by the EAG]

The company revised their base-case to include complication rates for the subset of this population, severe SCD, n=1,117, that has more than 2 baseline annualised VOC rates in this subgroup. The data are reported in Figure 3.

Acute complications	Company complication rates - base case, all cohort (n=1,117)
Acute chest syndrome	0.720
Acute kidney injury/infarction	0.200
Pulmonary embolism	0.080
Stroke	0.010
Leg Ulcers	0.390
Gallstones	0.410
Infectious and parasitic diseases	0.250

Chronic complications	Company complication rates - base case, all cohort (n=1,117)
Chronic kidney disease	0.770
Pulmonary hypertension	1.320
Avascular necrosis	3.500
Retinopathy	2.450
Heart failure	1.120
Neurocognitive impairment	0.780
Chronic liver disease	1.040

Figure 3: Acute and chronic complication rates (obtained from the company's model)

First, data from Udeze, selected based on the baseline number of VOCs, pertain to a population with double the rate of baseline VOCs compared with the decision problem population.

This subgroup includes two groups of age not included in the decision problem population of this appraisal, 219 children below 12 years old (19.6%) and 249 people older than 36 years of age (22.3%). Whilst in their response (a public document) the company provides only a generic description of the cohort, the company added breakdowns of baseline and complication rates for the cohort by age band in one table reported in the model (not in the public domain).

The table of data used by the company (≥ 2 VOCs, n=696 column 6 in Figure 4) shows that:

- Data for age bands not included in this decision problem are a driver of complication rates used by the company, specifically, higher rates of complications for people >36 years.

- The group with ≥ 2 VOCs at baseline overall has double the average baseline rate of VOCs [8.61 annualised rate] than people in the CLIMB SCD-121 study [4.2 annualised rate], therefore this subgroup is potentially much more severe than the population from which model efficacy data is derived.

Albeit with no restriction to the number of VOCs at baseline, the model relevant age group [12-35 years] still has an average annualised rate of 6.37 VOCs at baseline, higher than that in CLIMB SCD-121.

There is no information regarding the rate of VOCs with hospitalisations in the Udeze study.

UK BOI Study

Table 5. Acute Complications by Subgroup

Complication, Mean Rate PPPY (SD)	Age Subgroups			VOC Subgroups		Transfusion Subgroups	
	0–11 Years (n = 219)*	12–35 Years (n = 649)	≥ 36 Years (n = 249)*	<2 VOCs (n = 421)	≥ 2 VOCs (n = 696)	Baseline Transfusion (n = 303)	No Baseline Transfusion (n = 814)
Acute renal failure	-	0.06 (0.41)	0.43 (1.81)	0.03 (0.12)	0.20 (1.16)	0.23 (0.83)	0.10 (0.95)
Cerebral vasculopathy ^b	0.02 (0.13)	0.01 (0.07)	-	0.01 (0.08)	0.01 (0.12)	0.01 (0.10)	0.01 (0.11)
Gallstones	0.09 (0.38)	0.33 (1.87)	0.38 (2.07)	0.10 (0.44)	0.41 (2.16)	0.59 (3.09)	0.18 (0.73)
Infections (any)	0.11 (0.45)	0.21 (1.19)	0.26 (1.18)	0.12 (1.22)	0.25 (0.99)	0.24 (1.14)	0.19 (1.06)
Leg ulcers	0	0.23 (1.79)	0.58 (3.63)	0.05 (0.49)	0.39 (2.75)	0.35 (1.51)	0.23 (2.40)
Pulmonary embolism	0	0.03 (0.20)	0.18 (0.82)	0.02 (0.19)	0.08 (0.51)	0.08 (0.62)	0.05 (0.31)
Strokes ^b	-	0.01 (0.09)	0.03 (0.16)	0.01 (0.11)	0.01 (0.12)	0.02 (0.11)	0.01 (0.12)
VOCs (any)	2.36 (1.92)	6.37 (13.05)	7.52 (15.53)	1.27 (0.63)	8.61 (15.18)	7.22 (14.66)	5.32 (11.57)
Acute pain crises	1.90 (1.62)	5.66 (12.52)	6.82 (15.07)	1.05 (0.52)	7.68 (14.69)	6.40 (14.11)	4.73 (11.14)
Priapism	-	0.18 (1.14)	0.13 (0.85)	0.01 (0.08)	0.21 (1.21)	0.23 (1.19)	0.10 (0.86)
Acute chest syndrome	0.46 (0.60)	0.53 (0.91)	0.56 (1.16)	0.21 (0.30)	0.72 (1.10)	0.60 (1.21)	0.50 (0.79)

PPPY, per patient per year; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.

*In all reporting, patient numbers <5 were masked (i.e., reported as "-") to protect patient confidentiality, and secondary masking was applied where required to avoid back-calculation; *The maximum number of strokes/cerebral vasculopathy claims per person was assumed to be 3 based on clinician feedback.

Figure 4: Acute complications by subgroup

Based on the considerations above, the EAG believes that complication rates in the Company's base case may be from a more severe population than that in the decision problem population and that in the CLIMB SCD-121 study.

The company did not make any attempt to match the complication population with the CLIMB SCD-121 population. The crude rates in this age subgroup are somewhat closer, yet still 50% higher, than those in the CLIMB SCD-121 study. Whilst they are more in line with the decision problem population, they remain a source of overestimation of the ICER.

2.1.1.1 Detailed explanation and evidence base

Data in the Udeze study may lack comparability to the CLIMB SCD-121 data with respect to baseline comorbidities.

The model population included in the company's base-case assumes no comorbidity at baseline, other than 14% retinopathy and 3% neurocognitive impairment.

The Udeze report provides baseline data for the sample of n=1,117. These data are reported in Figure 5. First, the Udeze study is affected by a problem in classification of baseline complications, lacking clarity regarding how these numbers were derived: the definition of study variables states that, *"In HES APC, primary diagnosis (reason for admission) and secondary diagnoses were used to report health conditions that need secondary care."* [Udeze, 2023, Section 7.4.2 page 27]

In data tabulations however the expression "any record" as opposed to "no record" is used; it is unclear whether 'any record' means that there is a mention of comorbidity for each case, or whether it refers to data missingness.

If the expression refers to mentions of comorbidity, then the burden of comorbidity in the Udeze sample is far higher than baseline comorbidities in the model (that are derived from CLIMB SCD-121). Alternatively, the expression may mean that there is no information regarding history of comorbidities at baseline.

Acute complications	Baseline rates used in the model	Complications at baseline, "Any record" frequencies from Udeze 2023
Acute chest syndrome	0%	44%
Acute kidney injury/infarction	0%	4%
Pulmonary embolism	0%	2%
Stroke	0%	1%
Leg Ulcers	0%	5%
Gallstones	0%	22%
Infectious and parasitic diseases	0%	8%

Chronic complications	Baseline rates used in the model	Complications at baseline, "Any record" frequencies from Udeze 2023
Chronic kidney disease	0%	3%
Pulmonary hypertension	0%	?
Avascular necrosis	0%	15%
Retinopathy	14%	11%
Heart failure	0%	?
Neurocognitive impairment	3%	2%
Chronic liver disease	0%	4%

Figure 5: From Udeze, Table 6 Baseline demographics characteristics for the severe SCD cohort and for the matched general population, page 44

The entire table of comorbidity at baseline is reproduced in Appendix 0.

Further, the definition and measurement of event rates in the Udeze et al study is reported in the text below, directly quoted from the Udeze study report (Udeze 2023, page 32).

- For treatment use, HCRU and acute complications [...] each patient can experience the event of interest multiple times. [...] the number of events per patient per year (PPPY) was calculated as the total number of events per patient during follow-up, divided by the total number of years observed from index date until censor date. [...] specifically for strokes and cerebral vasculopathy [based on medical advice], an upper limit of 3 events per patient was applied. *Prevalence for acute complications was calculated based on the follow-up data only, by dividing the number of patients with the acute complication during follow up by the total number of patients.*
- For mortality and chronic complications [...] each patient could only experience the event of interest once. The rate was the total number of patients with the event, divided by the total number of person-years observed *for all patients* from their index date until the date of the event of interest (or censor date in case of no event), inclusive of both dates. *Rates were reported as events per 100 person-years. [...] patients were not included in the rate calculation if they had a record of the event of interest at baseline. Prevalence (for chronic complications) was calculated as the total number of patients with the relevant event at either baseline or during follow-up, divided by the total number of patients in the cohort.*

This approach provides the rate of one particular chronic complication event in people who did not have such event at baseline. As such, the rate represents new cases of one particular chronic state.

The approach however is still likely to overestimate rates for chronic complications because, for each complication, rates include events for people who reported another complication at baseline, therefore at higher risk than the population in the decision problem and CLIMB SCD-121. Similar limitations apply to the definition of acute complication rates.

2.1.2 Literature complication rates

The company provides a co-base-case using literature-derived data for acute and chronic complications (see Figure 6). Literature studies are far from providing accurate data to allow the EAG to identify best matching rates to the decision population.

Overall, these rates from the literature are lower than those reported in the Vertex UK BOI study, despite similar inclusion criteria used for restricting results to severe populations.

Risk of SCD related complications (Severe patients)

Acute complications	UK BOI Value	Literature Value	Source
Acute chest syndrome	6.000%	2.107%	Brousse 2023
Acute kidney injury/infarction	1.667%	0.117%	Yeruva 2016
Pulmonary embolism	0.667%	0.173%	Shah 2019
Stroke	0.083%	0.084%	Brousse 2023
Leg Ulcers	3.250%	0.831%	Singh 2016
Gallstones	3.417%	0.382%	Brousse 2023
Infectious and parasitic diseases	2.083%	0.224%	Brousse 2023

Chronic complications	UK BOI	Literature Value	Source
Chronic kidney disease	0.064%	0.153%	Brousse 2023
Pulmonary hypertension	0.110%	0.096%	Brousse 2023
Avascular necrosis	0.291%	0.321%	Brousse 2023
Retinopathy	0.204%	0.042%	American Academy of Ophthalmology
Heart failure	0.093%	0.317%	Brousse 2023
Neurocognitive impairment	0.065%	0.171%	Cahill 2019
Chronic liver disease	0.087%	0.087%	UK BOI Study
Post Stroke	-	0.130%	Brousse 2023

Figure 6: Literature derived information for acute and chronic complications

The company took the majority of complication rates from Brousse. This study reports the number of VOCs in the more severe population, 166.9 per 100-person-years, equivalent to 1.7 per year, based on number of hospitalisations. This number is more in line with the decision population of this appraisal. The study by Brousse et al also does not provide a rates breakdown by age for most outcomes; however, the study does provide age subgroups for some outcomes; it is unclear whether the company has adjusted the relevant rates in the study to match the age restrictions in the decision problem in this appraisal.

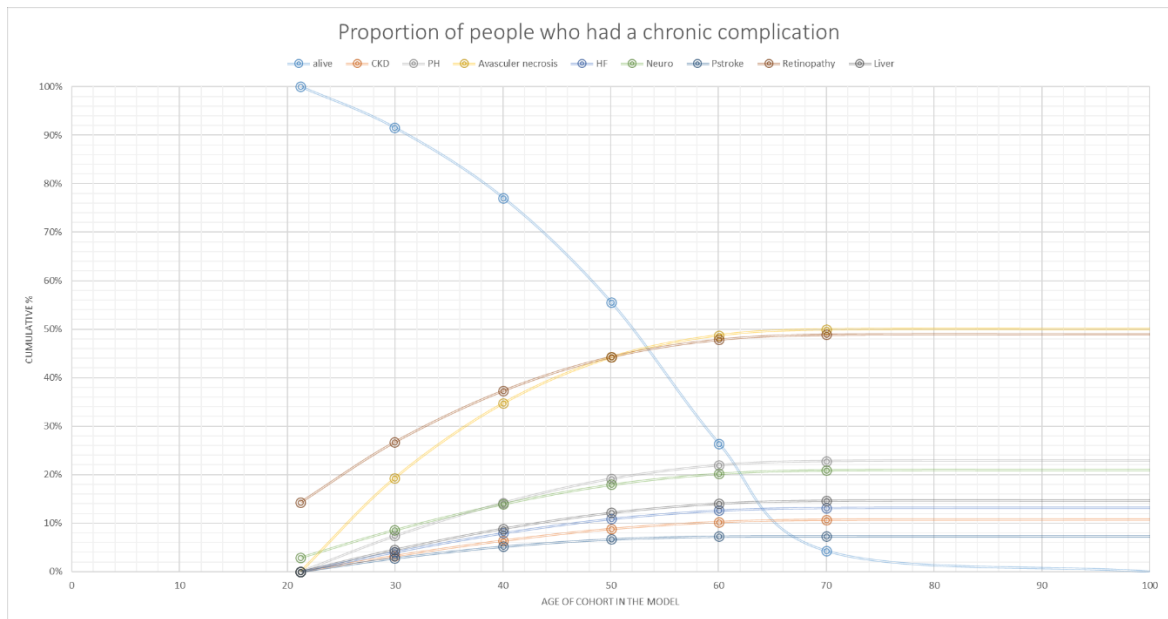


Figure 7: Model complication rates (cumulative), UK company's BOI study (Udeze et al., 2023), age 12-35

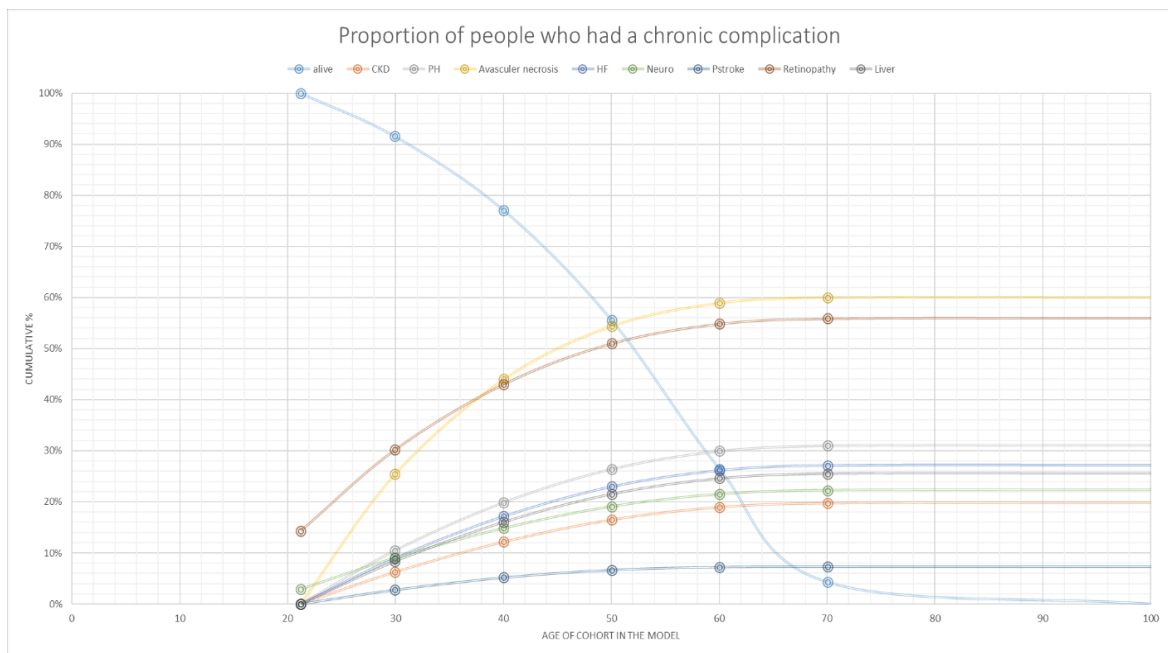


Figure 8: Model complication rates (cumulative), UK company's BOI study (Udeze et al., 2023), all sample (company's base-case)

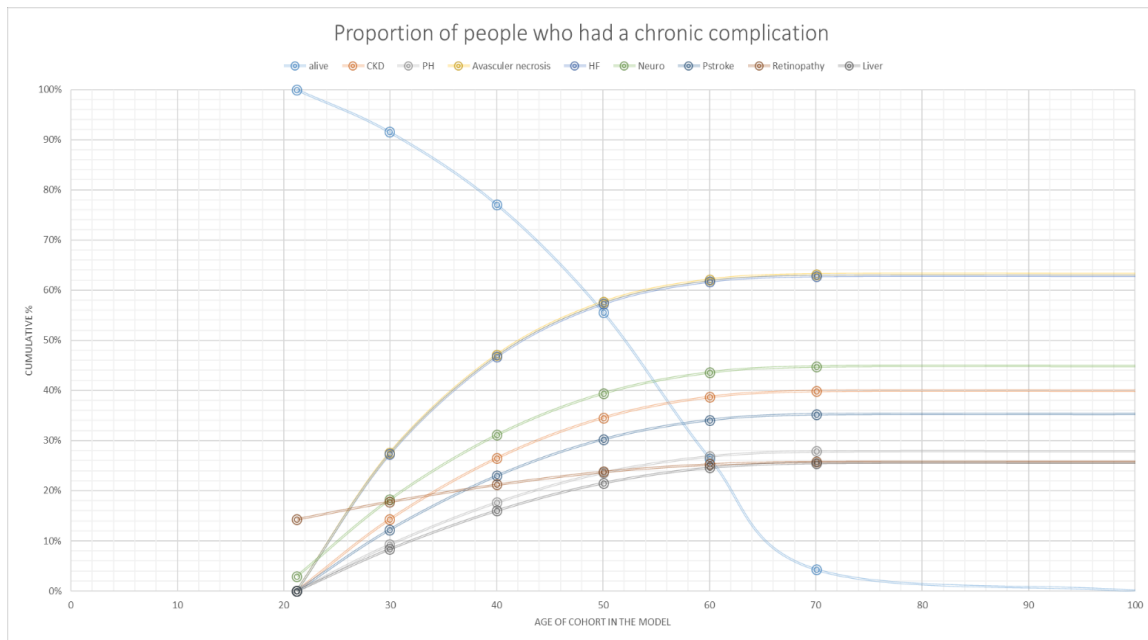


Figure 9: Model complication rates (cumulative), literature (company's base-case)

ID4016 – Update to proposed source for complications in the model

Background and implication of EAG proposed assumption on complication rates

During the second committee meeting (ACM2), there was a discussion on the appropriate source of complications rates for the standard of care arm in the model. The EAG, in its response to the Vertex ACD response, expressed a preference for a sub-group of patients reported in the Udeze et al. (2023) study, which limited complications rates to those experienced by the 12-35 age range, on the basis that it aligned with the decision problem.

Vertex disagreed with this at ACM2 and suggested that using the entire severe cohort from Udeze et al. (2023) was more appropriate, on the basis that capturing complications across all ages was important to better represent the disease progression of severe sickle cell disease (SCD) in the model. Vertex made the case that using all ages (from 2 years of age) from the severe SCD cohort from Udeze et al. (2023) was generalisable to the UK severe SCD population, on the basis that it captures the natural progression of the disease and the increase in the risk of complications as patients age.

Patients in the CLIMB SCD-121 clinical trial included those in the 12-35 age group, and the license indication for exa-cel includes *all* patients 12 years and older. For modelling purposes, and in line with the decision problem, the aim is to look at the entirety of the disease progression of patients with severe SCD. Patients in the model have a starting age of 22 years (taken from the baseline characteristics reported in the CLIMB SCD-121 clinical trial) and their disease progression and onset of complications is modelled until death (lifetime horizon).

The literature shows clear evidence for reduced life expectancy, severely impaired quality of life and accumulation of complications and co-morbidities with age. At ACM2 the clinical experts commented that complications beyond the clinical trial upper age limit are relevant to lifelong disease-related morbidity; they further expressed a strong preference for using higher literature estimates of complications based on their clinical experience and the often underestimation of complication rates they see documented in the literature. This was supported by online consultation comments submitted by patients, carers and clinicians who gave evidence on the progressive nature of the condition.

Vertex wrote to NICE following ACM2 to further clarify that applying the complication rates of a younger group of patients (12-35 years old) in the model, to all patients 12 years and over significantly underestimates the severity of SCD over a patient's entire lifetime. This is a particularly inaccurate reflection of the disease progression when the estimated median age of death for patients on standard of care (SoC) in the model is 52 years of age.

This submission provides further analysis addressing both the committee's and EAG's request for a source for complications rates that is aligned with the decision problem, and which also does not artificially limit the complications accrued by patients over their lifetime in the model. **All**

other committee assumptions from ACM2 are kept constant, and the only amendment in the model is the SoC complications rates.

Summary of scenarios

Table 1: Summary of scenarios

Decision Problem: Patients with severe SCD aged 12 years and above (aligned with exa-cel label)			
	Source for complications rates	EAG comment	Vertex comment
Vertex base case following ACD response	Udeze et al. (2023) severe SCD cohort aged 2+	Does not match the decision problem (EAG critique of Vertex's ACD response – section 1.8)	Appropriate on the basis it reflects a generalisable UK population from age of 2 years and older.
EAG preference	Udeze et al. (2023) limited to 12-35 cohort	Updated to match the decision problem (EAG critique of Vertex's ACD response – section 1.8)	Does not reflect the decision problem. EAG may be confused with the exa-cel trial inclusion criteria (which limited patient selection to 12-35 years of age) vs. the marketing authorisation and population in the scope, which includes <i>all</i> patients 12 years and over. Indeed, patients aged over 35 are eligible for exa-cel, if they meet the label criteria. The rate of complications, however, is applied to patients on SoC, while the age reported in the baseline characteristics of the exa-cel trial is relevant to inform the start age in the model, the rate of complications thereafter needs to reflect disease progression and the fact that patients on SoC continue to show onset of complications at a growing rate until they die.
Committee preference	Udeze et al. (2023) limited to 12-35 cohort	N/A	See above.
Vertex updated base case (new; post ACM2)	Udeze et al. (2023) limited to the <u>12+ population</u>	N/A	This new scenario not only matches the decision-problem (patients aged 12 and over with severe SCD), but it is a more accurate reflection of the lifelong disease-related morbidity that severe SCD patients endure. From the modelling perspective, it captures precisely the modelled age during the lifetime horizon, from model start to the end of the patient's journey. Lastly, it is evidence-based on the most recent UK study of severe SCD patients. (Udeze et al., 2023. A manuscript has

			been conditionally accepted for publication in a peer-reviewed journal, subject to minor amendments.)

Impact in the model

If one implements complications rates as the EAG has in the 12-35 scenario, the rates of complications don't change over the lifetime horizon in the model – and the impact of using the average rates from the 12-35 age group over the lifetime horizon is artificially misconstruing disease progression, with an overall underestimation of disease severity.

- Hence, when patients turn 35+ years in the model, as the time horizon elapses, they are developing complications at a much lower rate than they would otherwise develop as seen in the evidence, hence their overall QoL at the end of the time horizon (median age of survival 52 years of age) is heavily underestimated; as well as the cost of treating these patients.
- As seen in Udeze, rates of complications are higher in older patients as their disease progresses. E.g. Complication rates in the paediatric population are lower than in adulthood.

Vertex's ACM2 base case included risks of complications from all ages (including paediatric patients) in a conservative fashion, this is due to the fact that Udeze only presents ALL, or age subgroups but no 12+ group.

In response to the committee's concerns during ACM2, we have derived specific risks of complications for the 12+ population from Udeze (using a weighted approach) and as expected, the outcomes show negligible impact when compared to our initial approach.

EAG implementation of 12-35 cohort in the model

Vertex has identified some misalignment between the complications reported in the literature and the EAG's update of the model to reflect the 12-35 population. The implementation of the 12-35 cohort by the EAG is uncertain, as the EAG has hardcoded the values without explanation or formulae, but it appears the EAG is making additional assumptions on the risk values for developing complications. For example, from the data table in the model, that is copied from the Udeze et al study, 0% of patients 12-35 had heart failure (which we know is a significant complication that patients with severe SCD experience later in life). However, the EAG's version of the model states the rate for this complication is greater than 0%, but does not reference this figure. Of course, the risk of developing heart failure is an important consideration, and the value should not be 0% for the whole SoC arm - and the fact this is reported in the 12-35 population is evidence of the fact that using this age restricted band leads to inaccurate model results.

We believe deriving the risks of complications from a uniform cohort (Udeze) is the preferred option to address uncertainty instead of mixing derivation of risk from multiple sources that are based on different cohort characteristics.

This issue and other underestimated complications are addressed in the updated Vertex scenario below. All other committee preferred and optimistic assumptions are kept constant - the only update is the complications rates which are all derived from the Udeze.

Table 2: Updated complication rates and per cycle model risk of complications based on data from Udeze et al (2023) ages 12+ cohort

Complications	Annual Rate	Per Month Risk (Input)
Acute complications		
Acute chest syndrome (not included in the model as per committee's preference)	0.538	4.486%
Acute kidney infarction	0.163	1.355%
Pulmonary embolism	0.072	0.597%
Stroke	0.016	0.130%
Leg ulcers	0.327	2.725%
Gallstones	0.344	2.866%
Acute infections	0.224	1.866%
Chronic complications		
Chronic kidney disease	0.731	0.061%
Pulmonary hypertension	1.346	0.112%
Avascular necrosis	3.346	0.278%
Retinopathy	2.555	0.213%
Heart failure	1.036	0.086%
Neurocognitive impairment	0.859	0.072%
Liver complications	0.928	0.077%
Post-stroke	N/A	Calculation

Updated ICERs with complication rates for the 12+ population of severe SCD (aligned with decision problem)

Table 3: Updated ICERs

Scenario	Source/Details	Severity Modifier (3.5% disc.)	Severity Weighted ICER	Unweighted ICER
Scenario 1	Post-ACM2 committee preferred base case but using complication rates of <u>all age groups</u> from Udeze et al and a <u>1.5% discount rate</u> on costs and outcomes	1.2		
Scenario 2	Post-ACM2 committee preferred base case but using complication rates of <u>all age groups</u> from Udeze et al and a <u>3.5% discount rate</u> on costs and outcomes	1.2		
Scenario 3	Post-ACM2 committee preferred base case but using complication rates of <u>12+ age groups</u> from Udeze et al and a <u>1.5% discount rate</u> on costs and outcomes	1.2		
Scenario 4	Post-ACM2 committee preferred base case but using complication	1.2		

	rates of <u>12+ age groups</u> from Udeze et al and a <u>3.5% discount rate</u> on costs and outcomes			

Calculation of complication rates

The acute complication rates were calculated by taking a weighted average (using overall patient counts in each age group) of each age group's reported mean rate. For example, there were 898 patients in the combined cohort – 649 in the 12-35 age group and 249 in the 36+ age group. Thus, to calculate the weighted average rate for pulmonary embolism, the reported rate for patients aged 12-35 (0.003) was multiplied by 649/898 and the reported rate for patients 36+ (0.18) was multiplied by 249/898. These numbers were then added together to produce the weighted average annual acute complication rate. Lastly, this value is converted into a monthly rate in the model, in column D of the Raw_complication_risks sheet.

The risks for developing chronic complications were calculated by combining the person-years and event counts for both age groups and calculating the new rate by summing the total events by total patient-years; which is then converted into a risk in the model. For example, for pulmonary hypertension, the number of events in both cohorts (25 in ages 36+ and 25 in ages 12-35) are summed, as are the person years (977.93 and 2737.47, respectively). The summed number of events (50) is then divided by the summed person-years (3715.4) to calculate a rate per patient-year, which is multiplied by 100 to produce a rate per 100 patient-years, which is the reported outcome from the study. This is converted into a monthly risk in the model, in column D of the Raw_complication_risks sheet.

Title: Exagamglogene autotemcel for treating sickle cell disease- EAG response to company draft guidance form and additional work post ACM1

Produced by Warwick Evidence

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Rider on responsibility for report

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Contributions of authors

Jo Parsons (Assistant Professor), Martin Connock (Honorary Senior Research Fellow), Xavier Armoiry (Honorary Senior Research Fellow and Professor) and Amy Grove (Professor) reviewed and critiqued the clinical effectiveness evidence. Martin Connock reviewed and critiqued the statistics and undertook any additional statistical analyses. Xavier Armoiry reviewed and critiqued the mixed treatment comparisons. Naila Dracup (Information Specialist) critiqued the company's searches and undertook additional searches. Emanuela Castelnovo reviewed and critiqued the cost-effectiveness evidence and undertook additional economic analyses. Baba Inusa (Paediatric Haematologist) and Elizabeth Rhodes provided expert clinical advice. Peter Auguste (Assistant Professor) reviewed the cost-effectiveness evidence and co-ordinated the project and the report.

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Figures that are CIC have been bordered with blue. [REDACTED] is highlighted in pink.

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Content of this report

In this document, we provide results of the analyses requested by NICE on 9 May 2024 following ACM2. The analyses comprise using the committee's preferred assumptions, optimistic and pessimistic assumptions.

NICE technical team note: this set of results is based on a correction to the ‘gallstones’ complication rate in the model

Table 1: Committee preferred assumptions

VOC definition	All-events VOC rate (4.2 per year)
Complication source	Udeze (2023) 12-35 group
ACS	Excluded
Treatment withdrawals	Exclude exa-cel cost, but include outcomes
Utility (SoC)	0.81
Utility (exa-cel)	0.88
Discount rate	3.5%
Severity	To be determined by results, but present 1 and 1.2 for completeness

Table 2: Deterministic results based on committee’s preferred assumptions

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	██████	████	11.00						
Exa-cel	██████	████	17.79	██████	████	6.789	8.147	██████	██████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

SEVERITY MODIFIER = 1

Remaining QALYS

without the disease:	22.53
with the disease:	11.00
absolute shortfall:	11.53
proportional shortfall:	51.17%
QALY weight ⓘ:	x 1

Table 3: Optimistic scenario of committee's assumptions

VOC definition	All-events VOC rate (4.2 per year)
Complication source	Udeze (2023) 12-35 group
ACS	Excluded
Treatment withdrawals	Exclude exa-cel cost, but include outcomes
Utility (SoC)	0.81
Utility (exa-cel)	0.88
Discount rate	1.5%
Severity	To be determined by results, but present 1 and 1.2 for completeness

Table 4: Deterministic results based on committee's optimistic assumptions

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	██████	████	14.05	-	-	-	-	-	-
Exa-cel	██████	████	26.38	██████	████	12.324	14.789	██████	██████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

SEVERITY MODIFIER = 1

Remaining QALYS

without the disease:

22.53

with the disease:

14.11

absolute shortfall:

8.42

proportional shortfall:

37.36%

QALY weight [Ⓢ]:

x 1

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Table 5: Pessimistic scenario of committee's assumptions

VOC definition	All-events VOC rate (4.2 per year)
Complication source	Udeze (2023) 12-35 group
ACS	Excluded
Treatment withdrawals	Include exa-cel cost and outcomes
Utility (SoC)	0.81
Utility (exa-cel)	0.88
Discount rate	3.5%
Severity	To be determined by results, but present 1 and 1.2 for completeness

Table 6: Deterministic results based on committee's pessimistic assumptions

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALY with modifier	ICER (£/QALY)	ICER with severity modifier
Standard of care	██████	████	11.00	-	-	-	-	-	-
Exa-cel	██████	████	17.79	██████	████	6.789	8.147	██████	██████
ICER, incremental cost-effectiveness ratio; LYG, Life-years gained; QALY, quality adjusted life-years									

SEVERITY MODIFIER = 1

Remaining QALYS

without the disease:

22.53

with the disease:

11.05

absolute shortfall:

11.48

proportional shortfall:

50.95%

QALY weight ⁹:

x 1

- *'The efficacy in the company's model is based not on the ITT population (all of those who started the treatment pathway), but only those who go on to have exa-cel i.e., does not include 20% withdrawn and begins at the point of exa-cel being infused. This is our interpretation, but we would just like to double check.'*

We confirm this. All the exa-cel cohort is treated with exa-cel and has 96.6% efficacy of exa-cel (to account for the proportion in CLIMB SCD-121 that fail the primary endpoint).

Approximately 18.9% dropouts (■■% who fail apheresis) and ■■% who successfully pass apheresis but do not receive exa-cel are not part of the cohort, a cost 'uplift' is added to total cost of care to account for the cost of apheresis (approximately £43k multiplied by 19%, £8,990) although it is unclear how this is done because there is no formula in the model that does this.

- *'The cost of a VOC using the 'all-event, 4.2' rate, uses the appropriate costings. I think we heard in committee that 2.6 of these were inpatient hospitalisations, so, if possible, committee would like this proportion costs (the 2.6) as inpatient hospitalisations and the remaining proportion costed as day cases.'*

The company's base case uses the **National Schedule of NHS Cost (SA36A-C, Sickle-Cell Anaemia with Crisis)**.

The value applied in the model is £1,567 (unclear why not £1,587, probably a typo) (Table below, obtained from

https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://www.england.nhs.uk/wp-content/uploads/2020/11/22-23NT_Annex-DtA-National-tariff-workbook.xlsx&ved=2ahUKEwj7zvHZu4CGAxVMgf0HHfTeCJ4QFnoECAEQAAQ&usg=AOvVaw0hAp4RC-SZqJ1NFJ9kMEsg~)

The company's value is not the weighted average of all costed cases but the cost of cases with the highest complications score. No additional details provided.

The utility value for VOCs is derived from the 'NICE Crizanlizumab STA [ID1406] and uses a disutility of VOC is -0.46 per event for a duration of 12 days. Because crizanlizumab has had its marketing authorisation withdrawn, no documents regarding this appraisal available on the NICE website. The EAG cannot assess the utility value so identified.

HRG Code	HRG Name	Outpatient procedure (£)	Combined day case /ordinary elective spell (£)	Ordinary elective long stay trim point (days)	Non-elective spell (£)	Non-elective long stay trim point (days)	Per day long stay payment (for days exceeding trim point) (£)	Reduced short stay emergency adjustment applicable?	% applied in calculation of reduced short stay emergency adjustment	Reduced short stay emergency adjustment (£)
SA36A	Sickle-Cell Anaemia with Crisis, with CC Score 6+	-	1,587	13	4,780	20	342	YES	20.0%	956
SA36B	Sickle-Cell Anaemia with Crisis, with CC Score 2-5	-	737	5	2,734	13	342	YES	45.0%	1,230
SA36C	Sickle-Cell Anaemia with Crisis, with CC Score 0-1	-	534	5	1,704	8	342	YES	65.0%	1,108

Title: Exagamglogene autotemcel for treating sickle cell disease- Further analysis and critique

Produced by Warwick Evidence

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Rider on responsibility for report

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In this document, we provide an EAG viewpoint on:

- The new subgroup analysis of Udeze 12+, that it was implemented correctly
- The appropriateness of this source vs Udeze full, 12-35, or literature. Please also provide a view on the EAG's preference (if any). For example. if Udeze 12+ or Udeze 12-35 is preferred over Brousse et al severe population - include comments on whether implementation of Brousse et al complications is correct

During ACM2, the Committee preferred to use SCD complication rates for the subgroup 12-35 years of age at study entry. This is because the model population, reflecting the CLIMB SCD-121 trial, is restricted to people between 12 and 35 years of age, and because clinical opinion heard during the meeting (as well as during ACM1) suggested that exa-cel would be limited to people in that age band, with no or little history of complications.

The company did not accept this choice based on two arguments:

1. The marketing authorisation for exa-cel is not restricted by age.
2. The model covers the lifetime horizon.

The company proceeded to recalculate complication rates from the Vertex BoD study using the entire sample, including people aged above 35 years.

Complication rates for the two groups of age were combined as a weighted average, using weights proportional to the number of people in the respective age groups in the BoD study and generated corresponding ICERs.

First, whilst the license is unrestricted, the CLIMB SCD-121 data are restricted to age at entry ≤ 35 ; there are no data in the submission to support the case for reimbursement in people older than 35.

With regards to the claim that complication rates could be modelled as age-dependent, the EAG agrees that such approach is reasonable (in agreement with what is known about SCD), however, the data provided by the company is not fit for purpose to proceed because the company's implementation reflects several methodological misconceptions; the application of the revised complication rates increase biases and uncertainties in the model

rather than reducing them. The approach is affected by both misalignment in scope and several methodological errors.

Specifically, the following methodological issues apply:

1. The weights applied to complication rates should reflect the composition of the model population, in turn, reflecting the composition of CLIMB SCD-121. Specifically, the distribution of age in CLIMB SCD-121 and that in the Vertex BoD study are unmatched; rates applied to the model population are taken from a population (BoD) with a different age distribution. As age is a predictor of complication rates, the rates applied in the model are biased.
2. The age distribution at baseline (both in the model and the BoD study) is cross-sectional in nature, a 'photographic' description of the ages of individuals at the point of entry into the study, whilst complication data – and the application in the model – is longitudinal, meaning that complications occur over time as patients' age also increases. The BoD rates are calculated over the time after the index date; follow-up is on average 4.69 years [and up to 10 years].

This has two implications:

1. The company applied a constant rate in the model, recalculated for all ages 12+; this means that complication rates applied early in the model (starting at age 21 with max age =35 as per CLIMB SCD-121) are derived from an older population, including 28% of people older than 35, ranging up to 86 years old. As the model population is largest in early years, the bias may be potentially large.
2. The application of the 12-35 and 35+ sets of rates separately for early model ages and for later model ages is methodologically flawed. Because complication data are longitudinal, people aged 31 to 35 years at entry contribute complication data for the years of age 35-40; however, these rates are counted in the group 12-35; likewise, the 35+ age group includes complications for the years of age between 35+ and 41, overlapping, at least in part, the 12-35 years group. This means that applying two sets of rates in the model, using a cut-off (e.g., 35) will lead to double count of complications for the cycles corresponding to 35 to 40 of age.

This overlap is methodological (i.e., it depends on the way the company has framed the analysis) and it would occur regardless of the cut-off chosen. Alternatively, it could be argued, should rates of the group 12-35 be applied until – perhaps 40 years of age - or until

the effective recalculated mean age of that group at the end of follow-up. None of these solutions however are methodologically sound; the overlap between the two sets of complication rates cannot be resolved other than by a regression model that takes age at the time of the complication (not age at baseline) into account.

3. The cross-sectional nature of the index age in the Vertex BoD study is such that data from people 12-35 and 35+ cannot be equated to data derived from one unique population starting at 12 years old and followed-up longitudinally until older than 35 (max 86).

The two groups in the Vertex BoD are contemporary, with the older population showing a baseline VOC rate higher than that for the population in the model. The model does not include an estimation of VOCs over time - i.e., modelling SOC rates of VOCs over time [these data could be in the dataset, but no analysis has been made]. It is unknown whether the higher VOC rates are due to age or to some other uncontrollable factor, the direction of which cannot be assessed. For example, the older subgroup may be subject to survivor bias – i.e., people that are alive beyond 35 may be healthier than those alive at 20 years, because the sickest people may have been deceased before 35 years old. There may be differences due to temporal evolution in the healthcare practice: younger people may have been diagnosed earlier, may have received better healthcare and better treatment compared with that received by the older cohort, when they were younger. These factors could have driven VOC rates at baseline in either direction.

In general, it is not possible to exclude that younger and older people are 'different' groups for other reasons than just age and complication rates may be confounded. This means that stacking the two subgroups as if they were one longitudinal cohort, or mixing / weighting the two, may introduce uncontrollable biases and increase uncertainty in the model. Mixing and matching these two groups should be done in a way that controls for at least important differences between groups.

Finally, the application of higher rates for older people does require that the reverse logic also applies to younger people. The model starts at 21 years and rates applied to the early cycles are those including people potentially as old as 40-45 years, so complication rates in the model are overestimated in the early cycles. Should the model become one that tracks complication rates by age, then lower complication rates should be applied early as well.

We acknowledge that the extrapolation of 12-35 years rates to people older than 40-45 may conservatively underestimate complication rates. However, the model population is largest in early ages, and smallest at older ages. This means that the potential underestimation of complication rates at late cycles (smaller cohort, more discounted) in the model may be counterbalanced by the overestimation of complications in the early cycles (larger cohort, less discounted). Conversely, the 12+ entire population rates amplify overestimation in earlier cycles, and downplays underestimation in later cycles; therefore, the 12-35 population data remain preferable. The EAG advises against the application of two separate sets of complications before and after 35 years in the model because this approach is flawed.

The methodological impasse could be resolved analytically, estimating an equation for complication rates based on longitudinal data, controlling for age, VOC rates and other factors that may differ between BoD age groups – perhaps year of diagnosis if available, or prior treatments. Longitudinal patient-level analyses have been used for decades in the analyses of observational data and are a well-known statistical approach to handling data such as complication rates from the BoD. Such analyses, at the same time, would allow for more appropriate matching between BoD and model population characteristics.

Finally, a minor point regards the critique of the company to the EAG's method of incorporating complication rates. The EAG's modification was limited to changing the values for complications rates, using the values provided by the company as part of complication rates breakdowns by age groups at study index date (baseline). For anything else, the EAG used the company's functionality (i.e., derivation of probabilities from rates, propagation of rates via model formulae etc..) with no modification. It is unclear what the company considers inappropriate in this implementation.

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The submission still suffers from a major limitation in that no review of complication data/studies was conducted. The EAG's selection of the Brousse paper before ACM1 was to show that the model was highly reactive to complication rates assumed for SOC, contrary to the company's statements. Brousse was a plausible alternative - but not the only one - to the approach implemented by the company using data from Shah; Brousse had lower rates of complications, which suggested that the complication rates originally used in the model were certainly an overestimate, although by how much was a matter of selecting the best data source. Raw complication rates from Shah [reported in the paper but not considered by the company] were also tested by the EAG in the set of results submitted to ACM1 - however Shah suffered from a) limited range of complications and b) lack of definitions of the severe population. Therefore, Brousse was preferred in that instance.

For ACM2, the EAG expressed concerns - impacting all sources of complication data - that literature studies identified severe populations that were in fact more severe than the population in CLIMB SCD-121. The EAG argued that matching external populations to the model population was essential to avoid substantial overestimation of benefits from exa-cel. Baseline data that showed mismatching were a) age; b) VOCs rates and c) history of complications prior to receiving exa-cel.

The Vertex BOD study subgroup, at least, was matched to the model population [restricted to 12-35 despite unrestricted marketing authorisation] but the BOD population remained unmatched with respect to prior complications (much broader range and higher percentage) and definition of VOCs [whilst the model allows for non-hospitalisation VOCs, the BOD does not break down which VOCs were hospitalisations and which were not, in addition to having two definitions of VOCs - 'any VOCs' and 'SCD with crisis' whilst all other sources use hospitalisations therefore the assessment of comparability of data to CLIMB SCD-121 and matching should still be done based on hospitalisation VOCs.

The EAG's preference for the BOD study subgroup 12-35 relies on the fact that at least age is matched to that of the model starting cohort, i.e., at baseline [other sources do not specify

a restriction by age of the starting cohort] but overestimation of SOC complication rates may still be driven by higher VOC rates at baseline and higher burden of disease of the BOD cohort at baseline.

This approach is far from ideal - the EAG believes that overall, given the choice of sources operated by the company, matching could and should be conducted to align the severity of the model population to that of the model cohort [all sources allow matching, whether based on individual level patient data as the BOD or literature sources, matched on baseline averages].

**DSU OPINION ON THE COMPLICATIONS EVIDENCE AND
IMPACT ON COST EFFECTIVENESS FOR
THE SINGLE TECHNOLOGY APPRAISAL (ID 4016) OF
EXAGAMGLOGENE AUTOTEMCEL FOR TREATING
SICKLE CELL DISEASE**

REPORT BY THE DECISION SUPPORT UNIT

30th July 2024

Authors: Paul Tappenden¹, Allan Wailoo¹, Mon Mon Yee¹, Aline Navega Biz¹

¹ Sheffield Centre for Health and Related Research (SCHARR), University of Sheffield

ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) External Assessment Centre is based at the University of Sheffield with members at York, Bristol, Leicester and the London School of Hygiene and Tropical Medicine. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Centre for Health Technology Evaluation Programmes. Please see our website for further information www.nicedsu.org.uk.

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Conflicts of interest

Paul Tappenden and Aline Navega Biz are co-investigators on the ongoing NIHR-funded REDRESS trial of haploidentical stem cell transplantation (SCT) for people with severe sickle cell disease (NCT05392894). This transplantation approach does not reflect current practice and haploidentical SCT is not listed as a comparator in the final NICE scope for the appraisal of exagamglogene autotemcel. Allan Wailoo and Mon Mon Yee have no conflicts of interest to declare.

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1. BACKGROUND

The ongoing Single Technology Appraisal (STA) of exagamglogene autotemcel (exa-cel) for treating sickle cell disease (SCD) has identified that, after two Appraisal Committee meetings (ACMs), there remains uncertainty about the appropriate rates and implementation method for the inclusion of complications in the company's economic model. The cost-effectiveness results for exa-cel and the appropriate severity decision modifier may be sensitive to these values. The current version of the company's economic model includes seven acute complications and eight chronic complications.

Following ACM1, the company submitted evidence from an unpublished burden of illness study (Udeze *et al.*, 2023¹) based on an analysis of data obtained from the UK Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES). The overall population within this study includes a total of 1,117 patients aged 2 years (yrs) or over with a primary or secondary diagnosis of SCD who had at least two vaso-occlusive crises (VOCs) per year in the two consecutive years prior to the index date. Complication rates were calculated based on the number of events observed and the number of years of follow-up per patient from the index date to the event or censoring date. The analysis assumed that acute complications can recur, but chronic complications can occur only once. Within the full Udeze *et al.* study report, complication rates are presented according to broad age bands (0-11yrs, 12-35yrs and 36+yrs). The company and the External Assessment Group (EAG) have applied data on complication rates from Udeze *et al.*¹ in the economic model in different ways, based on different age subgroups. The selected complication rates mostly impact on the QALYs and costs for the standard of care (SoC) group. There are concerns that there are significant differences between the populations in Udeze *et al.*¹ and the CLIMB SCD-121 study² (which provides the main clinical evidence for exa-cel) and questions about which would be the appropriate population(s) from Udeze *et al.* for the economic modelling and the correct method to implement these complications.

The DSU understands that following ACM2, the Appraisal Committee has accepted that Udeze *et al.*¹ is an appropriate source of data to inform acute and chronic complication rates in the economic model. The EAG has stated a preference for the use of data on complication rates from the 12-35yrs subgroup of Udeze *et al.* at all ages in the economic model, as this reflects the age range specified in the inclusion criteria applied in CLIMB SCD-121.² Following ACM2, this approach was also included as part of the Appraisal Committee's preferred model assumptions. Following ACM2, the company submitted an additional document which provides new analyses which use complication rate data for the age 12+ subgroup of Udeze *et al.*,¹ based on the weighted mean of the rates in the 12-35yrs and 36+yrs subgroups.³ The company has argued that this new scenario matches the decision problem (patients aged 12+yrs with severe SCD) and that it is a more accurate reflection of the lifetime disease-related morbidity experienced by people with SCD.

In July 2024, NICE asked the DSU to undertake further work to address this issue. The DSU was asked to:

- Provide an overview of the different analyses presented from Udeze *et al.*¹ and an assessment of their suitability to the economic model
- Assess the method of implementing complication rates used in the economic model, determine the most appropriate method to apply complications rates in the economic model and implement it for all analyses.
- Consider any alternative analyses that may be preferred and, where these can be derived from the data already provided, implement these in the economic analysis.
- Demonstrate the impact on both cost effectiveness and, separately, the severity modifier calculations.
- Outline any additional analyses that may be undertaken using data from Udeze *et al.*¹ to inform the economic model.

This DSU report presents the results of a range of scenario analyses based on complication rate estimates reported by Udeze *et al.*¹ These analyses include the scenarios preferred by the EAG, the Appraisal Committee and the company following ACM2, as well as additional analyses undertaken by the DSU which attempt to reflect some degree of age-dependence in the modelled complication rates.

The report is structured as follows. Section 2 summarises the alternative approaches explored by the DSU and the DSU's scenario analyses undertaken using the company's economic model. Section 3 summarises the results of the DSU's scenario analyses. Section 4 provides a summary of the limitations of the available options for incorporating complication rates in the economic model and provides recommendations for decision-making.

2. DEFINITION OF THE PROBLEM AND APPROACHES EXPLORED BY THE DSU

2.1 Summary of approaches explored by the DSU

The DSU examined the full study report describing the methods and results of the Udeze *et al.* study¹ and an accompanying Microsoft Excel spreadsheet which provided summary complication rate estimates for patients aged 0-11yrs, 12-17yrs, 18-35yrs, 36+yrs, and 12-35yrs at their baseline assessment date (described as their 'index' age). The spreadsheet also provides calculations for the weighted mean complication rates in patients aged 12+yrs, based on the 12-35yrs and 36+yrs subgroups (the company's preferred analysis). The DSU also scrutinised the approach used to implement complication rates in the latest version of the company's executable model; the DSU did not identify any computation errors in this part of the model.

The DSU consulted the EAG to understand their views regarding the data reported by Udeze *et al.*¹ and to better understand what their preferred analysis of these data might entail. The EAG raised concerns that applying the 12+ subgroup data from Udeze *et al.* may overestimate SCD complication rates over the patient's lifetime, and they have stated that they would have preferred an analysis in which complications are predicted according to the age at which they occur. The EAG stated that they preferred the 12-35yrs subgroup because, in the absence of their proposed re-analysis of the Udeze *et al.* data, this was more conservative than other approaches proposed by the company. The mean age of patients within the 12-35 age band of Udeze *et al.* is 23.57 years, which is similar to the mean age of 21.2 years in CLIMB SCD-121, but will not reflect age as patients in the model get older. The EAG also raised concerns that the population in Udeze *et al.* is more severe than that in CLIMB SCD-121, evidenced for example by the higher baseline VOC rate (8.6 versus 4.2 per year). It is not clear to the DSU whether the relevant population for the decision problem in England is represented by CLIMB SCD-121 or the real-world CPRD-based evidence from Udeze *et al.* (or a subset of it).

The company's economic model tracks a cohort of patients with a start age of 21.2 years over their lifetime and estimates the proportions experiencing complications in each 1-month cycle. The relevance of Udeze *et al.* is in informing the estimates of these complication rates as the patient cohort ages. There is therefore a disparity between the reporting of "age at index date" in the Udeze *et al.* analysis rather than the age at which each complication was observed to occur. As suggested by the EAG, a more suitable analysis would provide estimates of complication rates by age of occurrence. In addition, the use of broad age categories for the reporting of complication rates may obscure the true relationship and risks introducing bias. For example, whilst the estimates from Udeze *et al.* are reported for the category of index age 36+yrs, there are approximately 82% of patients in the economic model SoC arm who survive beyond age 36 years (see Appendix, Figure 1). The ideal analysis would be based on a statistical model of the relationship between complications and age, but a more granular description of the data is first required to assess if this would be feasible. The DSU therefore asked the company (via NICE) whether the data from Udeze *et al.*¹ could be broken down into narrower age bands, and re-analysed according to the patient's age at which the complications occurred. This might then have provided some insight as to whether it would be possible to undertake further statistical analyses to predict complication rates according to each age, which could then be applied to each patient age in the economic model. However, in their response, the company stated that they do not have the granular level of data that the DSU requested, including age of occurrence of complications, as the study was not set up to collect this.

As no further analyses of the Udeze complication rate data were available, the DSU's analysis is therefore limited to additional analyses using the data previously provided by the company.

2.2 Scenario analyses conducted by the DSU

The DSU undertook scenario analyses using the most recently updated version of the company's model (version 5, dated 4th June 2024) to further explore the impact of age-specific complication rates on the cost-effectiveness of exa-cel. All analyses were conducted using the deterministic version of the model, with separate analyses undertaken using discount rates of 3.5% and 1.5% both for health outcomes and costs. All scenarios undertaken include the EAG's preferred assumptions about exa-cel treatment withdrawal (8.62% patients fail apheresis and 10.34% fail to receive exa-cel). In line with concerns about double-counting raised by the EAG, the rate of acute chest syndrome (ACS) was set equal to zero in all scenarios because these events are counted as VOCs elsewhere in the company's economic model.

The details of the additional scenario analyses are described below. The first four scenarios reflect analyses which have previously been presented by the company and/or the EAG. Whilst some of these scenarios (e.g., the company's weighted average approach for the 12+yrs population) attempt to reflect increasing complication rates in older patients, all of these analyses apply constant acute and chronic complication rates in every model cycle. The DSU undertook four additional scenario analyses in which different complication rates for specific age bands in Udeze *et al.*¹ are applied once patients reach a particular age in the model. Monthly rates of acute complications and monthly probabilities of chronic complications for each age band in the Udeze *et al.* data were calculated and implemented in the model by one member of the DSU (MMY). All analyses were then checked by another member of the DSU (PT).

Scenario using complication rates from the literature

This analysis includes complication rates reported from Brousse *et al.* 2023,⁴ Yeruva *et al.* 2016,⁵ Shah *et al.* 2019,⁶ Singh *et al.* 2016,⁷ Cahil *et al.* 2019⁸ and the American Academy of Ophthalmology.⁹ The rate of chronic liver disease was not available from the literature and therefore, the weighted average chronic liver disease rate for people aged 12-35yrs and 36+yrs in Udeze *et al.*¹ was applied in this scenario. This analysis reflects complication rates used in previous versions of the model and is presented here for information only.

Scenario using the complication rates of overall cohort data (2+yrs)

This analysis applies complication rates for the 2+yrs population in Udeze *et al.*¹ to all patients in every model cycle. This scenario corresponds to the company's preferred analysis presented following ACM1.

Scenario using complication rates for the 12-35yrs subgroup, EAG and Appraisal Committee's preferred approach

This analysis applies complication rates for the 12-35yrs subgroup from Udeze *et al.*¹ to all patients in every model cycle.

Scenario using the weighted average complication rates for the 12+yrs subgroup (12-35yrs and 36+yrs), company's preferred approach at ACM2

This analysis applies the weighted average complication rates for patients aged 12+yrs in Udeze *et al.*¹ to all patients in every model cycle. A weighting of 72.27% is applied to the 12-35yrs subgroup and a weighting of 27.73% is applied to the 36+yrs subgroup, based on the number of patients in each age band in Udeze *et al.*¹ (649 and 249 patients, respectively). This analysis is based on observed differences in complication rates by age, but then applies constant complication rates in every model cycle.

DSU Scenario 1: Age-dependent complication rates for the 12-35yrs and 36+yrs subgroups

This analysis applies the complication rates for the 12-35yrs subgroup from Udeze *et al.*¹ to modelled patients until they reach the age of 36 years, and then switches to the complication rates for the 36+yrs subgroup for all subsequent model cycles.

DSU Scenario 2: Age-dependent complication rates for the 18-35yrs and 36+yrs subgroups

This analysis applies the complication rates for the 18-35yrs subgroup from Udeze *et al.*¹ to modelled patients until they reach the age of 36 years, and then switches to the complication rates for the 36+yrs subgroup for all subsequent model cycles.

DSU Scenario 3: Age-dependent complication rates for 12-17yrs, 18-35yrs and 36+yrs subgroups, including a lag to account for follow-up duration

The median follow-up period in Udeze *et al.*¹ is 4.69 years. This analysis applies complication rates for each age band in the model including a 5-year lag to account for this follow-up time. This analysis applies the complication rates for the 12-17yrs subgroup for modelled patients aged <23 years, then switches to use complication rates for the 18-35yrs whilst modelled patients are aged 23-41 years, and then switches to use complication rates for the 36+yrs subgroup for all subsequent model cycles. In this way, the analysis attempts to align the age of patients in Udeze *et al.* with the appropriate time point in the modelled age.

DSU Scenario 4: Age-dependent complication rates for 18-35yrs and 36+yrs subgroups, including a lag to account for follow-up duration

This analysis is the same as DSU Scenario 3, but applies the 18-35yrs subgroup data for all modelled patients until they reach the age of 41 years. Complication rates for the 36+yrs subgroup are applied for all subsequent model cycles.

The rates of acute and chronic complication applied in these scenario analyses are summarised in Table 1.

Table 1: Comparison of complication rates

Complication	Udeze <i>et al.</i> 2023 ^{1†}						Literature value [‡]
	All cohort (N=1,117)	12-35yrs & 36+yrs cohort* (N=898)	12-35yrs cohort (N=649)	36+yrs cohort (N=249)	12-17yrs cohort (N=110)	18-35yrs cohort (N=539)	
Acute complications (annual rate)							
Acute chest syndrome [§]	0.72	0.54	0.53	0.56	0.04	0.05	0.26
Acute kidney injury/infarction	0.20	0.16	0.06	0.43	0.00	0.01	0.01
Pulmonary embolism	0.08	0.07	0.03	0.18	0.00	0.00	0.02
Stroke	0.01	0.02	0.01	0.03	0.00	0.00	0.01
Leg ulcers	0.39	0.33	0.23	0.58	0.00	0.02	0.10
Gallstones	0.41	0.34	0.33	0.38	0.03	0.03	0.05
Infectious and parasitic diseases	0.25	0.22	0.21	0.26	0.02	0.02	0.03
Chronic complications (annual rate per person-year)							Annual rate
Chronic kidney disease	0.01	0.01	0.00	0.02	0.00	0.00	0.02
Pulmonary hypertension	0.01	0.01	0.01	0.03	0.00	0.01	0.01
Avascular necrosis	0.04	0.03	0.03	0.06	0.02	0.03	0.04
Retinopathy	0.02	0.03	0.02	0.05	0.02	0.02	0.01
Heart failure	0.01	0.01	0.02	0.02	0.00	0.01	0.04
Neurocognitive impairment	0.01	0.01	0.01	0.01	0.01	0.01	0.02
Chronic liver disease	0.01	0.01	0.02	0.02	0.01	0.01	-
Post stroke	-	-	-	-	-	-	0.02

* Based on the weighted average of 72.27% of 12-35yrs cohort and 27.73% of 36+yrs cohort.

† In the model, the acute complications were converted into monthly rates and chronic complications into monthly probabilities.

‡ The values were based on the Brousse *et al.* 2023, Shah *et al.* 2019, Singh *et al.* 2016, Yeruva *et al.* 2016, Cahil *et al.* 2019 and the American Academy of Ophthalmology. In the model, the values of acute complications from Brousse *et al.* were converted into monthly probabilities.

§ In the model, the annual complication rate for ACS was assumed to be zero in all analyses presented.

3. RESULTS

The results of the DSU's scenario analyses are summarised in Table 2 (3.5% discount rates) and Table 3 (1.5% discount rates). Table 4 and Table 5 in the appendix present the mean number of acute complications and the number of life years with chronic complications predicted by each of the scenarios.

The model results shown in Table 2 and Table 3 suggest that when the severity modifier is excluded from the analysis, the incremental cost-effectiveness ratio (ICER) for exa-cel is moderately sensitive to the choice of complication rates. Across all eight scenarios, when using the Reference Case discount rates of 3.5%, the ICER for exa-cel versus SoC ranges from £[REDACTED] per quality-adjusted life year (QALY) gained (DSU Scenario 2 – age-dependent rates, 18-35yrs and 36+yrs subgroups) to £[REDACTED]

per QALY gained (EAG-preferred scenario – age-independent rates, 12-35yrs subgroup). Assuming non-Reference Case discount rates of 1.5% for both QALYs and costs suggests an ICER range of £[REDACTED] to £[REDACTED] per QALY gained. Assuming that the population has a mean age of 21.2 years and 44.2% of patients are female (based on CLIMB SCD-121), a QALY gain for the SoC group of 10.52 or less leads to a decision modifier of 1.2, whereas a QALY gain for the SoC group which is higher than this value leads to a decision modifier of 1.0. The decision modifier is 1.2 when complication rates are based on other literature, the whole Udeze cohort (2+yrs, age-independent), the Udeze 12+yrs subgroup (weighted average), DSU Scenario 1 (age-dependent, 12-35yrs and 36+yrs) and DSU Scenario 2 (age-dependent, 18-35yrs and 36+yrs). The other scenarios suggest a decision modifier of 1.0, although the DSU notes that the SoC group QALYs are fairly close to 10.52 in all scenarios except for the EAG's preferred Udeze 12-35yrs scenario.

Table 2: Summary of deterministic base case results with 3.5% discount rates (generated using the company's updated model [version 5])

Option	Total costs	Total LYGs*	Total QALYs	Inc. costs	Inc. LYGs*	Inc. QALYs	ICER	ICER (if severity modifier is 1.2)	Proportional QALY shortfall	Absolute QALY shortfall	Severity modifier†
Scenario using literature value[§]											
Exa-cel	████████	51.29	17.36	████████	22.07	7.58	████████	████████	56.58%	12.74	1.2
SoC	████████	29.22	9.78	-	-	-	-	-			
Scenario using overall cohort (2+yrs) complication rates											
Exa-cel	████████	51.29	17.60	████████	22.07	7.18	████████	████████	53.71%	12.10	1.2
SoC	████████	29.22	10.42	-	-	-	-	-			
Scenario using specific age-group complication rates (12-35yrs)											
Exa-cel	████████	51.29	17.79	████████	22.07	6.79	████████	████████	51.16%	11.52	1.0
SoC	████████	29.22	11.00	-	-	-	-	-			
Scenario using weighted average complication rates (12+yrs)											
Exa-cel	████████	51.29	17.60	████████	22.07	7.17	████████	████████	53.67%	12.09	1.2
SoC	████████	29.22	10.43	-	-	-	-	-			
DSU scenario 1: Age-dependent complication rates (12-35yrs and 36+yrs)											
Exa-cel	████████	51.29	17.68	████████	22.07	7.18	████████	████████	53.40%	12.02	1.2
SoC	████████	29.22	10.50	-	-	-	-	-			
DSU scenario 2: Age-dependent complication rates (18-35yrs and 36+yrs)											
Exa-cel	████████	51.29	17.65	████████	22.07	7.23	████████	████████	53.74%	12.10	1.2
SoC	████████	29.22	10.42	-	-	-	-	-			
DSU scenario 3: Age-dependent complication rates (12-17yrs, 18-35yrs and 36+yrs), including lag for mean follow-up time (~ 5yrs)[‡]											
Exa-cel	████████	51.29	17.79	████████	22.07	7.08	████████	████████	52.46%	11.81	1.0
SoC	████████	29.22	10.71	-	-	-	-	-			
DSU scenario 4: Age-dependent complication rates (18-35yrs and 36+yrs), including lag for mean follow-up time (~ 5yrs)[¶]											
Exa-cel	████████	51.29	17.69	████████	22.07	7.08	████████	████████	52.88%	11.91	1.0

SoC			29.22	10.61	-	-	-	-	-			

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality adjusted life year; SoC - standard of care; yr - year

*undiscounted

†based on absolute QALY shortfall

§ chronic liver disease rate is based on the weighted average of 12-35yrs and 36+yrs cohort from Udeze et al.

‡ In the model, the complication rate of 12-17yrs is applied to people aged under 23 years, the rate of 18-35yrs to people aged between 23 and 41 years, and the rate of 36+ to people aged over 41 years (by taking into account of ~5 yr mean follow-up period in the Udeze et al.)

¶ In the model, the complication rate of 18-35yrs is applied to people aged under 41 years, the rate of 36+yrs to people aged over 41 years (by taking into account of ~5 yr mean follow-up period in the Udeze et al.)

Table 3: Summary of deterministic base case results with 1.5% discount rates (generated using the company's updated model [version 5])

Option	Total costs	Total LYGs*	Total QALYs	Inc. costs	Inc. LYGs*	Inc. QALYs	ICER	ICER (if severity modifier is 1.2)	Proportional QALY shortfall	Absolute QALY shortfall	Severity modifier†
Scenario using literature value[§]											
Exa-cel	████████	51.29	25.73	████████	22.07	13.510	████████	████████	56.58%	12.74	1.2
SoC	████████	29.22	12.22	-	-	-	-	-			
Scenario using overall cohort (2+yrs) complication rates											
Exa-cel	████████	51.29	26.10	████████	22.07	12.90	████████	████████	53.71%	12.10	1.2
SoC	████████	29.22	13.20	-	-	-	-	-			
Scenario using specific age-group complication rates (12-35yrs)											
Exa-cel	████████	51.29	26.38	████████	22.07	12.32	████████	████████	51.16%	11.52	1.0
SoC	████████	29.22	14.05	-	-	-	-	-			
Scenario using weighted average complication rates (12+yrs)											
Exa-cel	████████	51.29	26.10	████████	22.07	12.89	████████	████████	53.67%	12.09	1.2
SoC	████████	29.22	13.21	-	-	-	-	-			
DSU scenario 1: Age-dependent complication rates (12-35yrs and 36+yrs)											
Exa-cel	████████	51.29	26.18	████████	22.07	13.02	████████	████████	53.40%	12.02	1.2
SoC	████████	29.22	13.17	-	-	-	-	-			
DSU scenario 2: Age-dependent complication rates (18-35yrs and 36+yrs)											
Exa-cel	████████	51.29	26.14	████████	22.07	13.08	████████	████████	53.74%	12.10	1.2
SoC	████████	29.22	13.06	-	-	-	-	-			
DSU scenario 3: Age-dependent complication rates (12-17yrs, 18-35yrs and 36+yr), including lag for mean follow-up time (~ 5 yrs)[‡]											
Exa-cel	████████	51.29	26.35	████████	22.07	12.86	████████	████████	52.46%	11.81	1.0
SoC	████████	29.22	13.49	-	-	-	-	-			
DSU scenario 4: Age-dependent complication rates (18-35yrs and 36+yrs), including lag for mean follow-up time (~ 5 yrs)[¶]											
Exa-cel	████████	51.29	26.21	████████	22.07	12.84	████████	████████	52.88%	11.91	1.0

SoC		29.22	13.37	-	-	-	-	-			

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality adjusted life year; SoC - standard of care; yr - year

*undiscounted

†based on absolute QALY shortfall

§ chronic liver disease rate is based on the weighted average of 12-35yrs and 36+yrs cohort from Udeze et al.

‡ In the model, the complication rate of 12-17yrs is applied to people aged under 23 years, the rate of 18-35yrs to people aged between 23 and 41 years, and the rate of 36+ to people aged over 41 years (by taking into account of ~5 yr mean follow-up period in the Udeze et al.)

¶ In the model, the complication rate of 18-35yrs is applied to people aged under 41 years, the rate of 36+yrs to people aged over 41 years (by taking into account of ~5 yr mean follow-up period in the Udeze et al.)

4. DISCUSSION

None of the available options for incorporating complication rates in the company's model are ideal. Given that the rates of several SCD complications are generally expected to increase as patients get older, the DSU's preferred analysis would be to reflect this age-dependence in the complication rates applied in the economic model. The application of the 12-35yrs subgroup data of Udeze *et al.*,¹ which is the currently preferred option by the EAG and the Appraisal Committee, does not account for this factor as constant rates are applied in every model cycle. The DSU also notes that the underlying 12-35yrs subgroup data may not be reflective of the complication risks for older patients ages in the model, as around 82% of SoC patients are predicted to survive beyond age 36 years (see Appendix, Figure 1). The company's suggested approach of using a weighted average of the 12-35yrs and 36+yrs subgroup in Udeze *et al.* is similarly problematic in that the underlying rate data incorporate different effects by age, but these are applied as constant age-independent rates in the economic model. As noted in the EAG's previous critique, this approach may inflate the complication risks for younger patients in the model.

In the absence of further statistical modelling of the Udeze *et al.* data to predict complication risks by age, the DSU's preferred approach is to apply age-band specific rates from Udeze *et al.*¹ in line with the age of patients in the model. This approach allows for some degree of age-dependence to be included in the modelled rates, although this relies on very broad age categories which may mask some of the true age/complication rate relationship. However, given the relatively low frequency of events per annum, more detailed modelling of this relationship may not be feasible. It may also be preferable to focus on the analyses which include a time lag for follow-up time to better reflect the age at which the complications occurred in the Udeze study, rather than the subject's age at the index date. However, the precise age at which complications occurred cannot be estimated which likely leads to inaccuracy in the model predictions. The use of complication rates for age-bands in the model is also limited in that it reduces the number of patients and events at those specific model ages – this is a particular issue for DSU Scenario 3, whereby the 12-17yrs subgroup is informed by only 110 patients. Notwithstanding these limitations, the DSU's preferred scenario is DSU Scenario 3. DSU Scenario 4 produces very similar results.

As is typical for trial- and real-world derived evidence, there are differences between the Udeze *et al.* study population(s) and the population included in the CLIMB SCD-121 study. These differences have been previously noted by the EAG and presented to the Appraisal Committee. Specifically, there is evidence that the Udeze *et al.* population is more severe at baseline than the trial population in terms of the annual VOC rate (6.4 per year vs 4.2 years) and complications at baseline. Udeze *et al.* identified patients in England at the point when they first met the eligibility criteria i.e., patients with an SCD diagnosis and ≥ 2 VOCs in two consecutive years. Applying the observed rates of complications from this study population assumes that these patients are reflective of those eligible for exa-cel and that the treatment benefit observed in CLIMB SCD-121 is applicable to this more severe population. The degree of overlap between Udeze *et al.* and the

clinical trial has not been reported and therefore it is not possible to address if some form of matching of patients to the trial population would be feasible, if this were considered to be a better reflection of the target population for England.

5. REFERENCES

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APPENDICES

Table 4: Summary of model-predicted mean number of acute complications per patient

Option	Acute chest syndrome	Acute kidney injury/infarction	Pulmonary embolism	Stroke	Leg ulcers	Gallstones	Infectious and parasitic diseases
Scenario using literature value							
Exa-cel	0.00	0.10	0.15	0.07	0.71	0.33	0.19
SoC	0.00	0.41	0.61	0.29	2.91	1.34	0.79
Scenario using overall cohort (2+ yrs) complication rates (N=1,117)							
Exa-cel	0.00	1.43	0.57	0.07	2.78	2.93	1.78
SoC	0.00	5.84	2.34	0.29	11.40	11.98	7.31
Scenario using specific age-group complication rates (12-35 yrs) (N=649)							
Exa-cel	0.00	0.43	0.21	0.07	1.64	2.35	1.50
SoC	0.00	1.75	0.88	0.29	6.72	9.64	6.14
Scenario using weighted average complication rates (12+ yrs) (N=898)							
Exa-cel	0.00	1.16	0.51	0.11	2.33	2.45	1.60
SoC	0.00	4.75	2.09	0.45	9.56	10.05	6.54
DSU scenario 1: Age-dependent complication rates (12-35 yrs and 36+ yrs) (N=898)							
Exa-cel	0.00	1.68	0.72	0.14	2.83	2.52	1.67
SoC	0.00	7.52	3.21	0.60	12.17	10.42	6.92
DSU scenario 2: Age-dependent complication rates (18-35 yrs and 36+ yrs) (N=788)							
Exa-cel	0.00	1.72	0.72	0.14	2.94	2.45	1.67
SoC	0.00	7.65	3.21	0.60	12.58	10.15	6.92
DSU scenario 3: Age-dependent complication rates (12-17 yrs, 18-35 yrs and 36+ yrs), including lag for mean follow-up time (~ 5 yrs) (N=898)							
Exa-cel	0.00	1.35	0.56	0.11	2.36	2.49	1.64
SoC	0.00	6.14	2.57	0.51	10.86	10.03	6.73
DSU scenario 4: Age-dependent complication rates (18-35 yrs and 36+ yrs), including lag for mean follow-up time (~ 5 yrs) (N=788)							
Exa-cel	0.00	1.41	0.59	0.12	2.66	2.39	1.62
SoC	0.00	6.23	2.62	0.52	11.31	9.87	6.72

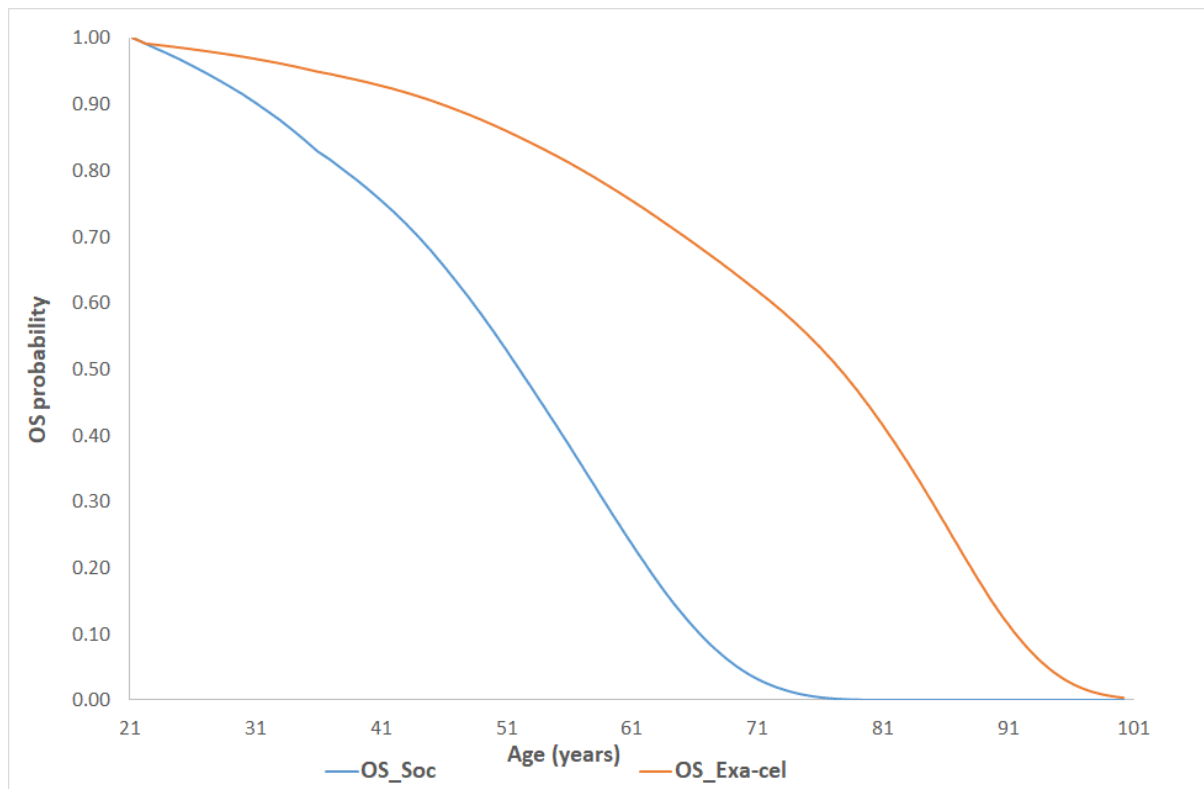
SoC - standard of care; DSU - Decision Support Unit; N - number; yr - year

Table 5: Summary of model-predicted mean life years with chronic complications

Option	Chronic kidney disease	Pulmonary hypertension	Avascular necrosis	Heart failure	Neuro-cognitive impairment	Post Stroke	Retino-pathy	Chronic liver disease
Scenario using literature value								
Exa-cel	2.46	1.63	4.49	4.45	4.09	2.13	7.98	1.33
SoC	7.57	5.15	12.88	12.80	8.86	6.62	6.25	4.24
Scenario using overall cohort (2+yrs) complication rates (N=1,117)								
Exa-cel	1.12	1.84	4.17	1.59	2.57	0.47	10.02	1.48
SoC	3.59	5.76	12.11	5.01	4.36	1.44	12.28	4.69
Scenario using specific age-group complication rates (12-35yrs) (N=649)								
Exa-cel	0.59	1.31	3.25	0.73	2.49	0.47	9.47	0.82
SoC	1.90	4.17	9.75	2.36	4.12	1.44	10.76	2.63
Scenario using weighted average complication rates (12+yrs) (N=898)								
Exa-cel	1.07	1.87	4.02	1.48	2.67	0.72	10.11	1.33
SoC	3.42	5.86	11.76	4.68	4.69	2.20	12.53	4.24
DSU scenario 1: Age-dependent complication rates (12-35yrs and 36+yrs) (N=898)								
Exa-cel	0.97	1.75	3.72	1.30	2.63	0.63	9.90	1.20
SoC	3.64	6.16	11.95	4.99	4.75	2.19	12.75	4.38
DSU scenario 2: Age-dependent complication rates (18-35yrs and 36+yrs) (N=788)								
Exa-cel	1.06	1.90	3.82	1.41	2.61	0.63	9.94	1.18
SoC	3.88	6.54	12.14	5.26	4.70	2.19	12.82	4.34
DSU scenario 3: Age-dependent complication rates (12-17yrs, 18-35yrs and 36+yrs), including lag for mean follow-up time (~ 5yrs) (N=898)								
Exa-cel	0.67	1.30	3.33	0.90	2.61	0.37	9.67	1.08
SoC	3.09	5.55	11.14	4.13	4.50	1.70	12.01	3.73
DSU scenario 4: Age-dependent complication rates (18-35yrs and 36+yrs), including lag for mean follow-up time (~ 5yrs) (N=788)								
Exa-cel	0.93	1.76	3.64	1.22	2.56	0.56	9.78	1.04
SoC	3.30	5.90	11.32	4.38	4.46	1.86	12.08	3.70

SoC - standard of care; DSU - Decision Support Unit; N - number; yr - year

Figure 1: Model-predicted overall survival



SoC - standard of care; OS - overall survival

Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Centre (EAC) report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:

Green - No key issues identified

Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)

Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation

The feasibility assessment indicates whether the Managed Access team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access team.

Topic name:

Topic ID:

Managed Access Lead:

Date of assessment(s):

Exagamglogene autotemcel for treating sickle cell disease

4016

Milena Wobbe

08/01/2024

Is Managed Access appropriate - Overall rating	Comments / Rationale
Committee judgement required	Data collection within Managed Access is feasible, with relevant data expected to be collected through the ongoing trial and an ongoing prospective observational cohort study. However, the majority of issues highlighted by the EAG cannot be resolved through further evidence collection and relate to the approach taken to model the benefit of exa-cel. The EAG have highlighted uncertainties that could somewhat be addressed through further data collection, such as changes in HRQoL, long-term safety profile and treatment durability. Longer-term data from the trial programme would be relevant to address these. However, with the exception of determining whether a 1.5% discount rate is appropriate (EAG14), these issues only have a relatively small impact on the ICERs presented. Additionally, the maximum length of data collection of 5 years (or the proposed 3 years by the company) would not fully resolve long-term uncertainties around safety or treatment durability and committee will need to make a judgement on whether the additional data would be sufficient to potentially enable a routine recommendation at the currently agreed price.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	Exa-cel for SCD meets the IMF eligibility criteria
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Unclear	Data collection within Managed Access is feasible, with relevant data expected to be collected through the ongoing trial and an ongoing prospective observational cohort study. However, the majority of issues highlighted by the EAG cannot be resolved through further evidence collection and relate to the approach taken to model the benefit of exa-cel. The EAG have highlighted uncertainties that could somewhat be addressed through further data collection, such as changes in HRQoL, long-term safety profile and treatment durability. Longer-term data from the trial programme would be relevant to address these. However, with the exception of determining whether a 1.5% discount rate is appropriate (EAG14), these issues only have a relatively small impact on the ICERs presented. Additionally, the maximum length of data collection of 5 years (or the proposed 3 years by the company) would not fully resolve long-term uncertainties around safety or treatment durability and committee will need to make a judgement on whether the additional data would be sufficient to potentially enable a routine recommendation at the currently agreed price.
Can data collection be completed without undue burden on patients or the NHS system	Yes	The ongoing RWE prospective observational cohort study would collect data from clinical practice, including in England. EBMT is an already established disease register. Clinics are resourced for data collection for EBMT and this is usually part of routine care, so unlikely to add further burden to the system.

Are there any other substantive issues (excluding price) that are a barrier to a MAA	Yes - Major	The EAG questions the robustness of the company's model and its suitability for decision making. Potential equality issues with data collection during managed access. These would be minimised

Further managed access activity	Rating	Comments / Rationale
pre-committee feasibility assessment update	Not applicable	
pre-committee data collection working group	Not applicable	
pre-committee patient involvement meeting	Not applicable	

Key questions for committee if Managed Access is considered	
1	Is the economic modelling and analyses provided suitable for making a managed access recommendation?
2	Would committee require further data collection to decide on whether a 1.5% discount rate is appropriate (see EAG14)?
3	Would 3 years (company proposal) or 5 years (maximum) of managed access sufficiently resolve the key uncertainties to potentially enable a routine recommendation at the currently agreed price?

Early Identification for Managed Access

Explanation on criteria

These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for the managed access.

Date agreed with NHSE

01/12/2023

Is the technology a potential candidate for managed access?

Rating	Rationale
Yes	Exa-cel is considered a promising innovative medicine as it would be expected to lead to significant clinical benefits and would address a high unmet need. It is therefore eligible to be considered for the Innovative Medicines Fund.

IMF prioritisation criteria	Supporting Evidence
Potential to address a high unmet need	SCD is a severe life-long disease resulting in severe pain, chronic haemolytic anaemia, widespread organ damage and shortened life expectancy. The treatment options are limited. Unmet need is high. Exa-cel is a gene therapy using a person's own stem cells, "correcting" them and then putting back into person's body. This should reduce VOCs, and the company claims that exa-cel has curative potential.
Potential to provide significant clinical benefits to patients	SCD has a high treatment burden for patient and reduces life expectancy significantly. Exa-cel is potentially curative.
represents a step-change in medicine for patients and clinicians	Patients who are suitable for transplant but where no donor is available can benefit from this therapy. This technology is also less risky than allogeneic stem-cell transplant and risk of rejection is also lower.
new evidence could be generated that is meaningful and would sufficiently reduce uncertainty	See uncertainties tab

Uncertainties

Explanation
This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team. The Managed Access Team will justify its decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating. Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	Rationale
Medium	A significant number of uncertainties relate to modelling queries. The EAG does not believe that the company's model is suitable for decision making and has not provided any alternative ICERs. However, it is likely that the biggest impact on the cost-effectiveness calculations stem from the severity modifier, the application of the non-reference case DCEA and long term durability. Only the latter could be (partially) resolved through data collection - although data collection is limited to 5 years in the IMF, so the committee may not be satisfied that this would be sufficiently long to resolve the uncertainty.

Key Uncertainties								
Issue	Key uncertainty	Company preferred assumption	ERG preferred assumption	Impact on ICER	Data that could sufficiently resolve uncertainty	Proposed primary data source	Likelihood data collection could sufficiently resolve uncertainty	Rationale / Notes
EAG1	Single-arm trial with short-term follow-up	Clinical effectiveness evidence is based on a small study with short term follow-up and no comparator (CLIMB SCD-121)	There seems no feasible alternative approach that can resolve the issues associated with this study design.	Unquantified	More patients followed-up for longer in CLIMB SCD-121 would help but cannot resolve the fundamental issues.	CLIMB SCD-121 / N/A	Low	Longer term data would resolve some uncertainty in the intervention arm, but the lack of comparator remains an issue
EAG2	Generalisability of trial outcomes to NHS practice	The CLIMB SCD-121 study uses data collected across 16 study centres world-wide but only 1 UK site. The EAG has concerns over the difficulty to determine if the evidence reflects characteristics of patient population, and characteristics of standard of care and treatment received (before and during the trial period) in England and Wales, based on the small sample from the UK.	No feasible alternative seems available given that the data presented is based on so few UK SCD patients.	Unquantified	The EAG considers that additional evidence is required because the number of patients providing clinical evidence is small and their duration of follow-up is short; this is particularly the case from a UK perspective because of the extreme sparsity of UK participants.	EBMT registry	Medium	Number of patients, in particular UK-based patients is small - this will likely remain but further evidence could be collected on those UK-based patients via the EBMT registry during a period in the IMF.

EAG3	Trial sample size	The EAG has concerns around the small sample size in the CLIMB SCD-121 study. Analyses beyond about 12 months were based on severely diminishing numbers of patients. The FAS supplies data for more patients and longer maximum follow-up, but numbers followed up diminish rapidly beyond about a year, and the evidence is inadequate for robust decision making. This small sample size in the trial informing efficacy evidence results in uncertainty about the efficacy of exa-cel and limits the scope of robust inferences that can be drawn from the evidence.	Given the noted shortcomings in the available evidence the EAG cannot suggest an alternative approach that would not suffer from similar fundamental deficiencies.	Unquantified	While evidence suggests strong effectiveness of exa-cel for a limited number of patients in the short term the demonstration of prolonged effectiveness requires more patients to be followed up for a longer period. CLIMB SCD-121 cannot provide evidence for a comparator so this issue can only be satisfactorily resolved in a study with more patients, longer follow up, and an appropriate comparator arm to exa-cel.	CLIMB SCD-121 and CLIMB SCD-131 trials and EBMT registry	Low	Whilst the relative clinical effectiveness of exa-cel can only be studied in a study with an appropriate comparator arm, it should be noted that the CLIMB SCD-121 and CLIMB-131 trials (as well as the registry) could collect further efficacy data. However, patients numbers are likely to remain limited.
EAG4	Short-term follow-up of participants	As the study is still ongoing there is a lack of long-term follow up data available. Currently, the efficacy and safety findings are based on short follow-up for a couple patients. The company suggest that exa-cel is likely to restore patients with severe SCD to full or near-full health, but as no long-term follow-up data is yet available; it is impossible to assess the efficacy of exa-cel beyond the short term.	The only feasible alternative appears to be to await longer term evidence from CLIMB trials and to then assess effectiveness.	High	The EAG acknowledges that patients participating in CLIMB SCD-131 will be monitored for up to 15 years following exa-cel infusion, but these longer-term data are not available. Currently, CLIMB SCD-131 is hardly relevant for the decision problem.	CLIMB SCD-131	Medium	Whilst further follow-up is being collected, it is unlikely that sufficient data could be collected within the time frame of managed access (a maximum of 5 years). The impact of patients being modelled as "cured" has a significant impact on ICER.
EAG5	Lack of control/comparator arm	CLIMB SCD-121 is a Phase 1/2/3 single-arm, open-label, multi-site, single-dose study. The EAG notes that as a single-arm study, there are no randomised comparators or control groups in the CLIMB SCD-121 trial. Without a control group the EAG was unable to determine, with a reasonable degree of certainty the true impact of exa-cel.	None seem feasible given the nature of CLIMB SCD-121.	Unquantified	The EAG note that this issue cannot be resolved given the study design of CLIMB SCD-121.	N/A	No further data collection possible / proposed	

EAG6	The model does not have the requisites for a Markov structure	The model structure is not organised as a Markov structure. Deaths are calculated by applying each acute complication a death rate specific to the event, corrected by the proportion of alive population. This approach implies that deaths are counted for each event independently from other events. Although the (incremental) death rates are applied to the “alive” population, the “alive” population is determined in a circular manner, subtracting the number of total deaths in the model from 1. This circularity provides no guarantee that the sum of deaths is less or equal to the total number of people in the cohort. The overall effect is that some people may “die twice” at each cycle in the model, i.e., people in the model are “double counted”. Because of the lack of face validity, rates of chronic complications and mortality calculated in the model may be biased.	Model rebuild using standard practices for Markov state-transition models.	Unquantified	Model rebuild using standard practices for Markov state-transition models.	Committee judgement required	No further data collection possible / proposed	
EAG7	Economic analyses do not account for costs and outcomes associated with treatment failures between apheresis and myeloablation.	The exa-cel cohort showed that approximately 20% of people eligible for exa-cel in fact do not receive it. Some of the dropouts are due failure of apheresis (the process used to harvest cells from the patient) whilst others fail to obtain enough exa-cel for reimplantation (i.e., exa-cel yield falls below the lower bound for therapeutic efficacy). The latter group undergoes apheresis, accrues the cost of manufacturing exa-cel but drops out of the process just before myeloablation. After dropping out of the process, these patients continue to receive SoC.	Apheresis and myeloablation are not part of SoC, therefore they are only necessary if people are meant to receive exa-cel. As such, costs and outcomes for these people must be included in the model as part of the NHS perspective.	Unquantified	A small decision tree to calculate the probability of dropout after apheresis and of dropout after manufacturing of exa-cel but before myeloablation should be added. Once dropouts are accounted for, costs and longer-term outcomes for these people should be included in the exa-cel arm.	Further evidence submission ahead of ACM	No further data collection possible / proposed	

EAG8	VOC rates as a predictor in a risk equation for acute and chronic complications	The model extrapolates all longer-term events from hazard ratios of each event, multiplied by the rate of VOCs at each cycle. The rate of VOC is applied in the model as mean number of events per month; for each complication, this rate is multiplied by a hazard ratio, as if the number of VOCs were a term in a risk equation. Yet the original study with all likelihood did not use VOCs in this way; in any case, the original risk equations are not published. In addition, the original study did not show that the risk of complications is zero when patients report no VOCs, but only that the risk is reduced. Therefore, applying the "number of VOCs" as a significant independent variable, associated with a specific coefficient for the risk of acute and chronic complications in the manner of the model originates from a misinterpretation of the analysis in the original study (Shah et al 2019). Therefore, the number of VOCs per cycle (the intermediate outcome) cannot be used as an intermediate (surrogate) outcome in the model.	VOCs should be used to stratify risk, i.e., it should be used to identify two groups with different risks of certain events. VOCs, per se, should be used as one of the modelling relevant outcomes.	Medium	Methods used to incorporate VOCs should be modified.	Further evidence submission ahead of ACM	No further data collection possible / proposed	ICERs are expected to increase
EAG9	Modelling of adverse events is partial to exa-cel short list and selected events.	Adverse events with exa-cel are available from the CSR of CLIMB SCD-121. The company's model does not include these events on grounds that the HRG cost for myeloablation (obtained from standard NHS costs sources) already incorporates the adverse events of busulfan (the drug used during myeloablation) and other AEs. Whilst this is true, NHS costs cannot include adverse events for products not yet used in clinical practice.	AEs for exa-cel should be incorporated.	Medium	Rates of adverse events from CLIMB SCD-121 should be incorporated in the model.	Further evidence submission ahead of ACM	No further data collection possible / proposed	ICERs are expected to increase
EAG10	Drug costs during apheresis, iron chelation regimens alongside blood transfusion should be modelled using distribution of patients' weight.	The costs of prescriptions that are patient-weight dependent should be calculated for all possible weights of the patient population (weight distribution). This is a well-established practice in cost-effectiveness modelling. The model does not allow for an easy incorporation of patient weight distribution because the formulae for calculating these costs are keyed into model traces, and across model cohorts and arms, all based on the average patient weight.	Costs for those drugs and relative procedures should be recalculated; the model should be modified to include an input for total costs of therapies by cycle.	Unquantified	Costs for those drugs and relative procedures should be recalculated; the model should be modified to include an input for total costs of therapies by cycle.	Further evidence submission ahead of ACM	No further data collection possible / proposed	

EAG11	The cost of supportive blood transfusions alongside implantations of exa-cel is not included in model costs.	The costs supportive blood transfusions alongside exa-cel have been included but limited to resource use well below the trial protocol. It is not known whether the use of supportive transfusions may become part of clinical protocols for the use of exa-cel. Whilst normally trial-driven costs should not be included in the model, the use of supportive transfusions may become a feature of the use of exa-cel in real practice.	Costs for supportive transfusions with exa-cel should be included in the model	Medium	Costs for supportive transfusions with exa-cel should be included in the model	Further evidence submission ahead of ACM	No further data collection possible / proposed	
EAG12	Range of acute and chronic complications included in the model is large, but risk reduction is based on assumptions	It is accepted practice that modelling of cost-effectiveness can rely on assumptions around certain parameters when evidence is missing. Nonetheless, the credibility of a model conceptualisation is a qualitative evaluation based both on the amount of evidence incorporated in the model as well as the plausibility of clinical relationships hypothesised in the model structure. For example, parameters and efficacy of exa-cel with regards to bone problems, neurocognitive problems, liver disease and sickle cell retinopathy are assumed based on parameters for pulmonary hypertension, in their turn based on assumptions. The extent of parameters and structural uncertainty in a cost-effectiveness model should not be overwhelming, to ensure that both the logic and the outputs of the model are plausible.	The gaps in the evidence should be recognised; the model should be grounded in evidence, most clinical events parameters should be derived from data, sparingly complemented by assumptions that can be logically defended. When certain clinical endpoints have no evidence base, they should be excluded from the model.	Unquantified	Either searching or developing more evidence for the major SCD endpoints could be helpful.	Further evidence submission ahead of ACM	No further data collection possible / proposed	
EAG13	Underestimation of uncertainty in modelling of overall survival in exa-cel and SoC. Distributions not appropriately parameterised and some key inputs excluded from the PSA.	The model PSA excludes stratified mortality rates and national statistics for background mortality. The use of these data in the model, including stratifications and data organised by age bands, is extensive; hence the exclusion from PSA drastically reduces the possibility of correctly accounting for uncertainty in the model.	Include all mortality data in the PSA.	Unquantified	Include all mortality data in the PSA.	Further evidence submission ahead of ACM	No further data collection possible / proposed	

EAG14	Inclusion of severity modifier and implementation of 1.5% discount rate	The calculation of the severity modifier is likely associated with extensive uncertainty that is difficult to quantify and may be underestimated in the base-case cost-effectiveness analysis, and the application of this modifier in addition to implementation of 1.5% discounting is likely to result in double counting and bias.	NICE stipulates that applying absolute and proportional shortfall calculations should include discounting at the reference-case rate of 3.5% per annum.	High	Model rebuild using standard practices for Markov state-transition models, which encompasses addressing the concerns raised and using a 3.5% discount rate.	CLIMB SCD-121, CLIMB SCD-131 / Committee judgement required	Low	According to the NICE manual, non-reference-case discounting can be applied when all of the following three criteria are met: - 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 If committee requests further HRQoL data, this could be addressed (partially) through a period within managed access by obtaining HRQoL data for people eligible for exa-cel but not receiving the intervention. It is not clear whether a period of up to 5 years would be sufficient to resolve this uncertainty. Committee judgement may depend on precedent set by ID4015 (exa-cel for treating transfusion-dependent beta-thalassaemia).
EAG15	Non-reference case distributional cost-effectiveness analysis	The inclusion of non-reference case distributional cost-effectiveness analysis. The underlying aversion to inequality appears to be based on opinion of a single expert and that a proxy for health deprivation has been employed.	Exclude DCEA from the base-case to be more in-line with NICE reference case.	High	Exclude DCEA from the base-case to be more in-line with NICE reference case.	Committee judgement required	No further data collection possible / proposed	

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	Rationale/comments
High	CLIMB SCD-131 is a long-term follow up study, collecting data on clinical outcomes. The efficacy of exca-cel is likely one of the main uncertainties the committee will want clarification on and the ongoing study protocol collects further data.

CLIMB SCD-121 Clinical trial data	
Anticipated completion date	Oct-24
Link to clinicaltrial.gov	https://clinicaltrials.gov/study/NCT03745287
Start date	Nov-18
Data cut presented to committee	Apr-23
Link(s) to published data	N/A
Description of trial	A Phase 1/2/3 single-arm, open-label study to Evaluate the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (CTX001) in Subjects With Severe Sickle Cell Disease, n=45 (estimated) - patients with severe SCD aged 12 - 35 years. Primary outcome measures are: - Proportion of subjects who have not experienced any severe vaso-occlusive crisis (VOC) for at least 12 consecutive months (VF12) - Proportion of subjects with engraftment (first day of three consecutive measurements of absolute neutrophil count [ANC] $\geq 500/\mu\text{L}$ on three different days) - Time to engraftment - Frequency and severity of collected adverse events (AEs) - Incidence of transplant-related mortality (TRM) within 100 days after CTX001 infusion - Incidence of TRM within 1 year after CTX001 infusion - All-cause mortality

CLIMB SCD-131 Clinical trial data	
Anticipated completion date	Sep-39
Link to clinicaltrial.gov	https://clinicaltrials.gov/ct2/show/NCT04208529
Start date	Jan-21
Data cut presented to committee	Sep-22
Link(s) to published data	N/A
Description of trial	This is a multi-site, observational study to evaluate the long-term safety and efficacy of CTX001 in subjects who received CTX001 in Study CTX001-111 (NCT03655678) or VX21-CTX001-141 (transfusion-dependent β-thalassaemia [TDT] studies) or Study CTX001-121 (NCT03745287) or VX21-CTX001-151 (severe sickle cell disease [SCD] studies; NCT05329649). n=114. Primary outcome measures are: - New malignancies - New or worsening hematologic disorders - All-cause mortality - Serious adverse events (SAEs) occurring up to 5 years after CTX001 infusion - CTX001-related AEs Quality of life data will be collected up to 5 years post CTX001 infusion

Data collected in clinical practice

Is RWE data collection within managed access feasible?	
Overall Rating	Rationale/comments
High	Whilst proposed data collection is feasible through the study protocol registered in the EU PASS Register following PRAC approval of the final protocol: "Long-term registry-based study of patients with β -thalassemia or sickle cell disease (SCD) treated with exagamglogene autotemcel (exa-cel)", concerns remain that it won't deliver necessary evidence in the timeframe allowed in the IMF. Furthermore, there is uncertainty over the number of patients who would be treated in the NHS during the IMF period.

Data Source	
Relevance to managed access	
Existing, adapted, or new data collection	Existing Further data would be collected through the European Society for Blood and Marrow Transplantation (EBMT) Registry.
Prior experience with managed access	Medium Registry has not previously been used within a NICE managed access agreement. However, a trial protocol, governance and deliverables have already been agreed as part of a research study.
Relevance of existing data items	High The study protocol uses the registries to collect the data, and has data collection through the registries integrated into the study design - therefore the relevance of the data items should be extremely high.
If required, ease that new data items can be created / modified	Not applicable
How quickly could the data collection be implemented	Normal timelines
Data quality	
Population coverage	High Data from approx. 80% of European transplant centres are received ; The EBMT Registry holds data on patients receiving a haematological transplant procedure, as well as gene and cell therapies. Specific to this study, the EBMT includes patients with SCD and TDT receiving an allogeneic or autologous HSCT procedure and is expected to include patients with SCD and TDT receiving gene therapies once such therapies are approved and available commercially.
Data completeness	Medium Data from approx. 80% of European transplant centres are received (75% autologous transplants, 80% for allogenic transplants). The risk of missing data or patients lost to follow-up are higher than in clinical trials. Does not measure HRQoL
Data accuracy	High New forms to be included into register to have sufficient detail.
Data timeliness	
Quality assurance processes	Yes The EBMT has robust quality assurance processes in place.
Data availability lag	High The data collected would be made available approximately 12 months after data-cut off.
Data sharing / linkage	
New data sharing arrangements required?	No

New data linkages required?	No	
If yes, has the governance of data sharing been established	Not applicable	
Analyses		
How easily could collected data be incorporated into an economic model	High	
Existing methodology to analyse data	Yes	
If no, is there a clear process to develop the statistical analysis plan	Not applicable	
Existing analytical capacity	High	
Governance		
Lawful basis for data collection	Yes	
Privacy notice & data subject rights	Yes	
Territory of processing	Yes	EBMT will collect data from Germany, France, Italy and the United Kingdom. There are 52 centres in the UK reporting outcomes in the EBMT currently.
Data protection registration	Yes	
Security assurance	Yes	
Existing relevant ethics/research approvals	Yes	Existing register. Research ethics and governance established as part of existing study protocol .
Patient consent	Yes	All personal data under the responsibility of the EBMT are processed according to the EU GDPR. However, the company have highlighted that lack of patient consent to give access to their data after treatment after exa-cel might be a barrier.
Funding		
Existing funding	Yes	
Additional funding required for MA	No	
If yes, has additional funding been agreed in principle	Not applicable	
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?		Question not applicable. This is a approved research study, rather than service evaluation.
Are any of the clinical assessments not validated for use or accepted clinical practice		Question not applicable. This is a approved research study, rather than service evaluation.
HRA question 3. Is the study designed to produce generalisable or transferable findings?		

Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation		Question not applicable. This is a approved research study, rather than service evaluation.
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?		Question not applicable. This is a approved research study, rather than service evaluation.
Burden		
Additional patient burden	No	
Additional clinical burden	No	According to the company: Patients will be routinely followed up by the transplant centres (as part of the transplant clinic for year 1 and the long-term effects monitoring clinics thereafter). These clinics are resourced for data collection for EBMT and this will be part of their routine care.
Other additional burden	No	

Other issues

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

The Managed Access Team will justify its decision, but broadly it is a matter of judgement on whether any issues identified, taken as a whole, are likely to lead to a barrier to a Managed Access Agreement being agreed, or operationalised in the NHS. No assessment is made whether a Commercial Access Agreement is likely to be reached between the company and NHS England, which could be a substantive barrier to managed access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	Rationale/comments
Yes - Major	The EAG's opinion is that it questions the company's model suitability for decision making. There are potential equality issues with data collection during managed access. These would be minimised through engagement with patient groups during any managed access.

Burden		Rating	Rationale / comments
	Expected overall additional patient burden from data collection?	Low	According to the company: Patients will be routinely followed up by the transplant centres (as part of the transplant clinic for year 1 and the long-term effects monitoring clinics thereafter). These clinics are resourced for data collection for EBMT and this will be part of their routine care.
	Expected overall additional system burden from data collection?	Low	Additional data collection would form part of the approved research protocol.
	Do stakeholders consider any additional burden to be acceptable	Not applicable	
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	Not applicable	

Patient Safety		Rating	Rationale / comments
	Have patient safety concerns been identified during the evaluation?	Yes	The company considers the safety of the treatment to be a key uncertainty to be addressed through managed access. Patients must be fit enough to undergo myeloablative conditioning with busulfan.
	Is there a clear plan to monitor patient safety within a MA?	Yes	Data collection proposed with EBMT Registry is a mandated post-authorisation safety study (PASS). This will collect SAEs and mortality.
	Are additional patient safety monitoring processes required	Unclear	SmPC is ready but does not give much detail on patient safety and adverse events. Standardised checks will be in place. Company and providers are bound to report AEs to each others; any further reporting structures will likely be met with resistance.

Patient access after MAA		Rating	Rationale / comments
	Are there any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Not applicable	This is a one-off treatment. All patients who receive treatment during a managed access period would continue to receive benefits of treatment in the event of a negative NICE guidance update.
	If yes, have NHS England and the company agreed in principle to the exit strategy	Not applicable	

	Rating	Rationale / comments

Service implementation	Is the technology disruptive to the service	Yes	No current service provision available that could offer exa-cel, so new service provision would need to be set up. Patient demand is somewhat unknown but there is a time lag of about 7 months between patient identification and treatment start.
	Will implementation subject the NHS to irrecoverable costs?	Unclear	
	Is there an existing service specification which will cover the new treatment?	No	A new service specification will need to be set up.

Patient eligibility		Rating	Rationale / comments
	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	
	If yes, are these different to what would be used if the technology had been recommended for routine use?	No	

Service evaluation checklist		Rating	Rationale / comments
	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes	
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	No	
	Any issues from registry specific questions	No	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes	
	Any issues from registry specific questions	No	

Equality		Rating	Rationale / comments
	Are there any equality issues with a recommendation with managed access	Yes	The company highlight patients in England with SCD are disproportionately represented in ethnic minority groups and lower socioeconomic communities which may impact willingness to be part of managed access. In the event of a managed access recommendation the NICE managed access team would proactively engage with patient groups during the managed access period to minimise any barriers to access due to data collection.

Timings		Rating	Rationale / comments
	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Yes	