National Institute for Health and Care Excellence

Health Technology Evaluation

Exagamglogene autotemcel for treating sickle cell disease [ID4016]
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Vertex	It is appropriate that the technology under evaluation in this topic is commissioned by the NHS, given the high degree of unmet need in this patient population and the health inequalities faced by people living with sickle cell disease (SCD).	Thank you for your comment. This appraisal has been scheduled into the work programme. No action needed.
	UK Forum on Haemoglobin Disorders	We welcome this appraisal as there is very significant unmet need for patients living with sickle cell anaemia. There are no curative options for patients apart from allogenic stem cell transplant which is not available for most patients.	Thank you for your comment. This appraisal has been scheduled into the work programme. No action needed.

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	Cell and Gene Therapy Catapult	It is timely and appropriate for NICE to assess this technology.	Thank you for your comment. This appraisal has been scheduled into the work programme. No action needed.
	Clinical Reference Group, Haemoglobinopathy, NHS England	We welcome this appraisal as there is very significant unmet need for patients living with sickle cell anaemia. There are no curative options for patients apart from allogenic stem cell transplant which is not available for most patients	Thank you for your comment. This appraisal has been scheduled into the work programme. No action needed.
	Sickle Cell Society	We believe this is a timely and appropriate evaluation. As reflected in the NICE scoping documentation, there are limited treatment options for people living with sickle cell disorder (SCD). Our position is clear. This current situation is frankly unacceptable, having regard to the fact that sickle cell is the country's largest genetic blood disorder. It is also timely because cell and gene therapy are potentially transformative medical innovations which have been successful for other conditions such as cancer, cystic fibrosis, leukaemia and metachromatic leukodystrophy (MLD). The opportunity to make potentially live changing results with gene and cell therapy for sickle cell is welcome. With regard to the proposed evaluation route, initially we were not clear as to why CTX001 was being appraised through an STA route rather than an HST route. On looking at it carefully we understand that it is to do with limited	Thank you for your comment. This appraisal has been scheduled into the work programme. Topics that are appraised through the HST programme need to meet all of the criteria and this topic does not meet the 'no more than 300 people in England are eligible for the technology' criteria. The term

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		number of patients who may be eligible for treatment. From our perspective there are two important points. First that the route of appraisal has sufficient flexibility. Secondly, there is a need for greater definition of severe sickle cell and the categories of patients who are likely to be eligible. We make this point because it is relative to use the term severe. A high proportion of people living with SCD may use severe to describe their condition, particularly at times of serious crises and/or with the impact of complications/fatigue on their quality of life.	'severity' has been removed from the remit (see wording section).
	Anthony Nolan (Patient)	CTX001 (brand name unknown) is an autologous, ex vivo CRISPR/Cas9 gene-edited therapy, which has been trialled in the treatment of patients with severe sickle cell disease. A novel SCD therapy, it employs CRISPR gene editing in autologous hematopoietic stem cells to disrupt the enhancer region required for expression of BCL11A, a repressor of fetal haemoglobin. It would be appropriate to evaluate this technology using the routine NICE appraisal methods for medicines. It is suggested that this gene editing technology has a similar safety profile to myeloablative conditioning and autologous hematopoietic stem cell transplantation. Clinical trial results suggest all patients demonstrated clinically meaningful increases in total haemoglobin (Hb) and Fetal haemoglobin (HbF) which occurred early and have been maintained over time. There remains a significant unmet need in supporting sickle cell patients. Current treatments are supportive rather than curative. Allo-HSCT is now available to both adults and paediatrics on the NHS – whilst it is potentially	Thank you for your comment. This appraisal has been scheduled into the work programme. No action needed.

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		curative, allogeneic transplants come with serious risk factors for patients, with 5-year survival positioned around 50%. It is estimated to affect 1 in 2000 live births and there are around 15,000 people with sickle cell disease in England1. However, BMT registry shows that during 2021-22, only 87 paediatrics patients with sickle cell anaemia received a transplant, with no adult transplant currently identified2. 1 - Sickle Cell Society (2018) Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK 2 - BSBMTCT Executive Summary Of Transplant & Cellular Therapy Outcomes In Uk/Roi A Report For Commissioners 13th Edition	
	British Society for Haematology (The Royal College of Physicians endorse this response).	We welcome this appraisal as there is very significant unmet need for patients living with sickle cell anaemia. There are no curative options for patients apart from allogenic stem cell transplant which is not available for most patients. In our view, it is appropriate to evaluate CTX001 for treating severe sickle cell disease. CTX001 is an expensive and potentially high risk novel technique for the management of those with sickle cell disease, and competes with several other treatment options including disease modification with hydroxycarbamide, an automated red cell exchange transfusion programme, fully matched sibling reduced intensity conditioning stem cell transplantation, and haplo-identical reduced intensity stem cell transplantation. Voxelotor and Crizanlizumab are, in my view, not appropriate comparators as their utility is not established in sickle cell disease.	Thank you for your comment. This appraisal has been scheduled into the work programme. Voxelotor and crizanlizumab will not be included as relevant comparators in the draft scope (see comparators).

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Wording	Vertex	The correct International Non-proprietary Name (INN) for the technology is exagamglogene autotemcel (exa-cel), and the scope should be updated throughout to reflect this. Exa-cel is a genetically modified autologous CD34+ cell enriched population that contains human haematopoetic stem and progenitor cells (hHSPCs) edited ex vivo by CRISPR/Cas9 at the erythroid-specific enhancer region of the BCL11A gene. Vertex suggests that 'severe' is removed from the scope. We would recommend exa-cel is used in keeping with the proposed marketing authorisation, which is [redacted]	Thank you for your comment. The technology name 'CTX001' has been amended to 'exagamglogene autotemcel' throughout the draft scope. Thank you for your comment. The remit has been amended.
	UK Forum on Haemoglobin Disorders	The term 'severe sickle cell disease' is broad and is subject to interpretation by referring clinicians, which may in turn lead to potential inequities to access of this treatment. However, if we were only to include patients who were included in the CLIMB SCD trial, we will exclude a very large and significant group of patients, namely those who had a stroke and are on blood transfusions for it. Our view is to broaden the scope to include patients who are currently eligible for stem cell transplant in the NHS, but do not have a matched sibling donor namely:	Thank you for your comment. The remit has been amended to remove 'severe' and reflect the wording submitted for regulatory approval. Exagamglogene autotemcel will be appraised within its

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		• History of >= 3 severe pain crises or other acute complications per year despite institution of supportive care measures (optimal treatment with hydroxycarbamide (HC) or transfusion therapy). Other acute complications would include acute hepatopathy or splenic sequestration or acute priapism. (This can be further refined using the CLIMB SCD trial inclusion criteria, namely patients with severe sickle cell disease having at least two vaso-occlusive crisis events per year for two consecutive years and documented severe sickle cell disease genotype) • Recurrence of acute chest syndrome despite optimum treatment with hydroxycarbamide (HC) or transfusion therapy • Clinically significant neurologic vascular event or deficit lasting over 24 hours and confirmed radiologically (i.e. stroke) or progressive cerebral vasculopathy • Administration of regular transfusion therapy, either by simple transfusion or exchange transfusion with the aim to prevent severe sickle complications by maintaining a low HbS%. Severe sickle complications include a history of >= 2 chest syndromes, >= 3 painful crises or severe recurrent priapism • Patients assessed as requiring transfusion but with red cell allo-antibodies/very rare blood type, rendering it difficult to continue/commence chronic transfusion • Patients requiring hydroxycarbamide/transfusion for treatment of SCD complications who cannot tolerate either therapy due to significant adverse reactions	marketing authorisation for sickle cell disease.

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		• Established end organ damage relating to SCD including but not limited to progressive sickle vasculopathy and hepatopathy.	
	Cell and Gene Therapy Catapult	Yes	Thank you for your comment. No action needed.
	Clinical Reference Group, Haemoglobinopathy, NHS England	The term 'severe sickle cell disease' is broad and is subject to interpretation by referring clinicians, which may in turn lead to potential inequities to access of this treatment. However, if we were only to include patients who were included in the CLIMB SCD trial, we will exclude a very large and significant group of patients, namely those who had a stroke and are on blood transfusions for it. Our view is to broaden the scope to include patients who are currently eligible for stem cell transplant in the NHS, but do not have a matched sibling donor namely: • History of >= 3 severe pain crises or other acute complications per year despite institution of supportive care measures (optimal treatment with hydroxycarbamide (HC) or transfusion therapy). Other acute complications would include acute hepatopathy or splenic sequestration or acute priapism. (This can be further refined using the CLIMB SCD trial inclusion criteria, namely patients with severe sickle cell disease having at least two vaso-occlusive crisis events per year for two consecutive years and documented severe sickle cell disease genotype)	Thank you for your comment. The remit has been amended to remove 'severe' and reflect the wording submitted for regulatory approval. Exagamglogene autotemcel will be appraised within its marketing authorisation for sickle cell disease.

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		• Recurrence of acute chest syndrome despite optimum treatment with hydroxycarbamide (HC) or transfusion therapy • Clinically significant neurologic vascular event or deficit lasting over 24 hours and confirmed radiologically (i.e. stroke) or progressive cerebral vasculopathy • Administration of regular transfusion therapy, either by simple transfusion or exchange transfusion with the aim to prevent severe sickle complications by maintaining a low HbS%. Severe sickle complications include a history of >= 2 chest syndromes, >= 3 painful crises or severe recurrent priapism • Patients assessed as requiring transfusion but with red cell allo-antibodies/very rare blood type, rendering it difficult to continue/commence chronic transfusion • Patients requiring hydroxycarbamide/transfusion for treatment of SCD complications who cannot tolerate either therapy due to significant adverse reactions • Established end organ damage relating to SCD including but not limited to progressive sickle vasculopathy and hepatopathy.	
	Sickle Cell Society	We believe the wording of the remit does reflect the issue of clinical effectiveness about the technology. However, without prejudice to any commercial considerations, it is well known that cell and gene therapy is significantly expensive. This therefore supports our argument for greater clarity on the definition of severe and the likely eligible patients is necessary.	Thank you for your comment. The remit has been amended to remove ‘severe’ and reflect the wording

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			submitted for regulatory approval.
	Anthony Nolan (Patient)	The wording of the remit is reflective of the wide parameters allowed as part of the technology's MHRA Innovation Passport. A single-arm, open-label, multi-site, single-dose Phase 1/2/3 study in subjects with severe sickle cell disease (SCD) is ongoing. Ages Eligible for Study: 12 Years to 35 Years. The remit should continue to reflect the widest parameters to which efficacy and improved quality of life can be assured.	Thank you for your comment. No action needed.
	British Society for Haematology (The Royal College of Physicians endorse this response).	The term 'severe sickle cell disease' is broad and is subject to interpretation by referring clinicians, which may in turn lead to potential inequities to access of this treatment. However, if we were only to include patients who were included in the CLIMB SCD trial, we will exclude a very large and significant group of patients, namely those who had a stroke and are on blood transfusions for it. Our view is to broaden the scope to include patients who are currently eligible for stem cell transplant in the NHS**, but do not have a matched sibling donor** namely: • History of >= 3 severe pain crises or other acute complications per year despite institution of supportive care measures (optimal treatment with hydroxycarbamide (HC) or transfusion therapy). Other acute complications would include acute hepatopathy or splenic sequestration or acute priapism. (This can be further refined using the CLIMB SCD trial inclusion criteria, namely patients with severe sickle	Thank you for your comment. The remit has been amended to remove 'severe' and reflect the wording submitted for regulatory approval. Exagamglogene autotemcel will be appraised within its marketing authorisation for sickle cell disease. The cost effectiveness of exagamglogene autotemcel will cover all

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		cell disease having at least two vaso-occlusive crisis events per year for two consecutive years and documented severe sickle cell disease genotype) • Recurrence of acute chest syndrome despite optimum treatment with hydroxycarbamide (HC) or transfusion therapy • Clinically significant neurologic vascular event or deficit lasting over 24 hours and confirmed radiologically (i.e. stroke) or progressive cerebral vasculopathy • Administration of regular transfusion therapy, either by simple transfusion or exchange transfusion with the aim to prevent severe sickle complications by maintaining a low HbS%. Severe sickle complications include a history of >= 2 chest syndromes, >= 3 painful crises or severe recurrent priapism • Patients assessed as requiring transfusion but with red cell allo-antibodies/very rare blood type, rendering it difficult to continue/commence chronic transfusion • Patients requiring hydroxycarbamide/transfusion for treatment of SCD complications who cannot tolerate either therapy due to significant adverse reactions • Established end organ damage relating to SCD including but not limited to progressive sickle vasculopathy and hepatopathy. The wording does partially reflect the issues of clinical and cost effectiveness, but does not, in our view, adequately consider the costs of current management, with the most severely affected individuals with sickle cell disease requiring frequent emergency admissions, end organ damage, and	relevant benefits and costs to the NHS.

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		financial and psychosocial impact of living with a lifelong unpredictable painful life shortening condition.	
Timing	Vertex	Given the fact that this group of patients has a high degree of unmet need, significant disease burden and lack of access to potentially transformative treatments, this topic should be prioritised by the NHS.	Thank you for your comment. NICE aims, where possible, to produce timely guidance in line with marketing authorisation. No action needed.
	UK Forum on Haemoglobin Disorders	There are very limited disease modifying therapies for sickle cell patients and more importantly there are no real curative treatments for patients suffering from frequent sickle cell crises apart from allogenic bone marrow transplant which is limit in its availability due to lack of suitable matched siblings. There is a high unmet need for this cohort of patients who live with a disease that can result in unpredictable, severe and often life-threatening complications. This should be viewed as a high priority for the NHS.	Thank you for your comment. NICE aims, where possible, to produce timely guidance in line with marketing authorisation. No action needed.
	Cell and Gene Therapy Catapult	It is appropriate for NICE to evaluate this topic urgently given the high unmet need on the patient population and the novel nature of the gene therapy technology.	Thank you for your comment. NICE aims, where possible, to produce timely guidance in line with marketing authorisation. No action needed.

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	Clinical Reference Group, Haemoglobinopathy, NHS England	There are very limited disease modifying therapies for sickle cell patients and more importantly there are no real curative treatments for patients suffering from frequent sickle cell crises apart from allogenic bone marrow transplant which is limit in its availability due to lack of suitable matched siblings. There is a high unmet need for this cohort of patients who live with a disease that can result in unpredictable, severe and often life-threatening complications. This should be viewed as a high priority for the NHS.	Thank you for your comment. NICE aims, where possible, to produce timely guidance in line with marketing authorisation. No action needed.
	Sickle Cell Society	NICE appraisal needs to fully take into account that SCD is significantly behind like conditions such as Haemophilia and Cystic Fibrosis when it comes to the range and choice of available safe and effective treatments. Cell and gene therapies are recognised as leading edge innovative and transformative technology in treating and curing certain conditions. There have been many examples including for like conditions such as Cystic Fibrosis. Earlier this week, a new gene therapy treatment; Libmeldy was also approved for treating MLD. From a patient advocacy perspective, it is vitally important to understand how far cell and gene therapy has travelled for SCD. Only 3 years ago another potential SCD gene therapy treatment was withdrawn for use in the UK by a company but deemed appropriate for the USA market. Our point here is simple- how far has CTX001 travelled in terms of safety and efficacy during those 3 years. We have noted the Abstract-LB2367 presented at the European Haematology Association conference in June 2022. Nevertheless, we would like to see more data and evidence of distance travelled for safety and efficacy.	Thank you for your comment. NICE aims, where possible, to produce timely guidance in line with marketing authorisation.

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		We strongly believe that more information for patients and health care professionals is needed. Whilst we have a basic understanding of the CRISPR model of existing haematopoietic stem cells, correcting them and replacing them. What is not so transparent to the patient community and indeed many health care professionals in the SCD space, is the side effects of cell and gene therapy for SCD. If it is to be used for those individuals with severe sickle cell, then it is quite possible that those individuals will also have other immune issues/health challenges, which may heighten risks and side effects. There are lessons about the impacts of side effects for bone marrow transplantation. We are collaborating with the REDRESS clinical trial to assess the effect of related haplo-donor haematopoietic stem cell transplantation compared to standard treatment. This is merely to illustrate that cell and gene therapy technology is still new and developing.	
	Anthony Nolan (Patient)	A significant clinical unmet need does exist for sickle cell patients in needing a curative treatment to their disease. Except for allo-HSCT in the most acute cases, carrying its own risk factors, most SCD patients are having to struggle with maintenance therapies to manage vaso-occlusive crises (VOCs). VOC treatments such as hydroxycarbamide, a myelosuppressive agent, usually decreases the rate of painful episodes by 50%1. RBC transfusions do play a role for managing acute and chronic complications in sickle cell disease. However, it is not without the risks of iron overload, alloimmunisation, and delayed haemolytic transfusion reactions4.	Thank you for your comment. No action needed.

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		Accessing these treatments have also been found to be problematic, with complicated and confused emergency clinical pathways, with poor communication with specialist haematological teams. This has too regularly left SCD patients in crisis, unsupported and poorly identified as needing acute specialist care to manage their acute, potentially life-threatening symptoms. 3 - Agrawal RK, Patel RK, Shah V, Nainiwal L, Trivedi B. Hydroxyurea in sickle cell disease: drug review. Indian J Hematol Blood Transfus. 2014 Jun;30(2):91-6. doi: 10.1007/s12288-013-0261-4. Epub 2013 May 24. PMID: 24839362; PMCID: PMC4022916. 4 - Stella T. Chou; Transfusion therapy for sickle cell disease: a balancing act. Hematology Am Soc Hematol Educ Program 2013; 2013 (1): 439–446. doi: https://doi.org/10.1182/asheducation-2013.1.439	
	British Society for Haematology (The Royal College of Physicians endorse this response).	There are very limited disease modifying therapies for sickle cell patients and more importantly there are no real curative treatments for patients suffering from frequent sickle cell crises apart from allogenic bone marrow transplant which is limit in its availability due to lack of suitable matched siblings. There is a high unmet need for this cohort of patients who live with a disease that can result in unpredictable, severe and often life-threatening complications. This should be viewed as a high priority for the NHS. Newer therapies such as Crizanlizumab and Voxeletor have become available, but neither are curative.	Thank you for your comment. NICE aims, where possible, to produce timely guidance in line with marketing authorisation. No action needed.

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		The sickle cell disease community have faced a long history of under provision and underfunding of services, and a lack of effective new treatment options, as well as stigmatisation and systemic prejudice. They are soon also likely to be disappointed by the lack of efficacy of Crizanlizumab and Voxelotor, both of which were hyped by the media. Fully matched sibling reduced intensity stem cell transplants for eligible patients over 19 years with sickle cell disease have been available and funded by NHS England for just over a year, but the majority of patients do not have a suitable donor. There is therefore relative urgency to evaluate CTX001 in order to provide treatment options for those with severe sickle cell disease.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Vertex	The background information is mostly accurate, but Vertex would suggest the following amendments to more fully illustrate the disease burden: <u>Disease background</u> • "Management in England focuses on reducing the chances of experiencing a sickle cell crisis by avoiding dehydration, sudden changes in temperature and infection" is not an accurate summary of overall management. Vertex suggests replacing this with the following context: 'Standard of care in England includes education about and	Thank you for your comment. The scope background has been amended.

Section	Consultee/ Commentator	Comments [sic]	Action
		prevention of the acute and chronic complications of SCD in addition to treatment of acute complications, particularly sickle cell crises, when they occur'. • The scope states "Hydroxycarbamide can also be used to increase the production of foetal haemoglobin, which improves blood cell hydration and reduces red blood cell adhesion. This can reduce both acute painful crises and acute chest syndrome (caused by reduced blood flow in the lungs) in people with recurrent painful crises". Vertex suggests amending this statement to reflect the fact that hydroxycarbamide has also been shown to reduce VOCs and acute chest syndrome in infants with the HbSS/HbSβ0 genotypes prior to the development of recurrent painful crises and should be discussed with the parents/carers of all infants with SCD. Hydroxycarbamide has also been shown to improve anaemia, reduce some long-term outcomes and improve survival. • The description of blood transfusions (exchange and top-up) for disease management in SCD is accurate, but it is important to note that transfusion therapy can be used to treat acute complications and can also be given regularly (i.e., long term transfusion therapy) to prevent disease complications. The availability of blood can be compromised by the chronic shortage of ethnically matched blood stocks available to treat patients of Black heritage and ensure optimal treatment outcomes. Moreover, overall supplies of donor blood are often low, particularly during the winter months during which patients with SCD are at greatest risk of experiencing VOCs, as demonstrated	Thank you for your comment. The draft scope background has been amended to better reflect the use of hydroxycarbamide for treating sickle cell disease. Thank you for your comment. The draft scope background has been updated to better reflect the use of blood transfusions for treating sickle cell disease.

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		by the recent 'Amber Alert' declared by NHS Blood and Transplant (NHSBT) in October 2022. Blood transfusion can also be complicated by iron overload and the risk of red cell alloimmunisation which can lead to delayed haemolytic transfusion reactions. • The scope states that 'Allogeneic stem cell transplants (SCT)...are not often performed because of the substantial risks involved.' Vertex note that allogeneic transplantation from HLA matched family donors are the most commonly performed type of allogeneic transplant and is the only type of allogeneic transplant commissioned in SCD. While allogeneic SCT does carry a risk of graft-versus-host disease (GvHD), the primary obstacle with this procedure is therefore a lack of matched donors, with fewer than 1 in 5 patients having a suitable donor required for this procedure. • Vertex recommends updating the disease background information to reflect the burden of illness that SCD patients face. People with SCD experience acute complications, including life-threatening VOCs, acute chest syndrome (ACS), splenic sequestration and stroke, as well as chronic end-organ damage. VOCs may often manifest as pain crises, which can start in childhood and thereafter occur with varying degrees of severity and frequency. Chronic organ complications become the main cause of morbidity and mortality in patients with SCD around the third decade of life. Although survival estimates have improved in the last few decades, life expectancy for patients with SCD is reduced by over 30 years compared to that of the general population. In an analysis of the UK Health Episodes Statistics (HES)	Thank you for your comment. The draft scope background has been amended to better reflect the use of allogenic stem cell transplants for treating sickle cell disease. Thank you for your comment. The scope background has been amended.

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		database examining mortality rates of patients with SCD in England from 2009 to 2018, the mean age at death was 46.7 years. • The continual unmet need faced by people with SCD is further illustrated by the preliminary results of a recent global longitudinal survey, in which despite receiving treatment for SCD, participants reported substantial impacts on all health dimensions of the EQ-5D-5L index, lower utility scores, increased pain and stiffness, high work productivity loss and activity impairment, and feelings of unfair treatment when seeking care, compared to the general population. In SWAY (Sickle Cell World Assessment Survey), an international cross-sectional survey of patients with SCD, 38% (817 of 2,145) of survey participants reported that SCD impacted their ability to perform daily household activities, including housework and taking care of children, while 62% (1,321 of 2,145) reported that SCD led them to avoid intense exercise. • SWAY results also indicate a substantial impact of SCD on social functioning – 32% (441 of 1,376) survey participants reported that SCD impacted their relationships with their spouse or partner xii. Furthermore, 60% (1,277 of 2,145) of SWAY survey participants reported that SCD had a high impact on emotional wellbeing, including frustration with symptoms and concern about worsening disease, while 39% (827 of 2,145) reported depression and 38% (807 of 2,145) reporting anxiety in the month prior to survey completion xii • Caregivers of children with SCD have been shown to have a lower quality of life compared with the general population. <u>The technology</u>	

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		• The correct INN for the technology is exagamglogene autotemcel (exa-cel), and the scope should be updated throughout to reflect this. Exa-cel is a genetically modified autologous CD34+ cell enriched population that contains human haematopoetic stem and progenitor cells (hHSPCs) edited ex vivo by CRISPR/Cas9 at the erythroid-specific enhancer region of the BCL11A gene.	Thank you for your comment. The technology name 'CTX001' has been amended to 'exagamglogene autotemcel'.
	UK Forum on Haemoglobin Disorders	This is a very complex disease but in lay terms this is reasonable. Blood transfusion is used for patients with frequent vaso-occlusive crisis or serious complications to reduce end organ damage. However, there are complications as a consequence of transfusion such as iron overload which need to be noted. In addition, blood is not fully matched for patients due to ethnic variations in blood groups and hence blood may sometimes not be available for patients needing emergency exchange transfusions or patients may develop complex and multiple antibodies against blood groups that make provision of blood challenging for patients.	Thank you for your comment. The draft scope background has been updated to better reflect the use of blood transfusions for treating sickle cell disease.
	Cell and Gene Therapy Catapult	No comment	Thank you for your comment. No action needed.
	Clinical Reference Group, Haemoglobinop	This is a very complex disease but in lay terms this is reasonable. Blood transfusion is used for patients with frequent vaso-occlusive crisis or serious complications to reduce end organ damage. However, there are complications as a consequence of transfusion such as iron overload which need to be noted. In addition, blood is not fully matched for patients due to ethnic variations in blood groups and hence blood may sometimes not be	Thank you for your comment. The draft scope background has been updated to better reflect the use of blood

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	athy, NHS England	available for patients needing emergency exchange transfusions or patients may develop complex and multiple antibodies against blood groups that make provision of blood challenging for patients.	transfusions for treating sickle cell disease.
	Sickle Cell Society	The scope is not accurate in that the numbers of people living with SCD is at least 18,000 (DHSC/NHS England –November 2022)	Thank you for your comment. The draft scope has been updated.
	Anthony Nolan (Patient)	The background text would benefit from including the following additional points: • Should clarify that allo-HSCT is available to both paediatrics and adults. And state the multiple mortality and late-effects that transplant can carry. • Should state that emergency admissions require contact to be made with specialist crisis teams or the patient's own clinical team to advise on acute management.	Thank you for your comment. The background section aims to provide a brief summary of the disease and how it is managed, it is not designed to exhaustive in its detail. Scope unchanged.
	British Society for Haematology (The Royal College of Physicians endorse this response).	This is a very complex disease but in lay terms this is reasonable. Blood transfusion is used for patients with frequent vaso-occlusive crisis or serious complications to reduce end organ damage. However, there are complications as a consequence of transfusion such as iron overload which need to be noted. In addition, blood is not fully matched for patients due to ethnic variations in blood groups and hence blood may sometimes not be available for patients needing emergency exchange transfusions or patients may develop complex and multiple antibodies against blood groups that make provision of blood challenging for patients.	Thank you for your comment. The draft scope background has been updated to better reflect the use of blood transfusions and allogenic stem cell

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		"Allogenic stem cell transplant is the only currently available therapy that can cure sickle cell disease and may be considered,[6] but is not done often because of the substantial risks involved.[7]" – should also include the fact that only reduced intensity fully matched sibling donor stem cell transplants are currently funded for the over 19 age group, and most patients will not have a suitable sibling donor, because sickle cell disease is an inherited disorder and some siblings will also be affected and family sizes are often small because of the additional burden of caring for a child with a long term health problem.	transplants for treating sickle cell disease.
Population	Vertex	Vertex suggests redefining the population to better align with the proposed indication, i.e., [redacted]	Thank you for your comment. The population has been amended to remove 'severe' and reflect the wording submitted for regulatory approval. No further changes have been made in order to keep the population broad in the scope. The committee will consider if it is appropriate to make a recommendation for a

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			narrower population and will only be able to make recommendations within the marketing authorisation for this technology.
	UK Forum on Haemoglobin Disorders	The definition of sickle cell patients eligible for treatment needs to be aligned with the trial inclusion criteria and also match with the inclusion criteria currently offered to those patients with matched sibling donors. This will help improve access of care to patients who do not have a matched donor.	Thank you for your comment. The population been amended to remove 'severe'. No further changes have been made in order to keep the population broad in the scope. The committee will consider if it is appropriate to make a recommendation for a narrower population and will only be able to make recommendations within the marketing authorisation for this technology.

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	Cell and Gene Therapy Catapult	To avoid ambiguity the definition of “severe” SCD should be clarified. It should also be noted that the CLIMB-121 trial focused on a narrower population that do not have access to a matched donor stem cell transplant. This subpopulation is likely to have a greater unmet need.	Thank you for your comment. The population been amended to remove ‘severe’. No further changes have been made in order to keep the population broad in the scope. The committee will consider if it is appropriate to make a recommendation for a narrower population and will only be able to make recommendations within the marketing authorisation for this technology.
	Clinical Reference Group, Haemoglobinopathy, NHS England	The definition of sickle cell patients eligible for treatment needs to be aligned with the trial inclusion criteria and also match with the inclusion criteria currently offered to those patients with matched sibling donors. This will help improve access of care to patients who do not have a matched donor.	Thank you for your comment. The population been amended to remove ‘severe’. No further changes have been

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			made in order to keep the population broad in the scope. The committee will consider if it is appropriate to make a recommendation for a narrower population and will only be able to make recommendations within the marketing authorisation for this technology.
	Sickle Cell Society	Yes but see point above about accuracy of the population.	Thank you for your comment. No action needed.
	Anthony Nolan (Patient)	The defined populations is in line with the parameters of the single-arm, open-label, multi-site, single-dose Phase 1/2/3 study.	Thank you for your comment. No action needed.
	British Society for Haematology (The Royal College of	The definition of sickle cell patients eligible for treatment needs to be aligned with the trial inclusion criteria and also match with the inclusion criteria currently offered to those patients with matched sibling donors. This will help improve access of care to patients who do not have a matched donor.	Thank you for your comment. The population been amended to remove

Section	Consultee/ Commentator	Comments [sic]	Action
	Physicians endorse this response).	Given the potential risk of this treatment only the most severely affected, usually HbSS or HbS beta zero genotypes rather than HbSC and HbS beta plus thalassaemia who are usually much more mildly affected.	'severe'. No further changes have been made in order to keep the population broad in the scope. The committee will consider if it is appropriate to make a recommendation for a narrower population and will only be able to make recommendations within the marketing authorisation for this technology.
Subgroups	Vertex	The draft scope does not describe any subgroups and it is not appropriate that subgroups be examined in this appraisal.	Thank you for your comment. No action required.
	Cell and Gene Therapy Catapult	If the current population definition remains the same, then a subgroup of patients who do not have access to a matched donor stem cell transplant could be considered separately since the unmet need may be greater and the cost-effectiveness of CTX001 may differ for these patients.	Thank you for your comment. The population has been amended to remove 'severe'.

Section	Consultee/ Commentator	Comments [sic]	Action
			The committee will consider if it is appropriate to make a recommendation for a narrower population and will only be able to make recommendations within the marketing authorisation for this technology.
	Sickle Cell Society	No subgroups have been suggested in the scope, hence questioning the definition of severe sickle cell and to whom it applies.	Thank you for your comment. The wording throughout the draft scope has been amended to remove 'severe'. No action needed.
	Anthony Nolan (Patient)	N/A	Thank you for your comment. No action required.
	British Society for Haematology,	As above – subgroups including more mildly affected individuals including those with HbSC and HbS beta plus thalassaemia are unlikely to benefit from this relatively high-risk treatment strategy.	Thank you for your comment. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	(The Royal College of Physicians endorse this response).		
Comparators	Vertex	Allogeneic stem cell transplants should not be considered a comparator, as patients with a HLA-matched related haematopoietic stem cell donor were not eligible to participate in the CLIMB-121 study. Therefore, this intervention is not aligned with our anticipated marketing authorisation, namely: [redacted]	Thank you for your comment. Allogenic stem cell transplant has been removed from the comparator list in line with the trial that excluded people who had a matched donor available.
	UK Forum on Haemoglobin Disorders	Comparators such as standard of care, hydroxyurea are appropriate as is transfusion with the associated caveats that response to hydroxyurea on a lifetime basis varies and blood transfusion has associated risks including impact of blood shortages and lack of suitable donors. Allogeneic stem cell transplant is available to a minority of patients. Direct comparison with CTX001 and stem cell transplant may be redundant because it is very likely that only patients who cannot have a sibling SCT due to lack of suitable donor will be initially eligible for CTX001 treatment**.**	Thank you for your comment. Allogenic stem cell transplant has been removed from the comparator list.
	Cell and Gene Therapy Catapult	Stem cell transplant should be removed as a comparator for any analyses that focus on patients that do not have access to this treatment.	Thank you for your comment. Allogenic stem cell transplant has

Section	Consultee/ Commentator	Comments [sic]	Action
			been removed from the comparator list.
	Genetic Alliance UK	It is important to note that not everyone with sickle cell disease is able to tolerate hydroxycarbamide meaning those individuals have even fewer alternative treatment options to choose from.	Thank you for your comment. No action needed.
	Clinical Reference Group, Haemoglobinopathy, NHS England	Comparators such as standard of care, hydroxyurea are appropriate as is transfusion with the associated caveats that response to hydroxyurea on a lifetime basis varies and blood transfusion has associated risks including impact of blood shortages and lack of suitable donors. Allogeneic stem cell transplant is available to a minority of patients. Direct comparison with CTX001 and stem cell transplant may be redundant because it is very likely that only patients who cannot have a sibling SCT due to lack of suitable donor will be initially eligible for CTX001 treatment.	Thank you for your comment. Allogenic stem cell transplant has been removed from the comparator list.
	Sickle Cell Society	The comparators are broadly correct. However, Crizanlizumab was very recently approved under a managed access scheme. Whilst this is currently subject to review, it remains the fact that there are patients receiving Crizanlizumab. Again, as far as the scope is concerned, it would have been helpful for NICE to explain the rationale for not including this as a comparator. The comparator of standard treatment serves to illustrate how bereft SCD is for a range of safe and effective treatments, when the most common standard treatment Hydroxyurea is not tolerated by some SCD patients, because of its side effects.	Thank you for your comment. Crizanlizumab was not included as a relevant comparator for this appraisal because it is recommended in managed access. Technologies that NICE has recommended with managed access are

Section	Consultee/ Commentator	Comments [sic]	Action
			not considered established practice in the NHS and are not considered suitable comparators. No action needed.
	Anthony Nolan (Patient)	Comparators look to be in line with standard of care	Thank you for your comment. No action needed.
	British Society for Haematology (The Royal College of Physicians endorse this response).	Comparators such as standard of care, hydroxyurea are appropriate as is transfusion with the associated caveats that response to hydroxyurea on a life time basis varies and blood transfusion has associated risks including impact of blood shortages and lack of suitable donors. Allogeneic stem cell transplant is available to a minority of patients. Direct comparison with CTX001 and stem cell transplant may be redundant because it is very likely that only patients who cannot have a sibling SCT due to lack of suitable donor will be initially eligible for CTX001 treatment. CTX001 is an expensive and potentially high-risk novel technique for the management of those with sickle cell disease, and competes with several other treatment options including disease modification with hydroxycarbamide, an automated red cell exchange transfusion programme, fully matched sibling reduced intensity conditioning stem cell transplantation, and haplo-identical reduced intensity stem cell transplantation.	Thank you for your comment. Allogenic stem cell transplant has been removed from the comparator list. Crianlizumab has not been included as a comparator because technologies that NICE has recommended with managed access are not considered established practice in the NHS and are not considered suitable comparators. Voxelotor

Section	Consultee/ Commentator	Comments [sic]	Action
		Voxelotor and Crizanlizumab are, in my view, not appropriate comparators as their utility is not established in sickle cell disease.	has not been included because it is not established clinical practice.
Outcomes	Vertex	The outcomes listed are appropriate, except for the following omissions: free from inpatient hospitalisation for VOCs for 12 months, reduction in annualised rate of VOCs, duration of VOC-free status. In addition, Vertex suggest rewording the outcome “complications arising from sickle cell crises” to read “complications arising from sickle cell disease”.	Thank you for your comment. The wording for the outcome “complications arising from sickle cell crises” has been amended to “complications arising from sickle cell disease”. However, the examples of additional outcomes have not been added to the outcomes list, in order to keep the outcomes listed broad.
	UK Forum on Haemoglobin Disorders	These are appropriate but the term complications arising from sickle cell crisis is very unclear. Is the outcome looking at events that happen to patients during a VOC or is the intention to look at complications that occur as part of sickle cell disease such a pulmonary hypertension and sickle nephropathy. If the intention is to assess ability of this therapy to prevent long term complications, then the wording needs to be corrected to state, ‘complications arising as a consequence of sickle cell disease’.	Thank you for your comment. The wording for the outcome “complications arising from sickle cell crises” has been amended to

Section	Consultee/ Commentator	Comments [sic]	Action
		We would suggest the following outcomes: • changes to haematological parameters (haemoglobin levels) • proportion of subjects not needing any disease modifying treatment, including blood transfusion, hydroxyurea, crizanlizumab and voxelotor following treatment with CTX001 gene therapy • proportion of subjects who have not experienced any sickle vaso-occlusive episodes for at least 12 consecutive months • proportion of subjects who have not had any further stroke or progression of cerebrovascular disease in those with established cerebrovascular disease • proportion of subjects able to come off long term opioids 12 months following treatment • proportion of subjects who have no progression of organ dysfunction, as measured by echocardiogram, pulmonary function tests, glomerular filtration rate, • time to engraftment • proportion of subjects with no off-target effects of CTX001 gene therapy, including development of therapy related myelodysplasia or leukaemia • mortality • adverse effects of mobilisation, myeloablation, neutropaenia • health-related quality of life.	"complications arising from sickle cell disease". However, the examples of **additional outcomes** have **not been added** to the outcomes list, in order to keep the outcomes listed broad.
	Cell and Gene Therapy Catapult	No comment	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Clinical Reference Group, Haemoglobinopathy, NHS England	These are appropriate but the term complications arising from sickle cell crisis is very unclear. Is the outcome looking at events that happen to patients during a VOC or is the intention to look at complications that occur as part of sickle cell disease such a pulmonary hypertension and sickle nephropathy. If the intention is to assess ability of this therapy to prevent long term complications, then the wording needs to be corrected to state 'complications arising as a consequence of sickle cell disease' We would suggest the following outcomes: • changes to haematological parameters (haemoglobin levels) • proportion of subjects not needing any disease modifying treatment, including blood transfusion, hydroxyurea, crizanlizumab and voxelotor following treatment with CTX001 gene therapy • proportion of subjects who have not experienced any sickle vaso-occlusive episodes for at least 12 consecutive months • proportion of subjects who have not had any further stroke or progression of cerebrovascular disease in those with established cerebrovascular disease • proportion of subjects able to come off long term opioids 12 months following treatment • proportion of subjects who have no progression of organ dysfunction, as measured by echocardiogram, pulmonary function tests, glomerular filtration rate, • time to engraftment • proportion of subjects with no off-target effects of CTX001 gene therapy, including development of therapy related myelodysplasia or leukaemia • mortality	Thank you for your comment. The wording for the outcome "complications arising from sickle cell crises" has been amended to "complications arising from sickle cell disease". However, the examples of **additional outcomes** have **not been added** to the outcomes list, in order to keep the outcomes listed broad.

Section	Consultee/ Commentator	Comments [sic]	Action
		• adverse effects of mobilisation, myeloablation, neutropaenia • health-related quality of life.	
	Sickle Cell Society	Yes, the outcomes listed are appropriate. However, we are disappointed that the draft scope makes no reference to the burden of SCD especially linked to quality-of-life outcome. Whilst NICE will say that its focus is on its twin pillars of clinical effectiveness and cost effectiveness and that it cannot stray beyond those boundaries, we believe that NICE needs to use its flexibilities but also have a voice about health disparities and unmet need when considering these appraisal submissions for SCD. It is perverse that in our view, NICE has in fact contributed to the widening of health disparities for the SCD community, just by comparing the number of new and innovative treatments that have been approved by NICE/NHS England for like conditions over the years. The majority of people living with SCD are young, albeit with a growing older population. Approximately 60-65% of them live in the most deprived areas of the country.	Thank you for your comments. The outcomes in the draft scope include health-related quality of life. The committee will consider health inequalities issues that are raised as part of the appraisal.
	Anthony Nolan (Patient)	The outcome measures listed in the draft scope are considered appropriate to capturing key benefits and contraindications of this technology.	Thank you for your comments. No action required.
	British Society for Haematology (The Royal College of Physicians	Yes – outcomes are appropriate. However, the term complications arising from sickle cell crisis is very unclear. Is the outcome looking at events that happen to patients during a VOC or is the intention to look at complications that occur as part of sickle cell disease such a pulmonary hypertension and sickle nephropathy. If the intention is to assess ability of this therapy to prevent long term complications then the	Thank you for your comment. The wording for the outcome “complications arising from sickle cell crises” has been amended to

Section	Consultee/ Commentator	Comments [sic]	Action
	endorse this response).	wording needs to be corrected to state 'complications arising as a consequence of sickle cell disease' We would suggest the following outcomes: • changes to haematological parameters (haemoglobin levels) • proportion of subjects not needing any disease modifying treatment, including blood transfusion, hydroxyurea, crizanlizumab and voxelotor following treatment with CTX001 gene therapy • proportion of subjects who have not experienced any sickle vaso-occlusive episodes for at least 12 consecutive months • proportion of subjects who have not had any further stroke or progression of cerebrovascular disease in those with established cerebrovascular disease • proportion of subjects able to come off long term opioids 12 months following treatment • proportion of subjects who have no progression of organ dysfunction, as measured by echocardiogram, pulmonary function tests, glomerular filtration rate, • time to engraftment • proportion of subjects with no off-target effects of CTX001 gene therapy, including development of therapy related myelodysplasia or leukaemia • mortality • adverse effects of mobilisation, myeloablation, neutropaenia • health-related quality of life.	"complications arising from sickle cell disease". However, the examples of **additional outcomes** have **not been added to** the outcomes list, in order to keep the outcomes listed broad.
Equality	Vertex	People with SCD are predominantly of African or Caribbean heritage. Therefore, they are subject to a number of challenges related to their condition which manifest as health inequalities. NICE should take account of	Thank you for your comment. The committee will consider

Section	Consultee/ Commentator	Comments [sic]	Action
		issues relating to health inequalities faced by people with SCD who regularly experience VOCs, as it has done recently in the appraisal of crizanlizumab for SCD. SCD predominantly affects individuals of African or Caribbean heritage, who disproportionately experience health inequalities and are overrepresented in lower socioeconomic groups that are more likely to have suboptimal clinical outcomes, with significant variations in care depending on clinical proficiency or the patient's locality, inadequate or non-existent community care, and chronic underinvestment in appropriate service resources.	any relevant equality issues when it makes recommendations. The equality issues raised have been formally considered in the equality impact assessment. The scope also references that the prevalence of sickle cell disease is highest in people with African or African-Caribbean family background.
	UK Forum on Haemoglobin Disorders	There are serious health inequalities faced by patients with sickle cell disease and no treatment that mitigates the disease in the long term. Hydroxyurea does not provide effective management for all patients and aside from supportive care or transfusion with associated risks and disease burden there is no access to curative therapy. This disorder is life shortening for those with severe disease. This population has not been supported by health services to the level that other disorders of a similar level of prevalence have.	Thank you for your comments. The committee will consider any relevant equality issues when it makes recommendations. The equality issues raised have been formally considered in the equality impact assessment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Cell and Gene Therapy Catapult	The scope correctly identifies that this condition mainly impacts patients from certain ethnic communities. The impact of health inequalities should be considered by the committee.	Thank you for your comments. The committee will consider any relevant equality issues when it makes recommendations. The equality issues raised have been formally considered in the equality impact assessment. No action required. The scope also references that the prevalence of sickle cell disease is highest in people with African or African-Caribbean family background
	Genetic Alliance UK	NICE has acknowledged the importance of reducing health inequalities and at the end of the NICE methods and processes review, there was a commitment to investigate a modifier to reduce health inequalities. Until the work on this has been considered further, we would strongly recommend that the committee take steps to understand:	Thank you for your comments. The committee will consider any relevant equality issues when it makes recommendations. The equality issues raised have been formally

Section	Consultee/ Commentator	Comments [sic]	Action
		• the depth and breadth of inequalities (health and otherwise) experienced by people living with sickle cell disease in the UK today; • the impact of historical inequity and injustice on clinical practice and evidence-based medicine; • how these may have contributed to the basis upon which health technology assessment processes and tools have been developed; • how the application of these tools may unduly disadvantage people living with sickle cell disease if they are applied without due consideration and flexibility.	considered in the equality impact assessment. No action required.
	Clinical Reference Group, Haemoglobinopathy, NHS England	There are serious health inequalities faced by patients with sickle cell disease and no treatment that mitigates the disease in the long term. Hydroxyurea does not provide effective management for all patients and aside from supportive care or transfusion with associated risks and disease burden there is no access to curative therapy. This disorder is life shortening for those with severe disease. This population has not been supported by health services to the level that other disorders of a similar level of prevalence have.	Thank you for your comment. The committee will consider any relevant equality issues when it makes recommendations. The equality issues raised have been formally considered in the equality impact assessment.
	Sickle Cell Society	NICE will be aware that we have already questioned you about your commitment to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.	Thank you for your comment. The committee will consider any relevant equality

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		Data shows that people living with SCD are often disadvantaged by health and healthcare services. The recent Sickle Cell and Thalassaemia All Party Report; No One's Listening, highlights those negative experiences. Then add to that, with the exception of Crizanlizumab under the managed access scheme, there have been no new UK treatment options for people living with SCD in over 25 years. The reality is that these issues in the main are faced by people from black, asian and minority ethnic backgrounds. The draft scope is silent on these issues, despite NHS England making a commitment to tackle health inequalities. The usual retort is that health inequalities is not NICE appraisal decision business. If that is the case this equality section is in our opinion, more of a shield of protection rather than one that provides genuine NICE leadership on the subject matter. An enhanced range of SCD treatment options is part of the action necessary to address health disparities, unmet need and the burden of SCD.	issues when it makes recommendations, in line with Principle 9: Aim to reduce health inequalities. The equality issues raised have been formally considered in the equality impact assessment. The scope also references that the prevalence of sickle cell disease is highest in people with African or African-Caribbean family background.
	Anthony Nolan (Patient)	SCD tends to be found in individuals of African descent. Ensuring equitable care and support for all patients, whatever their background is of paramount importance. Matching Rh blood groups for transfusions can be complicated by shortage of supplies within domestic populations. Inequities within hospital care, access to specialised services, and the impact of lower socio-economic status for some patients, can all have adverse impacts on their health outcomes and quality of life.	Thank you for your comment. The committee will consider any relevant equality issues (including socioeconomic factors) when it makes recommendations in line with Principle 9: Aim to reduce health

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		A single dose treatment, with pro-longed or curative efficacy has the potential to transform patients' lives for the better.	inequalities. The equality issues raised have been formally considered in the equality impact assessment. The scope also references that the prevalence of sickle cell disease is highest in people with African or African-Caribbean family background.
	British Society for Haematology (The Royal College of Physicians endorse this response).	There are serious health inequalities faced by patients with sickle cell disease and no treatment that mitigates the disease in the long term. Hydroxyurea does not provide effective management for all patients and aside from supportive care or transfusion with associated risks and disease burden there is no access to curative therapy. This disorder is life shortening for those with severe disease. This population has not been supported by health services to the level that other disorders of a similar level of prevalence have. Similarly research and developments in sickle cell disease have been significantly less than in malignant haematology disorders.	Thank you for your comment. The committee will consider any relevant equality issues when it makes recommendations, in line with Principle 9: Aim to reduce health inequalities. The equality issues raised have been formally considered in the equality impact assessment. The scope

Section	Consultee/ Commentator	Comments [sic]	Action
		Almost all those with sickle cell disease are non-white and there is a significant history of under resourcing and de-prioritising their care, as well as stigmatisation and prejudice. This cannot continue.	also references that the prevalence of sickle cell disease is highest in people with African or African-Caribbean family background.
Other considerations	Vertex	As mentioned in the equalities section, NICE should consider the impact that exa-cel may have on the health inequalities faced by patients with sickle cell disease, and capture this in its decision-making.	Thank you for your comment. The committee will consider any relevant equality issues when it makes recommendations, in line with Principle 9: Aim to reduce health inequalities.
	UK Forum on Haemoglobin Disorders	Please do consider the impact of a potentially curative treatment option on a population that has very limited disease modifying treatments available to it.	Thank you for your comment. The committee will consider the potentially curative nature of exagamglogene autotemcel when it makes recommendations.

Section	Consultee/ Commentator	Comments [sic]	Action
	Cell and Gene Therapy Catapult	No comment	Thank you for your comments. No action required.
	Clinical Reference Group, Haemoglobinopathy, NHS England	Please do consider the impact of a potentially curative treatment option on a population that has very limited disease modifying treatments available to it.	Thank you for your comment. The committee will consider the potentially curative nature of exagamglogene autotemcel when it makes recommendations.
	Sickle Cell Society	CTX001 could potentially be a candidate for managed access if there is a clearer definition of severe sickle cell. The company should set that out more clearly. Patients who may have regular crises would deem that severe not only based on genotype. The caveat about CTX001 being a candidate for managed access, is understanding what additional data would be collected particularly if CTX001 is for a limited number of people living with SCD.	Thank you for your comment. The wording throughout the draft scope has been amended to remove 'severe'. The committee will consider the suitability of exagamglogene autotemcel as a candidate for managed access when it makes

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			recommendations. No action needed.
	British Society for Haematology (The Royal College of Physicians endorse this response).	Please do consider the impact of a potentially curative treatment option on a population that has very limited disease modifying treatments available to it. Resources to support patients undergoing this form of treatment – those with cancer undergoing similar treatment including Cat-T cell treatments have considerable additional resources and support through cancer organisations. – there is no equivalent for those with sickle cell disease, and SCD services are chronically underfunded and under staffed and so will not be able to make up this short fall. There will be a need for help with transport costs (some patients will live a significant distance from the treatment centres and many having had chronic health throughout their lives, will start with significant financial, social, educational and psychological challenges) and for hotels or other accommodation, as well as support staff such as key workers or transplant Clinical Nurse Specialists to help them navigate and cope with their complex treatment.	Thank you for your comment. The committee will consider the potentially curative nature of exagamglogene autotemcel and the relevant costs associated with exagamglogene autotemcel when it makes recommendations.
Questions for consultation	Vertex	**1. If recommended, would voxelotor be a relevant comparator to [CTX001]?** Vertex would not consider voxelotor to be a relevant comparator to exa-cel as it is not indicated for recurrent pain associated with VOCs, amelioration of recurrent pain was not a focus of the voxelotor clinical trial programme and	Thank you for your comment. Voxelotor will not be added as a comparator. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		the pivotal clinical trial did not show a significant reduction in acute pain episodes. Moreover, voxelotor is indicated for a different target population, i.e. people with haemolytic anaemia due to SCD. Equally, at the time of writing, voxeletor has not been recommended by NICE. **2. Where do you consider [CTX001] will fit into the existing care pathway for sickle cell disease?** It is anticipated that exa-cel would be positioned for patients with recurrent VOCs, instead of established (or standard) care. Allogeneic stem cell transplants should not be considered a comparator as patients with a HLA-matched related haematopoietic stem cell donor were not eligible to participate in the CLIMB-121 study, in line with its proposed marketing authorisation for patients in whom a human leukocyte antigen (HLA)-matched related haematopoietic stem cell (HSC) donor is not available. **3. How is severe sickle cell disease defined? Is it defined by phenotype (number of occlusive crises) or genotype (as suggested in the trial)?** 'Severe SCD' is a subjective term with no standard definition. Although people with the HbSS and HbSβ0-thalassaemia genotypes are more likely to have VOCs than the other genotypes, the incidence of VOC is variable in all genotypes and the classically 'less severe' genotypes, e.g. Sβ+ thalassaemia, may experience frequent pain and repeated crises; therefore, genotype alone is not an indicator of disease severity.	Thank you for your comment. Allogenic stem cell transplant has been removed as a relevant comparator. The relevant NICE pathway will be considered upon publication of this appraisal. Thank you for your comment. The wording throughout the draft scope has been amended to remove 'severe'. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Disease phenotype: patients with increased numbers of VOCs do have increased risk of acute and chronic complications and reduced survival. However, the number of VOCs does not fully correlate to outcomes in SCD. Therefore, Vertex suggests that 'severe' is removed from the scope. We would recommend exa-cel is used in keeping with the proposed marketing authorisation, which is: treatment of sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises who have the βS/βS, βS/β+ or βS/β0 genotype, for whom a human leukocyte antigen (HLA)-matched related haematopoietic stem cell (HSC) donor is not available. **4. Would [CTX001] be a candidate for managed access?** Vertex believes exa-cel is an appropriate candidate for managed access via the Innovative Medicines Fund given the highly innovative nature of the treatment, which has the potential to deliver life-long benefit in an area of high unmet need, and which represents a step change from the current standard of care in SCD. **5. Do you consider that the use of [CTX001] can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Yes – in addition to improvements in EQ-5D-5L, the CLIMB-121 study (NCT03745287) also measured other aspects of patient reported quality of	Thank you for your comment. The committee will consider the suitability of exagamglogene autotemcel as a candidate for managed access when it makes recommendations. Thank you for your comment. Any additional benefits which are not captured

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		life improvements using instruments not incorporated into QALY calculations; namely, the Numeric Pain Rating Scale (NRS), Work Productivity and Activity Impairment questionnaire (WPAI), Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT), pain visual analogue scale (VAS) and the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me). SCD carries a significant societal burden for patients who frequently engage with the healthcare system for their treatment, and for their supporting care givers xiii. People with SCD also do not benefit from free prescriptions for the various medications they frequently require to treat pain and the other complications resulting from sickle cell disease, including the prevention of infection; thus they are also subject to significant financial burden. In England SCD predominantly affects individuals of African or Caribbean heritage, who disproportionately experience health inequalities and are overrepresented in lower socioeconomic groups that are more likely to have suboptimal clinical outcomes, with significant variations in care depending on clinical proficiency or the patient's locality, inadequate or non-existent community care, and chronic underinvestment in appropriate service resources .The degree of unmet need for health inequalities in these communities has been recognised by NHS England, with £1 billion of funding being directed to areas with the highest levels of health inequalities as part of the Long Term Plan. Over the last 30 years there has been a paucity of investment and innovation in SCD, coupled with limited understanding of the disease among health care	by the QALY will be considered by the committee when it makes recommendations. The committee will consider any relevant equality issues when it makes recommendations.

Section	Consultee/ Commentator	Comments [sic]	Action
		professionals, leading to substandard levels of care for patients, fear/mistrust of engaging with the system, and injury or death due to lack of joined-up care. xviii	
	UK Forum on Haemoglobin Disorders	**1. If recommended, would voxelotor be a relevant comparator to CTX001?** Voxelotor is not a relevant comparator as this was not shown to impact on recurrent VOC in the trial. Its primary outcome was to reduce haemolysis and anaemia in patients with the haemolytic sickle cell disease. **2. Where do you consider CTX001 will fit into the existing care pathway for sickle cell disease?** UKFHD hopes that if CTX001 is approved it will be used to treat patients with recurrent VOC instead of standard of care. Patients with matched siblings who are willing and able to donate would not be eligible for this therapy and would be offered a matched sibling transplant. These are two different treatment modalities. **3. How is severe sickle cell disease defined? Is it defined by phenotype (number of occlusive crises) or genotype (as suggested in the trial)?** There is no standard definition for severe sickle cell disease and the disease phenotype (clinical behaviour) can change during a patient's life lime. It is not clear what the definition of 'severe' genotype in this scope is. HbSS and other compound heterozygous sickle cell diseases where the HbS mutation could	Thank you for your comment. Voxelotor will not be added as a comparator. No action required. Thank you for your comment. The relevant NICE pathway will be considered upon publication of this appraisal. Thank you for your comment. The wording throughout the draft scope has been amended to remove

Section	Consultee/ Commentator	Comments [sic]	Action
		be co-inherited with HbC, Beta+ or Beta0 thalassaemia, HbD Punjab, HbO-Arab can be potentially severe and life-limiting. Our view is to include all genotypes. As some patients with HbSS or HbS beta0 thal may genotypically be in the more severe class they may never have a sickle crisis or only rarely whereas those with sickle Beta + although genotypically mild, may have complications from sickle or frequent VOC events which make them clinically severe. We suggest the CTX001 trial indication is used to define the population eligible for treatment. **4. Would CTX001 be a candidate for managed access?** We would strongly support this. **5. Do you consider that the use of CTX001 can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Yes, most definitely. QALY assessments are limited in their scope. The impact of reduced financial burden on patients and their carers, the avoidance of long-term complications and the associated impact on patients ability to lead a near normal life will all positively impact on patients and their families. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.	'severe'. No action needed. Thank you for your comment. No action required. Thank you for your comment. Any additional benefits which are not captured by the QALY will be considered by the committee when it makes recommendations. If the EQ-5D is not thought to

Section	Consultee/ Commentator	Comments [sic]	Action
			adequately capture the health benefits associated with treatments a clear rationale and evidence should be presented.
	Cell and Gene Therapy Catapult	**1. If recommended, would voxelotor be a relevant comparator to CTX001?** Based on the recent appraisal consultation document for voxelotor it should not be considered a comparator. **2. Where do you consider CTX001 will fit into the existing care pathway for sickle cell disease?** In a treatment pathway in which CTX001 comes after allogenic stem cell transplant (i.e. if CTX001 will only be offered to patients who do not have access to this treatment), then allogenic stem cell transplant should not be considered as a comparator. **3. Would CTX001 be a candidate for managed access?** Based on the innovative nature of this product and the high unmet need in the patient population, CTX001 could be considered as a candidate for the	Thank you for your comment. Voxelotor will not be added as a comparator. No action required. Thank you for your comment. Allogenic stem cell has been removed as a comparator. The relevant NICE pathway will be considered upon publication of this appraisal. Thank you for your comment. The committee will consider the suitability of exagamglogene

Section	Consultee/ Commentator	Comments [sic]	Action
		innovative medicines fund to facilitate patient access while further evidence is generated to reduce uncertainty. 4. **Do you consider that the use of CTX001 can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** SCD may also have a burden on caregivers and certain aspects, such as the need for regular transfusions may not fully be accounted for in the QALY calculation.	autotemcel as a candidate for managed access when it makes recommendations. Thank you for your comment. Any additional benefits which are not captured by the QALY will be considered by the committee when it makes recommendations.
	Clinical Reference Group, Haemoglobinopathy, NHS England	1. **If recommended, would voxelotor be a relevant comparator to CTX001?** Voxelotor is not a relevant comparator as this was not shown to impact on recurrent VOC in the trial. Its primary outcome was to reduce haemolysis and anaemia in patients with the haemolytic sickle cell disease. 2. **Where do you consider CTX001 will fit into the existing care pathway for sickle cell disease?** The CRG hopes that if CTX001 is approved it will be used to treat patients with recurrent VOC instead of standard of care. Patients with matched siblings who are willing and able to donate would not be eligible for this	Thank you for your comment. Voxelotor will not be added as a comparator. No action required. Thank you for your comment. The relevant NICE pathway will be considered upon

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		therapy and would be offered a matched sibling transplant. These are two different treatment modalities. **3. How is severe sickle cell disease defined? Is it defined by phenotype (number of occlusive crises) or genotype (as suggested in the trial)?** There is no standard definition for severe sickle cell disease and the disease phenotype (clinical behaviour) can change during a patient's life time. It is not clear what the definition of 'severe' genotype in this scope is. HbSS and other compound heterozygous sickle cell diseases where the HbS mutation could be co-inherited with HbC, Beta+ or Beta0 thalassaemia, HbD Punjab, HbO-Arab can be potentially severe and life-limiting. Our view is to include all genotypes. As some patients with HbSS or HbS beta0 thal may genotypically be in the more severe class they may never have a sickle crisis or only rarely whereas those with sickle Beta + although genotypically mild, may have complications from sickle or frequent VOC events which make them clinically severe. We suggest the CTX001 trial indication is used to define the population eligible for treatment. **4. Would CTX001 be a candidate for managed access?** We would strongly support this.	publication of this appraisal. Thank you for your comment. The wording throughout the draft scope has been amended to remove 'severe'. No action needed. Thank you for your comment. No action required.

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		5. Do you consider that the use of CTX001 can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Yes, most definitely. QALY assessments are limited in their scope. The impact of reduced financial burden on patients and their carers, the avoidance of long-term complications and the associated impact on patients ability to lead a near normal life will all positively impact on patients and their families. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.	Thank you for your comment. If the EQ-5D is not thought to adequately capture the health benefits associated with treatments a clear rationale and evidence should be presented. Any additional benefits which are not captured by the QALY will be considered by the committee when it makes recommendations.
	British Society for Haematology (The Royal College of Physicians endorse this response).	**1. If recommended, would voxelotor be a relevant comparator to CTX001?** Voxelotor is not a relevant comparator as this was not shown to impact on recurrent VOC in the trial. Its primary outcome was to reduce haemolysis and anaemia in patients with the haemolytic sickle cell disease. **2. Where do you consider CTX001 will fit into the existing care pathway for sickle cell disease?**	Thank you for your comment. Voxelotor will not be added as a comparator. No action required. Thank you for your comment. The relevant

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		The CRG hopes that if CTX001 is approved it will be used to treat patients with recurrent VOC instead of standard of care. Patients with matched siblings who are willing and able to donate would not be eligible for this therapy and would be offered a matched sibling transplant. These are two different treatment modalities. **3. How is severe sickle cell disease defined? Is it defined by phenotype (number of occlusive crises) or genotype (as suggested in the trial)?** There is no standard definition for severe sickle cell disease and the disease phenotype (clinical behaviour) can change during a patient's life lime. It is not clear what the definition of 'severe' genotype in this scope is. HbSS and other compound heterozygous sickle cell diseases where the HbS mutation could be co-inherited with HbC, Beta^{+} or Beta^{0} thalassaemia, HbD Punjab, HbO-Arab can be potentially severe and life-limiting. Our view is to include all genotypes We suggest the CTX001 trial indication is used to define the population eligible for treatment. **4. Would CTX001 be a candidate for managed access?** We would strongly support this. **5. Do you consider that the use of CTX001 can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Yes most definitely.	NICE pathway will be considered upon publication of this appraisal. Thank you for your comment. The wording throughout the draft scope has been amended to remove 'severe'. No action needed. Thank you for your comment. No action needed. Thank you for your comment. If the EQ-5D is not thought to adequately capture the health benefits

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		QALY assessments are limited in their scope. The impact of reduced financial burden on patients and their carers, the avoidance of long-term complications and the associated impact on patients' ability to lead a near normal life will all positively impact on patients and their families. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.	associated with treatments a clear rationale and evidence should be presented. Any additional benefits which are not captured by the QALY will be considered by the committee when it makes recommendations.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Neonatal and Paediatric Pharmacists Group (NPPG)
Cianna's Smile