SMC2852

exagamglogene autotemcel dispersion for infusion (Casgevy®)

Vertex Pharmaceuticals Limited

05 December 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

exagamglogene autotemcel (Casgevy®) is accepted for use within NHSScotland.

Indication under review: for the treatment of sickle cell disease in patients 12 years of age and older with recurrent vaso-occlusive crises who have the β^S/β^S, β^S/β^+ or β^S/β^0 genotype, for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available.

In a single-arm open-label study, 97% (28/29) of patients remained free from severe vaso-occlusive crises for at least 12 consecutive months after receiving an exagamglogene autotemcel (exa-cel) infusion.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Exagamglogene autotemcel (hereafter referred to as exa-cel) is a patient-specific, cell-based therapy consisting of haematopoietic stem and progenitor cells that have been collected from the patient and edited ex vivo using CRISPR/Cas9 gene editing technology. These modified cells are then infused back into the patient resulting in increased foetal haemoglobin (HbF) production. In patients with severe sickle cell disease, HbF reduces sickle cell haemoglobin (HbS) concentrations which prevents red blood cells from sickling. The minimum recommended dose of exa-cel is 3 x 10^6 $CD34^+$ cells/kg administered as a one-time, single dose intravenous infusion. See the Summary of Product Characteristics (SPC) for further detail.[1, 2] It is an advanced therapeutic medicinal product (ATMP).

1.2. Disease background

Sickle cell disease is a chronic autosomal recessive condition caused by mutations in the beta-globin gene which results in the production of abnormal haemoglobin, HbS. The most severe and common form is sickle cell anaemia, which is caused by the β^S/β^S genotype. Other genotypes that are less common include β^S/β^0 which is severe and β^S/β^+ which is mild to moderate in severity. During low-oxygen conditions, red blood cells containing HbS become rigid and sickle-shaped and can clump together which causes blockages in blood vessels. This can lead to recurrent episodes of acute severe pain known as vaso-occlusive crises (VOC). Other acute and chronic complications include anaemia, chronic haemolysis, stroke, acute chest syndrome, infections, priapism, splenic sequestration, organ failure and early mortality. Sickle cell disease is more common in people of Mediterranean, Middle Eastern, African and Asian ethnic origin. With currently available treatment, median life expectancy is approximately 40 to 50 years.[1, 3, 4, 13]

1.3. Treatment pathway and relevant comparators

The aim of sickle cell disease management is to avoid painful VOCs, relieve symptoms and minimise complications. Options include pain relief, hydration, prevention of infections and red blood cell (RBC) transfusions with or without iron chelation therapy (to treat iron overload secondary to regular RBC transfusions). Hydroxycarbamide is currently the only pharmacological treatment licensed and available in the UK for the prevention of VOCs in sickle cell disease. However, it is associated with bone marrow suppression and other adverse effects that can cause issues with tolerability and compliance, and is potentially teratogenic. Allogeneic haematopoietic stem cell transplant (HSCT) is the only potentially curative treatment available for select patients with sickle cell disease. However, it is not a relevant comparator for this submission because exa-cel is only licensed for patients that do not have a suitable stem cell donor available.[1, 3, 5-7]

The submitting company considered that standard of care, consisting of hydroxycarbamide and RBC transfusions with iron chelation therapy is the relevant comparator for the indication under review.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Exa-cel received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway and has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency.

Eligibility for a PACE meeting

Exa-cel meets SMC orphan criteria in this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of exa-cel for the treatment of sickle cell disease is from the single-arm study, CLIMB SCD-121 and ongoing long-term follow-up study, CLIMB-131. Details are summarised in table 2.1.

Table 2.1. Overview of relevant studies[1, 8]

Criteria	CLIMB SCD-121 and CLIMB-131
Study design	CLIMB SCD-121 was a 2-year multicentre, open-label, single-arm, phase I/II/III study. CLIMB-131 is an ongoing 13-year long-term follow-up, phase III study that enrolled patients who completed or discontinued CLIMB SCD-121 (patients with beta-thalassaemia were also included in CLIMB-131 but are not relevant to this submission and will not be discussed further).
Eligible patients	• 12 to 35 years of age. • Diagnosis of severe SCD defined by at least two severe VOC episodes (see primary outcome for definition) per year in the 2 years before screening whilst receiving appropriate supportive care. • β^S/β^S, β^S/β^0, or β^S/β^+ genotype. • Eligible for autologous HSCT as per investigator's judgement but with no available 10/10 HLA-matched donor. • Karnofsky performance status of ≥80% for patients aged ≥16 years and Lansky performance status of ≥ 80% for patients aged < 16 years.
Treatments	Single minimum dose of exa-cel of at least 3.0×10^6 $CD34^+$ cells/kg of body weight via intravenous infusion following standard for autologous HSCT (mobilisation, apheresis and myeloablation). The maximum dose was 20×10^6 $CD34^+$ cells/kg body weight.
Primary outcome	The proportion of patients who had not experienced any severe VOC for ≥ 12 consecutive months (VF12) after exa-cel infusion. A severe VOC was defined as an event of acute pain that led to a visit to a medical facility and the administration of pain medications (opioids or intravenous non-steroidal anti-inflammatory drugs) or RBC transfusion, acute chest syndrome, priapism that lasted for more than 2 hours and led to a visit to a medical facility, or splenic sequestration. The evaluation of VF12 started 60 days after the last RBC transfusion for post-transplant or SCD management.
Secondary outcomes	• Proportion without inpatient hospitalisation for severe VOC for ≥12 consecutive months after exa-cel infusion (HF12) (key secondary outcome). • Duration of severe VOC-free period in patients that achieved VF12.
Statistical analysis	The PES included all patients who received an exa-cel infusion and had at least 16 months follow-up and ≥ 14 months follow-up after RBC transfusion for post-transplant support or SCD management. The FAS included all patients that received an exa-cel

	infusion. The familywise type I error rate was controlled using an alpha spending approach for tests at the interim and final analyses and sequential testing of the primary and key secondary outcome (HF12).

Abbreviations: FAS = full analysis set; Hb = haemoglobin; HbF = foetal haemoglobin; HLA = human leukocyte antigen; HSCT = haematopoietic stem cell transplant; PES = primary efficacy set; RBC = red blood cell; SCD = sickle cell disease; VOC = vaso-occlusive crisis

The submitting company provided results from two data-cuts to support the efficacy and safety of exa-cel for this submission. The April 2023 data cut-off was not pre-specified and was performed for regulatory purposes. The pre-specified August 2024 data cut-off is the most recent set of results with the longest follow-up and has been used in the economic analysis. At the April 2023 data cut-off, median follow-up was 17.5 months in the full analysis set (FAS) and 23.6 months in the primary efficacy set (PES). At the August 2024 data cut-off, median follow-up was 33.2 months in the FAS. At baseline, the mean annualised rate of severe VOCs was 4.2 and has been used to inform the economic model.[1, 9, 10]

Table 2.2: Primary and selected secondary outcomes from CLIMB SCD-121 and CLIMB-131 in the PES[1, 9, 10]

	Exa-cel	
Data cut-off	**April 2023**	**August 2024**
Primary outcome: proportion of patients without a severe VOC for ≥12 consecutive months (VF12) within 24 months after exa-cel infusion		
n/N (%)	28/29 (97%)	37/42 (88%)
VOC-free ≥12 consecutive months (VF12) in CLIMB SCD-121 and CLIMB-131		
n/N (%)	28/29 (97%)	39/42 (93%)[a]
Secondary outcomes		
Duration of severe VOC-free period in patients who achieved VF12 in CLIMB SCD-121 and CLIMB-131		
Achieved VF12, n	28	39
Mean duration	20.7 months	30.9 months
Proportion without inpatient hospitalisation for severe VOC for ≥12 consecutive months (HF12) in CLIMB SCD-121 and CLIMB-131 (key secondary outcome)		
n/N (%)	29/29 (100%)	41/42 (98%)
Proportion of patients with sustained HbF ≥20% for ≥ 12 consecutive months in CLIMB SCD-121		
n/N (%)	29/29 (100%)	NR
Annualised RBC units transfused for SCD indications 12 months after exa-cel infusion		
Mean annualised units at baseline	8.7	NR
Mean annualised units after exa-cel	0.0	NR

Abbreviations: PES: primary efficacy set; NR: not reported; VOC: vaso-occlusive crisis [a]Two patients who did not achieve VF12 in CLIMB SCD-121 achieved VF12 in CLIMB-131.

At the April 2023 data cut-off in the PES, mean Hb levels increased from 9.1 g/dL at baseline to 12.7 g/dL at 6 months and were maintained at ≥ 12 g/dL for the duration of the two year follow-up in CLIMB SCD-121. The mean proportion of total Hb compromised with HbF increased from 5.2% at baseline to 43% at 6 months and was maintained at ≥ 40% over the duration of the two year follow-up.[1] Results from the August 2024 data cut in the FAS were consistent up to 42 months with data from CLIMB-131 included.[9, 10]

The mean proportion of alleles with the intended genetic modification in $CD34^+$ cells of the bone marrow was ≥ 85% from 6 months onwards (up to 24 months follow-up) in the PES and FAS in the April 2023 and August 2024 data cut-offs.[1, 9]

2.2. Health-related quality of life outcomes

Health-related quality of life (HRQoL) was assessed using EQ-5D-5L, Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT), Pain Numeric Rating Scale (NRS) and Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) questionnaires were measured in adults (n=29 or 30) in the PES at the August 2024 data cut-off.[10]
There were intra-patient improvements in the EQ-5D-5L visual analogue scale, Pain NRS scores, bone marrow transplant subscale scores and domains of the ASCQ-ME questionnaire that exceeded the threshold for minimally clinically important differences and were sustained up to 36 months.[12]

There were also clinically meaningful improvements observed in HRQoL outcomes assessed in the adolescent population of the PES (n=12) including Pain NRS and PedsQL (includes physical and psychosocial health) and a trend towards improvement in EQ-5D-Y.[12]

3. Summary of Safety Evidence

Evidence from CLIMB SCD-121 and CLIMB-131 support the safety of exa-cel for the treatment of patients with sickle cell disease. However, there are no comparative safety data available.

At the April 2023 data cut-off, 43 patients had received an infusion of exa-cel and were included in the safety analysis. The median dose was 4.0 (range: 2.9 to 14.4) x 10^6 $CD34^+$ cells/kg and including data from the long-term CLIMB-131 study, the median follow-up was 17.5 months (range: 1.2 to 46.2 months). All patients reported a treatment-emergent adverse event (AE); all of these were related or possibly related to busulfan (a myeloablative conditioning treatment given between two to seven days before an exa-cel infusion) and 30% were considered related or possibly related to exa-cel. The proportion of patients reporting a grade 3 or higher AE was 95%, and 37% reported a serious AE (9.3% related or possibly related to busulfan and none related or possibly related to exa-cel). No patients discontinued the study due to an AE.[1] Results were similar at the August 2024 data cut-off.[9]

Around half of patients (53%) experienced febrile neutropenia within 3 weeks of exa-cel infusion; these were grade 3 or 4 severity in 46% of patients and resolved within 12 days of onset. None were considered related to exa-cel. Grade 3 or 4 infections occurred in 23% of patients and 21% were serious, including cases of pneumonia (9.3%) and sepsis (4.7%). The SPC notes that patients should be monitored for signs of infection. No patients experienced graft failure or graft-versus-host-disease.[1, 2]

Over 70% of AEs, serious AEs and grade ≥ 3 AEs occurred in the first 6 months of treatment, the time-adjusted rate decreased at each subsequent 6-month interval to 24 months. The UK regulator stated that all serious AEs were reflective of busulfan conditioning, the autologous HSCT process and underlying disease, these are generally well recognised and may be managed according to local procedures. However as exa-cel is a novel treatment, long-term safety outcomes will be monitored as part of the risk management plan.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Exa-cel is the first gene therapy licensed for the treatment of sickle cell disease. Patients with sickle cell disease without a suitable stem cell donor have very limited treatment options.
- In patients who had experienced ≥ 2 severe VOCs per year, treatment with an exa-cel infusion resulted in a VOC-free period of ≥ 12 consecutive months (VF12) in 88% (37/42) of patients in CLIMB SCD-121 at the latest August 2024 data cut-off. With longer follow-up in CLIMB-131 an additional two patients subsequently achieved VF12. This is beneficial to patients as recurrent VOCs are associated with acute pain, progressive tissue damage and eventual organ failure.[9, 10, 13]
- At the August 2024 data cut-off most patients (98%) were free from inpatient hospitalisation for severe VOCs for ≥ 12 consecutive months (HF12) which was a key secondary outcome. In results reported from the earlier April 2023 data cut no patients required RBC transfusions starting 12 months after exa-cel. These are clinically relevant advantages for patients.[9, 10, 13]
- Regulators considered exa-cel to be generally safe and well tolerated in the short-term. No specific safety concerns were identified in relation to exa-cel. Most were related to busulfan conditioning, the autologous HSCT process and underlying disease which can be anticipated and managed by experienced clinical teams.[1, 13]
- Exa-cel is a one-off treatment that offers benefit to most patients after a single infusion.

4.2. Key uncertainties

- Evidence from CLIMB SCD-121 and CLIMB-131 is limited to 46 patients with a median follow-up of 33.2 months at the most recent August 2024 data cut-off. Although this may demonstrate short-term efficacy and safety, uncertainty remains regarding sustained efficacy, characterisation of the long-term safety profile and consequences of CRISPR-Cas9 gene editing. This is particularly relevant as sickle cell disease is a lifelong chronic condition.[1, 10]
- There were several methodological issues with CLIMB SCD-121 and CLIMB-131 which make the exact magnitude of benefit less certain including how a severe VOC was defined, the single-arm, open-label nature of the studies and changes to methodology of CLIMB SCD-121 during the study.[1, 13]
- It is uncertain why recurrence of severe VOC episodes affected some patients but not others, and what factors may influence the timing and frequency of an episode(s) post exa-cel infusion (at the August 2024 data cut-off, two patients had ≥1 severe VOC before achieving VF12, four patients who had achieved VF12 experienced a subsequent severe VOC and three patients did not achieve VF12). However, when compared with the VOC rate before treatment, the number of events was substantially reduced for most patients. The submitting company suggests that acute pain events may relate to pre-existing chronic

pain syndromes or organ damage secondary to sickle cell disease however, in those with an initial response, loss of efficacy cannot be ruled out. As part of the conditional marketing authorisation, the UK regulator has requested annual updates of patients who have experienced ≥1 VOC, the dose received, bone marrow and peripheral blood allele edit percentage and foetal haemoglobin levels. This may help to identify factors associated with recurrent VOC events. [1, 9, 10]

- There was a high discontinuation rate from CLIMB SCD-121 before exa-cel was administered; 27% (17/63) of patients enrolled did not receive exa-cel. There were 12 patients who discontinued the study after starting the mobilisation process including five because of inadequate cell collections. It is uncertain if the same discontinuation rate will be reflected in clinical practice, and what patient and disease characteristics influence the ability to successfully manufacture exa-cel. Ongoing and planned exa-cel studies in patients with sickle cell disease may provide additional information to help select those most likely to benefit.[13]
- The study did not include patients aged over 35 years or with a Karnofsky performance status of < 80% in adults or a Lansky performance status < 80% in adolescents aged < 16 years and therefore it is uncertain if results are generalisable to older or less fit patients. Patients included in the studies had at least two severe VOC episodes per year prior to exa-cel treatment, it is uncertain if results would be generalisable to those with fewer severe annual episodes or with a high frequency of less severe events.

4.3. GB conditional marketing authorisation specific obligations

As part of the specific obligations set out by the MHRA, the company will submit the final clinical study report from CLIMB SCD-121 and the interim clinical study report from CLIMB-131 (both due August 2026) with annual updates from CLIMB-131 until the study completes. The additional data from these clinical study reports will provide longer term evidence for efficacy and safety outcomes and may address uncertainty relating to duration of effect and the extended safety profile. However, other uncertainties relating to methodological limitations will remain.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that exa-cel fills an unmet need for patients with severe sickle cell disease due to the chronic nature of the condition, the debilitating effects of VOCs and associated complications, and the lack of effective disease-modifying treatments. They indicated it represents a therapeutic advance as it offers patients suitable for HSCT but with no matched donor the opportunity to receive a potentially curative option which would reduce reliance on other treatments such as RBC transfusions, have significant positive health benefits and improve quality of life. They anticipated it would be used in patients for whom hydroxycarbamide or RBC transfusion is unsuitable or ineffective.

4.5. Service implications

There would be significant service implications associated with the introduction of exa-cel. This includes establishing a multidisciplinary team to identify eligible patients, additional clinical planning and capacity for pre-transplant work-up, the transplant procedure, post-transplant support and the management of complications. Although education sessions and new protocols

may need to be developed, existing measures may already be in progress as exa-cel has previously been made available via the ultra-orphan pathway for the treatment of beta-thalassemia (SMC2709). Independence from RBC transfusions would be advantageous for patients and the service as time to administer and risk of developing complications may be reduced.

The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of exagamglogene autotemcel, as an **orphan** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Severe sickle cell disease (SCD) is a lifelong condition with a high rate of morbidity and mortality that affects children and adults. It is characterised by frequent and unpredictable vaso-occlusive crises (VOCs) that cause severe acute pain. Other symptoms include chronic fatigue and pain, long-term organ damage and life-threatening complications such as stroke and acute chest syndrome. Patients require frequent hospital admissions to treat VOCs and manage symptoms. The average life expectancy is approximately 40 years.

- Living with the disease also has a significant effect on mental health as daily life is restricted by the need to manage symptoms and avoid triggering a crisis. There is extensive disruption to education, employment, and family and social life which can cause patients to become withdrawn and isolated. Having a family member with SCD is extremely difficult for parents and loved ones as seeing them in pain can be stressful and emotionally draining.

- PACE participants agreed there is a significant unmet need for new, effective and potentially curative treatments for severe SCD. There has been a lack of innovative drug development and research in this disease area compared with similar genetic blood conditions. Allogenic haematopoietic stem cell (HSCT) is the only current curative treatment option, but most patients do not have a suitable matched donor. Hydroxycarbamide the only medicine licensed for SCD in Scotland, is not always effective, and many have concerns about side effects. Patients often require repeated red blood cell transfusions which require attendance at hospital, venous access and can have serious side effects.

- Exa-cel is a gene therapy given as a single treatment that could offer consistent and durable benefits to eligible patients who do not have a curative option. A major advantage over current curative-intent treatment with HSCT is that exa-cel is not reliant on the availability of a stem cell donor. In the CLIMB study, 98% of patients were free from hospitalisation for severe crises for >12 months, and 93% were free of severe crises. This could allow patients to live with markedly reduced pain and without the constant fear of unplanned hospital admissions and

life-threatening events. Increased haemoglobin levels will improve fatigue and negate the need for regular red blood cell transfusions. These benefits would have a positive impact on patients' wellbeing, giving them the opportunity to live a near normal life.

- The initial work-up and process for exa-cel manufacture and administration are complex procedures associated with significant side effects. However, patients may consider this burden outweighed by the potential improvements.

Additional Patient and Carer Involvement

- We received a joint patient group submission from Anthony Nolan and the Sickle Cell Society, which are both registered charities. Anthony Nolan has received 1% pharmaceutical company funding in the past two years, with none from the submitting company. Sickle Cell Society has received 7% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from Anthony Nolan and the Sickle Cell Society participated in the PACE meeting. The key points of the joint submission from both organisations have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

An economic case was presented and is summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	A lifetime time horizon of 80 years was used, with a model starting age of 21 years.
Population	Patients with SCD who are 12 years of age and older with recurrent VOCs who have the β^S/β^S, β^S/β^+ or β^S/β^0 genotype, for whom a HSCT is appropriate and an HLA-matched related HSC donor is not available. This matches the licensed indication.
Comparators	The comparator was standard of care (SoC), consisting of hydroxycarbamide and RBC transfusions with iron chelation therapy.
Model description	A cohort Markov state-transition model was used. The Markov model has three SCD severity health states: Severe SCD, Improved SCD, and Cured from SCD. In addition, the Markov model included SCD-related acute and chronic complications as sub-states. A death state was included in the model.
Clinical data	CLIMB SCD-121 and CLIMB-131 were the main sources of clinical efficacy evidence for exa-cel.[1, 8] Data from the August 2024 data cut-off were used to inform most inputs. For exa-cel, key clinical inputs were the treatment response parameters. The proportion of patients with functionally cured SCD (92.9%) was the proportion VOC-free for at least 12 consecutive months. The remaining were the proportion with VOC reduction (that is, Improved SCD) and the proportion with no benefit (that is, Severe SCD) (2.4%). The proportion with VOC reduction was based on patients that experienced significant reductions in VOC frequency, and the proportion with no benefit was based on one patient treated with exa-cel who experienced multiple VOCs 8.8 months after infusion.[1, 9, 10] Baseline clinical inputs of patient demographics, annual VOCs, hydroxycarbamide utilisation, and chronic complications were from CLIMB SCD-121. Utilisation of RBC transfusions and iron chelation therapy were from literature.[18,19] Standardised mortality ratios (SMRs) for non-functionally cured SCD patients were estimated from literature.[20,21] Complication risks for

	acute and chronic complications were from literature.[22]
Extrapolation	SoC patients entered the model in the Severe SCD health state and remained there for the model time horizon. Hence, SoC patients experienced no reduction in baseline annual VOCs of 4.2, complication risks, hydroxycarbamide use or baseline RBC transfusions with iron chelation therapy. Exa-cel patients progressed through a series of tunnel states to reflect the treatment phase, response phase, and maintenance phase. In the 12-month treatment period, exa-cel patients entered the model in the Severe SCD health state, with a baseline annual VOC frequency of 4.2. The treatment phase included pre-mobilisation, mobilisation and apheresis, myeloablative conditioning and exa-cel infusion, and engraftment. In the response phase, exa-cel patients were either functionally cured and transitioned to the Cured from SCD health state (92.9%), transitioned to the Improved SCD health state, or remained in the Severe SCD health state (2.4%). Patients that transitioned to the Cured from SCD health state no longer experienced VOCs or complications, patients that transitioned to Improved SCD had a relative reduction in annual VOCs (the scale of the reduction has been classified as academic in confidence by the submitting company) and a reduced risk of complications, and patients that remained in Severe SCD retained the baseline VOCs and complication risks. RBC transfusions also ceased in the Cured from SCD health state. The maintenance phase was structurally identical to the response phase, as the model did not assume any treatment waning. Mortality in the model was estimated with age-based SCD SMRs for Severe and Improved SCD. For patients functionally cured from SCD, mortality was estimated by applying an assumed SMR of 1.25, to account for the potential impacts of SCD prior to being functionally cured and pre-transplant myeloablative conditioning. Acute complications were extrapolated using rates from the literature and applied on a per-cycle basis. Chronic complications were also extrapolated using literature-based rates, with per-cycle incidence contributing to cumulative prevalence over time.
Quality of life	Utility values for uncomplicated SCD and functionally cured SCD were derived from EQ-5D data collected in the CLIMB SCD-121 study, using baseline values and changes from baseline at 36 months, respectively. The uncomplicated SCD utility value was applied as the baseline health state utility value in the model for Severe SCD and Improved SCD patients. A series of disutilities were then applied to this, including transplant related disutilities, VOCs, and acute and chronic complications. Utilities were also adjusted for age. Caregiver disutilities were considered as a scenario and assumed that caregivers of SCD patients less than or equal to 26 years of age experience utility decrements based on the patient's complications.
Costs and resource use	Costs included treatment acquisition, administration (covering pre-transplant, transplant and post-transplant), RBC transfusions, iron chelation therapy, and adverse events. Patients who withdrew prior to exa-cel infusion incurred a pre-transplant cost uplift and did not incur exa-cel transplantation and treatment-related costs. Disease monitoring, VOCs, acute and chronic complications, and terminal costs were also included in the model. A scenario analysis included societal costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. SMC would wish to present the with-PAS cost-effectiveness results that were used for decision-making. However, SMC is unable to publish these results due to commercial in confidence concerns regarding the PAS.

6.2. Results

The base case estimated that exa-cel was associated with higher costs, but also improved health outcomes, compared to SoC. SMC is unable to present the decision-making economic results as these were classified as commercial in confidence by the submitting company.

*Other data were also assessed but remain confidential.**

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in Table 6.3 below.

Table 6.3: Scenario analyses

	Parameter	Base case	Scenario	ICER (£/QALY)
	Base case			*CiC*
1	Discount rate (costs and outcomes)	3.5%	1.5%	*CiC*
2	Societal benefits	Excluded	Included	*CiC*
3	Baseline age	21 years	12 years	*CiC*
4	Functionally cured (%)	VF-12 CLIMB SCD-121 or CLIMB 131 (92.9%)	VF-12 under 24 months CLIMB-131 (88.1%)	*CiC*
5	Baseline VOCs per year	4.2 VOCs	2.7 VOCs	*CiC*
6	Complication risk cured SCD	Same risk as general population	Increased risk (1.25) compared to the general population	*CiC*
7	ACS complication	Included	Excluded	*CiC*
8	Severe SCD mortality	Literature SMRs reweighted	Literature SMRs not reweighted	*CiC*
9	Carer utility	Excluded	Included	*CiC*
10	Utility values functionally cured SCD	Month 36 change from baseline	Month 24 change from baseline	*CiC*
11	Medicine costs	Base case	Contract pricing	*CiC*
12	Treatment withdrawal prior to exa-cel	Outcomes excluded	Outcomes included	*CiC*
13	DCEA	Excluded	Included	*CiC*
14	Combined scenario: • 2.7 VOCs per year (Scenario 5) • exclusion of ACS as complication (Scenario 8) • using Month 24 change from baseline to obtain Cured SCD utility (Scenario 11)			*CiC*

Abbreviations: ACS = acute chest syndrome; CiC = commercial in confidence; DCEA = distributional cost-effectiveness analysis; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years; SCD = sickle cell disease; SMR = standardised mortality ratio; VOCs = vaso-occlusive crises; VF12= absent from any severe VOCs for at least 12 consecutive months. Note: Hydroxycarbamide is available under a confidential contract price.

*Other data were also assessed but remain confidential.**

6.4. Key strengths

- The comparator in the economic study was appropriate.
- Deterministic sensitivity analysis parameters were varied through appropriate ranges of 95% confidence intervals or 20% variation around the mean.
- The sources used to value costs included in the economic evaluation were appropriate.

6.5. Key uncertainties

- There was uncertainty in the long-term treatment effect assumed in the model. Once exa-cel patients enter the Cured from SCD health state they no longer incur VOCs or SCD-related complications. However, it is noted that four patients in CLIMB SCD-121 and CLIMB-131, who had achieved the endpoint of VOC-free for at least 12 consecutive months, experienced a subsequent severe VOC. Without longer term follow-up data the assumed treatment effect remains uncertain. In addition, there was no scenario analysis to explore a waning effect as the company viewed there to be no mechanism of action that would lead to treatment waning.
- The complications included in the model were subject to uncertainty, limiting the face validity of the complication profile in the economic model. Firstly, the complication risk equations were derived from a population with a higher VOC rate (5.8 per year) than the modelled cohort (4.2 per year from CLIMB SCD-121), which may lead to overestimation of complication risks and associated costs and disutility.[22] Secondly, the risk equations were applied independently and uniformly over time, without accounting for how complication risks may evolve, interact, or influence mortality. However, the application of more complex risk equations to address these issues may have been challenging. Finally, the acute complication of acute chest syndrome may have been double counted, as it was included in the VOC definition in CLIMB SCD-121 and the complication risk literature.[22] A scenario analysis excluded it (Scenario 7). As complications were more prevalent in the SoC arm, these limitations are likely to bias the economic results in favour of exa-cel.
- The annual number of VOCs in the model was subject to uncertainty. The base case applied 4.2 annual VOCs, which was the mean annualised rate of severe VOCs per year for the prior two years before screening in CLIMB SCD-121. However, the mean annualised rate of inpatient hospitalisations for severe VOCs was 2.7 per year in the study. As VOCs in the economic model incur elective inpatient costs, it may have been more appropriate to use this figure. This was considered in a scenario analysis (Scenario 5).
- There were uncertainties with utility values. Firstly, there were multiple timepoints available from baseline to derive the functionally cured SCD utility value. The more conservative value using the change from baseline at Month 24 was considered in a scenario analysis (Scenario 10). Secondly, the utility value for functionally cured SCD patients was similar to EQ-5D UK population norms.[23] This may have been reasonable if cured SCD patients are expected to return to a general population health-related quality of life. However, if there are lasting complications or residual impacts from SCD, this utility may overestimate the actual health-related quality of life.

- A distributional cost-effectiveness analysis (DCEA) was part of the submission. The DCEA assessed the equity impact of exa-cel across different socioeconomic groups. As part of the analysis, cost-effectiveness results were weighted based on an inequality aversion parameter. A key area of uncertainty was this weighting, the Atkinson inequality aversion parameter, which used a base case value of 11. Wider literature has reported lower Atkinson inequality aversion parameters of 1.4 and 3.5, which would increase the equity-weighted incremental cost-effectiveness ratio (ICER) towards the standard cost-effectiveness base case ICER.[24]
- The cost of hydroxycarbamide in NHS practice is lower than the price used in the economic model as a national framework contract price is in place for this medicine. Using the national framework contract price has minimal impact on the cost-effectiveness results.

7. Conclusion

The Committee considered the benefits of exa-cel in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in quality of life was satisfied. In addition, as exa-cel is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted exa-cel for use in NHSScotland.

8. Guidelines and Protocols

The Scottish Paediatric and Adult Haemoglobinopathy Network (SPAH) has published a number of guidelines on management of sickle cell disease, including the use of hydroxycarbamide, RBC transfusions and iron chelation therapy, stem cell transplants, acute chest syndrome and painful sickle cell crisis management.[14, 15]

The British Society for Haematology (BSH) has published a number of guidelines on management of sickle cell disease, including the use of hydroxycarbamide and RBC transfusions, monitoring and management of iron overload and management of acute chest syndrome.[16]

The European Haematology Association Red Cell and Iron Specialised Working Group (EHA SWG) and the European Blood and Marrow Transplant (EBMT) group published a joint consensus statement on recommendations for selecting good sickle cell disease candidates for gene therapy in March 2025.[17]

9. Additional Information

9.1. Product availability date

08 August 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per treatment (£)
exagamglogene autotemcel	**Minimum recommended dose of 3 x 10^6 $CD34^+$ cells/kg, administered as single dose intravenous infusion.**	**1,651,000**

Costs from eMC Dictionary of Medicines and Devices Browser on 08 September 2025. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including **23 October 2025**.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the

operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.