National Institute for Health and Care Excellence

Health Technology Evaluation

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia

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 Pharmaceuticals Ltd (company)	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 patients with transfusion dependent beta-thalassaemia (TDT).	Thank you. NICE aims to advance equality of opportunity, eliminate unlawful discrimination and foster good relations between people with particular protected characteristics and society as a whole. In addition, the principles that guide the development of NICE guidance and standards includes the aim to

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			reduce heath inequalities. During the appraisal, the committee will consider the evidence submitted by stakeholders including related to unmet need and health inequalities for people with the condition.
	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 who are transfusion dependent for beta-thalassaemia. 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 hemoglobin. It would be appropriate to evalutate this technology using the routine NICE appraisial methods for medicines. It is suggested that this gene editing technology has a similar safety profile to myeloablative conditioning and autologous hematopoietic stem cell transplantion.	Thank you

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		Clinical trial results suggest all patients demonstrated clinically meaningful increases in total hemoglobin (Hb) and Fetal hemoglobin (HbF) which occurred early and have been maintained over time. There remains a significant unmet need in supporting patients with beta-thalassaemia. Current treatments are supportive rather than curative. Allo-HSCT is now availiable to both adults and paedatrics on the NHS – whilst it is the only curative treatment, allogeneic transplants come with serious risk factors for patients, with 5-year survival positioned around 50%. The National Haemoglobinopathy Registry reports that in 2020/21 approximately 1000 people were registered with beta-thalassaemia major and approximately 260 with beta-thalassaemia intermedia[1]. 75 paediatric patients received a stem cell transplant in the year up to April 2022[2]. [1] - The National Haemoglobinopathy Register. (2021) Annual data report 2020/21. https://nhr.mdsas.com/wp-content/uploads/2022/03/NHR_DataReport2021.pdf. Accessed November 2022. [2] - BSBMTCT Executive Summary Of Transplant & Cellular Therapy Outcomes In Uk/Roi A Report For Commissioners 13th Edition	
	The Essenelle Foundation (patient)	I think this is a very valid topic to evaluate and I think it's necessary	Thank you

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	United Kingdom Thalassaemia Society (patient)	The United Kingdom Thalassaemia Society agrees that the application titled "CTX001 for treating transfusion-dependent beta-thalassaemia ID4015" should be appraised by NICE, given the unmet and unfulfilled need of a potential curative and innovative treatment options for individuals living with and families affected by this severe inherited blood condition.	Thank you
	British Society for Haematology (professional) Endorsed by Royal College of Physicians	We welcome this appraisal as there is very significant unmet need for patients living with transfusion dependant thalassaemia syndromes. There are no curative options for patients apart from allogenic stem cell transplant which is not available for most patients. The burden of disease and its associated complications as well as side effects of chelation therapy place a life long burden on patients and their families It is appropriate to evaluate CTX001 in patients with transfusion dependent anaemia. While it is an expensive and potentially high risk novel technology, there is already agreement that all patients with a suitable sibling donor would go direct for Allogenic BMT at an early age providing a strong precedent for the need for such curative options at an early age.	Thank you
	UK forum on Haemoglobin Disorders (professional)	We welcome this appraisal as there is very significant unmet need for patients living with transfusion dependant thalassaemia syndromes. There are no curative options for patients apart from allogenic stem cell transplant which is not available for most patients. The burden of disease and its associated complications as well as side effects of chelation therapy place a life long burden on patients and their families. The burden of Iron overload if left uncontrolled leads to multi-organ failure and premature death	Thank you
	Cell and Gene Therapy	It is timely and appropriate for NICE to assess this technology.	Thank you

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	Catapult (general commentator)		
	Haemoglobinopathy Clinical Reference Group, NHS England	We welcome this appraisal as there is very significant unmet need for patients living with transfusion dependant thalassaemia syndromes. There are no curative options for patients apart from allogenic stem cell transplant which is not available for most patients. The burden of disease and its associated complications as well as side effects of chelation therapy place a lifelong burden on patients and their families	Thank you
	National Haemoglobinopathy Panel, England (professional)	We welcome this appraisal as there is very significant unmet need for patients living with transfusion dependant thalassaemia syndromes. Bone marrow transplantation is the only cure and it is funded for adults in the UK. The burden of Iron overload if left uncontrolled leads to multi-organ failure and premature death	Thank you
Wording	Vertex Pharmaceuticals Ltd (company)	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.	Thank you. The name of the technology has been changed to exagamglogene autotemcel throughout the scope, in other documents related to this topic and on the website.
	Anthony Nolan (patient)	The wording of the remit is relfective of the wide parameters allowed as part of the technology's single-arm, open-label, multi-site, single-dose Phase 1/2/3 study in subjects with transfusion-dependent β-thalassemia (TDT).	Thank you

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		The remit should continue to reflect the widest parameters to which efficacy and improved quality of life can be assured. [3] - A Safety and Efficacy Study Evaluating CTX001 in Subjects With Transfusion-Dependent β-Thalassemia - https://clinicaltrials.gov/ct2/show/NCT03655678	
	The Essenelle Foundation (patient)	The wording does reflect the issues	Thank you
	United Kingdom Thalassaemia Society (patient)	YES	Thank you
	British Society for Haematology (professional) Endorsed by Royal College of Physicians	There is a mix of terminology in the scope that needs correction. Thalassaemia major is defined primarily by the genetic mutations and in the majority (but not in all) will mean transfusion dependence. It is recommended that the terminology is kept as transfusion dependant beta thalassaemia (clinical definition). This will mean that patients with conditions such as HbE beta thalassaemia who are transfusion dependant and those with severe beta plus globin mutations (severe end of the thalassaemia intermedia gene spectrum) who are also transfusion dependant will be included in the transfusion dependant population. These patients are also more likely to develop alloantibodies to transfused red cells as they often require transfusion after the age of 2 years are therefore more likely to mount an immune response 1. We recommend the inclusion criteria for the scope are kept in line with the clinical trial inclusion criteria which was >100ml/kg/year or 10 units of packed red cells in the prior 2 years.	Thank you. The scope was intentionally focused on transfusion-dependent beta thalassaemia rather than beta thalassaemia major, also including severe forms of thalassaemia major. However, the background has now been clarified and explicitly notes that it includes haemoglobin E

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		The wording of the remit seems appropriate	beta thalassaemia. The definition of what constitutes transfusion-dependence can be proposed by the company and discussed by committee during the development of the appraisal. However, this definition has been added to the description of the trial in the section 'the technology'.
	UK forum on Haemoglobin Disorders (professional)	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
	Cell and Gene Therapy Catapult (general commentator)	Yes	Thank you
	Haemoglobinopathy Clinical Reference Group, NHS England	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology

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	National Haemoglobinopathy Panel, England (professional)	We suggest the terminology is revised to include other thalassaemia syndromes which may evolve in severity and become transfusion dependent with life threatening complications such as EBeta Thalassaemia and similar combinations. These patients often require transfusion soon after the age of 2 years are therefore more likely to mount an immune response 1. We recommend the inclusion criteria to be based on transfusion requirement of >100ml/kg/year or 10 units of packed red cells in the prior 2 years	Please see response to British Society for Haematology
Timing issues	Vertex Pharmaceuticals Ltd (company)	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
	Anthony Nolan (patient)	A significant clinical unmet need does exist for sickle cell patients in needing a curative treatment to their disease. People with the most severe type, beta thalassaemia major, may need a blood transfusion about once a month to mainitain target hemoglobin levels. Regular transfusions carry not just the need to find matching blood donors, but also to manage iron overloading as a restul of multuple transfuions. Iron overload can make it difficult for these organs to work properly. For example, iron overload in the endocrine system may cause diabetes as well as fertility and other hormonal issues. The iron buildup can also lead to other serious complications, including organ damage and organ failure, if it is not treated effectively. Removal of the spleen and gallbladder also put beta thalassaemia patients at unessecary surgical risk.	Thank you

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	The Essenelle Foundation (patient)	There are not many options for the NHS to offer to the community that this technology will serve so its imperative that it is done.	Thank you
	United Kingdom Thalassaemia Society (patient)	There is an urgent need for this appraisal to be conducted due to a variety of factors that we are continuing to discover. In recent times, looking at the data, we have observed that the heterogeneity with regards to the severity amongst individuals living with transfusion dependent beta thalassaemia is more profound that once published. Not only do individuals living with TDT are at a higher incidence of morbidity and mortality than the general public, we have uncovered that this is also further reduced within select ethnic backgrounds than once believed. Looking at our data from surveys conducted in 2021, we found that individuals of Asian and Southeast Asian origin had a considerably decreased life expectancy and health related quality of life than those of other ethnic origins due to the development of secondary conditions earlier in life. This was astounding and heart breaking it was reported that those individuals had poorer overall health outcomes. Consequently, due to the inequalities that continue to undermine and impact treatment options for the entire TDT population in addition to need for improved physical and psychological health, reduction in the progress and development of related secondary conditions and the need for an improved	Thank you. The issues raised by the stakeholder have been summarised in the Equalities Impact Assessment for this topic. NICE aims to advance equality of opportunity, eliminate unlawful discrimination and foster good relations between people with particular protected characteristics and society as a whole. In addition, the principles that guide the development of NICE guidance and standards includes the aim to reduce heath inequalities. During the appraisal, the committee will consider the evidence

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		health related quality of life, UKTS feels strongly that the need for this treatment option should be a priority of the NHS.	submitted by stakeholders including related to unmet need and health inequalities for people with the condition.
	British Society for Haematology (professional) Endorsed by Royal College of Physicians	There is a high degree of unmet need for disease modifying treatments in this population. Current treatment options simply include regular blood transfusion and iron chelation to prevent complications of iron overload. Only 30% of patients have a suitable sibling donor. The remainder of patients are reliant on regular blood transfusions and iron chelation therapy which is difficult to tolerate and comes with its own health complications. These patients have had no real progress in their management for at least a decade and this appraisal should be prioritised to address their unmet need.	Thank you
	UK forum on Haemoglobin Disorders (professional)	This is timely to avoid similar inequalities reported in the recent Sickle cell APPG No one's listening report (ref) There is a high degree of unmet need for disease modifying treatments in this population. Current treatment options simply include regular blood transfusion and iron chelation to prevent complications of iron overload.	Thank you. NICE aims to advance equality of opportunity, eliminate unlawful discrimination and foster good relations between people with particular protected characteristics and society as a whole. In addition, the principles that guide the development of NICE

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			guidance and standards includes the aim to reduce heath inequalities. During the appraisal, the committee will consider the evidence submitted by stakeholders including related to unmet need and health inequalities for people with the condition.
	Cell and Gene Therapy Catapult (general commentator)	It is appropriate for NICE to evaluate this topic urgently given the high unmet need of beta-thalassaemia and the novel nature of the gene therapy technology	Thank you
	Haemoglobinopathy Clinical Reference Group, NHS England	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
	National Haemoglobinopathy Panel,	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology

Section	Stakeholder	Comments [sic]	Action
	England (professional)		

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Vertex Pharmaceuticals Ltd (company)	**Disease background** The background section should be updated to more fully capture the disease burden: • NICE states in the draft scope that '*Beta-thalassaemia major is the most severe type which is transfusion-dependent requiring regular red blood cell (RBC) transfusions. However, people with severe forms of thalassaemia intermedia may also require regular RBC transfusions*.' However, a more appropriate description would be as follows. *'Beta-thalassaemia major is the most severe type of beta-thalassaemia and is transfusion-dependent requiring regular RBC transfusions from early and throughout life. It includes homozygous beta-thalassaemia and heterozygous beta-thalassaemia including severe beta-thalassaemia/HbE. Some patients with severe forms of beta thalassaemia intermedia may also require regular RBC transfusions and will therefore also be included within the transfusion dependent beta-thalassaemia group.*[i] *Transfusion dependence in the exa-cel clinical trial was defined as a history of at least 100ml/kg year or 10 units/year of packed RBC transfusion in the prior 2 years*.' • Equally, NICE states that the most severe cases can lead to heart failure or liver complications. Liver complications are more often caused by iron overload and indeed in the more severe cases of beta-thalassaemia the patient will die early in life (mostly in infancy) from	Thank you. Disease background The background section is meant to be a summary. However a few changes have been made as noted below. The background has now been clarified and explicitly notes that it includes haemoglobin E beta thalassaemia. The definition of transfusion dependence has been added to the description of the trial in the section 'the technology'. The description of long-term consequences of

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		intractable heart failure unless the anaemia is corrected by regular blood transfusion. Patients who are untreated or poorly transfused develop growth retardation, pallor, jaundice, poor musculature, hepatosplenomegaly, leg ulcers, extramedullary haematopoiesis and skeletal abnormalities. • NICE says '*repeated transfusions are associated with an increased risk of bloodborne infections and graft versus host disease'*. Graft versus host disease is a very rare complication of blood transfusion and is unusual in the UK where red cell units are carefully matched for blood group. Repeated transfusions are associated with an increased risk of allo-immunisation which can lead to difficulties in obtaining appropriately matched blood and delayed haemolytic transfusion reactions. • It is correct to say that patients require lifelong transfusions to manage their transfusion-dependent thalassaemia (TDT) but it is important to note that despite regular transfusions patients often experience fatigue and pain in the days and weeks before their next transfusion. • While TDT is currently managed with regular transfusions, and iron chelation therapy, patients still experience significant disease burden evidenced by the fact that the median age of death is only 45 in the UK.[ii] • Furthermore, patients experience significant morbidity throughout their lives as a result of their condition and required treatment, most commonly endocrine disorders such as hypoparathyroidism, and insulin dependent diabetes.[ii]	beta thalassaemia and current treatments has been amended a bit. However, more details on this and the impact of the condition on the patient and their carers can be described within the stakeholder submissions and discussed by committee during the appraisal. <u>The technology</u> The name of the technology has been changed to exagamglogene autotemcel throughout the scope, in other documents related to this topic and on the website.

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		• TDT impacts other aspects of patients' lives such as education and employment. Patients undergoing regular transfusions are required to regularly attend hospital for their treatment, which is disruptive to school, university and working life. Recent research found that approximately 30% of patients are unemployed or unable to work full time owing to their condition. On average, patients spent over 15 hours a month managing their condition, and experience elevated rates of anxiety and depression.[iii,iv] • When considering the impact of TDT on patients' quality of life (QoL), it is important to consider the fact that generic tools, such as the EQ-5D, are not able to accurately reflect the disease burden for a number of reasons, including the fact that EQ-5D measures a patient's QoL on a single day, rather than over time. In addition, given that TDT is a chronic condition that patients experience from birth, there is a response shift and ceiling effect seen with QoL outcomes reported, which lack face validity. This is clearly illustrated in the Zynteglo (betibeglogene autotemcel) appraisal [ID968] where the company reported that patients in their clinical trial were returning QoL at baseline nearing population average for the UK, as measured by EQ-5D. • The humanistic impact on caregivers and families of patients with TDT is substantial. Parents and caregivers have to make considerable time sacrifices related to treatment schedules (including transportation and preparation for treatment) and care for individuals with TDT. In addition, parents of patients with TDT often report feeling worried about their child's future and experience feelings of guilt and self-blame due to the hereditary nature of the condition.[iv] Caregivers of	

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		patients with TDT highlight increased frequency of depression and anxiety as main contributing factors to their reduced HRQoL.[v] **<u>The technology</u>** The INN of 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 is exagamglogene autotemcel (exa-cel), and language should be updated throughout to reflect this.	
	Anthony Nolan (patient)	The background text looks to be comprehensive.	Thank you
	United Kingdom Thalassaemia Society (patient)	UKTS does not think all the information provided in the background is accurate and complete. The following reasons are worth considering. The background information text states 1) "the condition is categorised by a reduced production of healthy red blood cells" Whilst this is partially accurate, the text should read " the condition is categorised by a reduced **or absence** production of healthy red blood cells." 2) "there are two basic groups" "There are two main forms of thalassaemia .."	Thank you. The background section is meant to be a summary. However several amendments have been made following comments from stakeholders. As a result, some of the changes suggested by the stakeholder have been addressed. However, more details can be described within the stakeholder submissions and discussed by committee

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		3) " In transfusion dependent beta thalassaemia, haemoglobin production is reduced to such a low level that normal growth, development and quality of life can only be achieved by red cell transfusions from infancy." In transfusion dependent beta thalassaemia, haemoglobin production is reduced to such a low level that normal growth, skeletal and endocrine development and quality of life can only be achieved by red cell transfusions from infancy. It is important to note, that the incidence of severe and chronic bone and joint pain and the development of extra medullary haematopoiesis can also be consequence of poor transfusion protocol. 4) " the frequency of blood transfusions can vary but it is typically every 3 to 4 weeks, and repeated transfusions are associated with an increased risk of blood borne infections and GVHD." "the frequency of blood transfusions can vary but it is typically every 2 to 4 weeks, and repeated transfusions are associated with an increased risk of blood borne infections, transfusion reactions which can be due but not limited to allo-immunisations, GVHD etc"(1). 5) " Treatment with transfusions can cause too much iron to build up in the body and lead to complications including liver cirrhosis …." Treatment with transfusions can cause too much iron to build up in the body and lead to complications but are not limited to liver cirrhosis, endocrine complications such as diabetes, hypothyroidism, hypogonadotropic	during the appraisal. Regarding the proportion with a matched donor, this has been changed to say 10-30% as other stakeholders also cited the 30% value.

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		hypogonadism, sterility, heart dysfunction and failure, severe and chronic bone and joint pain"[(1)]. 6) "who have a matching donor (approximately 30% of people with TDT) The study quoted with regards to the approximate number of people with an appropriate match represents the population in Italy. In the UK, less than 10 % of the TDT population have access to an appropriate match or meet the criteria for this curative option[(1)].	
	United Kingdom Thalassaemia Society (patient) (continued)	Whilst there can be some consistency when it comes to appropriate treatment and clinical management, the condition has an enormous impact on everyday life for both the patients and their care givers. **Anaemia** Individuals living with a moderate to severe form of thalassaemia exist on a significantly lower haemoglobin level than that of the general population. As a result of this, individuals can often report symptoms of anaemia such as fatigue, headaches, lethargy, tachycardia, however, they can also experience a lack of concentration, reduction in cognitive abilities, mood disturbances experience moderate to severe bone pain as a result of ineffective haematopoiesis. This can often result in bone and skeletal deformities, extramedullary pseudo tumours, splenomegaly (a considerable number of patients have been splenectomised), increase risk of thromboembolic events due to asplenia, cardiovascular disease, pulmonary hypotension, ulcers in extremities such as	Thank you. The background section is meant to be a summary. More details of the impact of the condition on the patient and their carers can be described within the submissions and discussed by committee during the appraisal.

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		legs, a higher risk of fractures, bone disease, osteopenia/ osteoporosis syndrome[(2)]. It is also common for individuals' thalassaemia to present with gall stones from their 30s often requiring a cholecystectomy and have diseases of the bile duct and the liver resulting in an increase in bilirubin, liver enzymes etc. Patients also experience jaundice resulting in the yellowing of skin and the whites of the eyes which can significantly negatively affect their self-esteem and body image. Due to asplenia, individuals can have a compromised immune system and require daily prophylactic treatment with antibiotics. When an individual has an infection, this can result in an exacerbation of their symptoms and need for a transfusion. Often, this necessitates the care and support of a carer or member of their family to help them complete the basic everyday tasks. **Transfusions** Some people may also experience difficulties with aspects of personal care and moving around may be which may be worse during days /weeks before a transfusion. Additionally, there can be an issue with successful cannulation especially if their haemoglobin levels are low, due to vascular depletion). Additionally, as the individual grows older, the scarring of peripheral veins can worsen resulting in multiple attempts by the most experience health care professionals.	

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		This can be very distressing for patients as not only can it painful, but it can result in temporary nerve damage which can affect patient's use of their hands for up to three months. This is extremely painful and can really impact on a person's ability to complete everyday activities. When peripheral cannulation is no longer an option, patients are offered central lines/ catheters which help to alleviate some of the cannulation issues but comes with its own challenges in maintaining an infection free line. This is not always possible and can easily result sepsis which can be life threatening. Having central lines in situ can impact on patients' ability to partake in exercise, sports etc. Some individuals with NDT beta thalassaemia can also experience transfusion reactions due to alloimmunisation etc. Transfusion reactions range from fever, rigors, urticaria, oedema, severe debilitating bone pain, haemolytic reactions, anaphylactic reactions and transfusion related graft version host disease. Due to the severity of the reactions leading to rapid depletion of haemoglobin levels (i.e haemolytic reactions), transfusion burden can increase. Consequently, this not only affects quality of life but also increases iron stores. If this is not addressed adequately, it can result in severe organ damage. **Transfusions** Some people may also experience difficulties with aspects of personal care and moving around may be which may be worse during days /weeks before a transfusion. Additionally, there can be an issue with successful cannulation especially if their haemoglobin levels are low, due to vascular depletion). Additionally, as	

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		the individual grows older, the scarring of peripheral veins can worsen resulting in multiple attempts by the most experience health care professionals. This can be very distressing for patients as not only can it result in severe pain, it can also cause temporary nerve damage which can affect patient's use of their hands for up to three months each time it occurs. This is extremely painful and significantly impacts on a person's ability to complete everyday tasks and activities. When peripheral cannulation is no longer an option, patients are offered central lines/ catheters which help to alleviate some of the cannulation issues but comes with its own challenges in maintaining an infection free line. This is not always possible and can easily result sepsis which can be life threatening. Having central lines in situ can impact on patients' ability to partake in exercise, sports etc. Some individuals with transfusion dependent thalassaemia can also experience transfusion reactions due to alloimmunisation etc. Transfusion reactions range from fever, rigors, urticaria, oedema, severe debilitating bone pain, haemolytic reactions, anaphylactic reactions and transfusion related graft version host disease. Due to the severity of the reactions, some people with thalassaemia, transfusion burden also increases which not only affects their quality of life but also affects their iron burden. If this is not addressed adequately, it can result in severe organ damage. **Iron Chelation** Individuals with transfusion dependent thalassaemia can often be prescribed iron chelating agents to remove excess iron received from increased gastro-intestinal absorption of iron, which is much higher than that in the general population and most likely due to a paradoxical suppression of hepcidin[(3)]. Additionally, excess iron can also be accumulated due to blood transfusions.	

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		Whilst treatment options have improved greatly over the year, adherence to iron chelating medication remains a significant challenge within the thalassaemia population affecting every individual at some or most part of their lives. In the UK, there are three chelating agents available which is prescribed according to patient needs. For those on desferrioxamine therapy, this can be used up to seven days a week for an infusion period of 12-24 hours depending on iron burden. Often this is done through a subcutaneous infusion self- administer by the patients or their care givers and can be painful especially after repeated needle punctures. The injection sites can often become painful, inflamed, and often results in medication deposits or scarred tissue which has been described as painful bumps under the skin by the patient and care givers. Over time it becomes difficult to find viable injection sites. This can severely impact on a person's quality of life and their ability to comply with their treatment. Depending on the severity of the iron burden, desferrioxamine can also be administered intravenously with the use of central lines and indwelling peripheral catheters. This, however, can result in thrombosis and line infection leading to sepsis. Desferrioxamine also can cause side effects such as skin irritation, audiologic and ophthalmologic disturbances, toxicity etc. With regards to the oral iron chelators, whilst this has been described by patients as being "life changing", adherence is also an issue as patients are required to take medication several times a day which is not always convenient	

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		for them. As with any medication, oral chelators cause a variety of side effects which can hinders their ability to comply with treatment. Often if the side effects are severe and they can result in organ damage, patients are then required to go back on subcutaneous therapy rather than have the combination which is offered to most patients. Individuals with thalassaemia are also required to attend regular hospital appointments outside their transfusion routine for monitoring for iron overload, side effects and other routine tests. These are in the form of Cardiac MRIs, ECHOS, liver MRIs, DEXA scans, CT and XRAY scans, audiology, ophthalmology etc. Individuals with thalassaemia can also develop a myriad of secondary conditions related to iron overload obtained during regular blood transfusions and from absorption from the gastrointestinal tract. As iron is not excreted or used to produce haemoglobin, it can deposit in vital organs of the body leading to people with thalassaemia developing multiple organ failure and other secondary conditions which can impact on daily life(2). Some of the secondary conditions are as follows; **1) Liver and Gall Bladder Diseases** a. Hepatitis or hepatic dysfunction b. Gall bladder disease c. Liver Fibrosis d. Liver Failure e. Hepatocellular Carcinoma	

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		2) Endocrine and Metabolic Dysfunction a. Impaired glucose tolerance/ diabetes mellitus b. Low bone mass (osteopenia/ osteoporosis syndrome) c. Growth hormone deficiency d. Hypogonadism e. Hypothyroidism f. Hypoparathyroidism g. Adrenal insufficiency **3) Cardiac Dysfunction** a. Tachycardia b. Atrial Fibrillation c. Pulmonary Hypertension d. Cardiac Failure 4) **Pulmonary thrombosis/ Thrombotic Events** **5) Spleen** a. Enlargement/Splenomegaly b. Splenectomised **6) Pain Syndrome** a. Bone and joint pain b. headaches	

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		7) Dental Issues **8) Chelator Side Effects and Toxicity** a. Audiology disturbances b. Ophthalmology c. Nephrotic Syndrome d. Neutropenia e. Growth Delay f. Local and allergic reactions g. Over-chelation-toxicity **9) Rheumatology** a. Rheumatoid arthritis b. Auto-immune conditions- Raynaud's syndrome etc **10) Psychological** a. Anxiety b. Depression c. Lack of Self Esteem/ Self confidence d. Guilt e. Post Traumatic Disorder Having to cope with the daily implications of the condition, in addition to acquiring secondary conditions as identified above, can seriously impact an individual's quality of life. The majority of patients with thalassaemia have acquired many secondary conditions.	

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		Iron overload can also cause hormonal and fertility issues. Most men with thalassaemia have low testosterone levels and thus requires treatment with testosterone injections every three months. Low testosterone can cause a myriad of problems such as decrease muscle mass/ strength, decreased body hair, swelling/tenderness of the breast tissue, increased fatigue, hot flashes, sleep disturbances, impotency, and fathering children. Not only does this cause physical complications it can also result in psychological issues such as memory/ concentration loss, depression, lack of self-esteem, body issues and even put pressure on relationships. Patients can be very embarrassed to talk about these issues. In women, menstrual cycles are disrupted and irregular, affecting fertility. Patients may find this hard to express / openly discuss and may not have come to terms with what this means for their future life choices. Individuals with thalassaemia are often underweight and can be short in stature- this is particularly noted in cases with men(4). As puberty is often delayed, people with thalassaemia can look very young in appearance(4). Consequently, they are often treated or spoken to like children which can often cause them some distress in wanting to disclose their need to rely on others when they are unwell. They can often feel very embarrassed about talking about how reliant they are on others and have often spoken about the guilt they feel on not being able to care of provide for themselves. Those who live alone may find it difficult to disclose that they would benefit from extra support. The nature of thalassaemia care and treatment has significant logistical and financial implications that include a heavy burden of travel to a specialist regional centre or clinic, difficulties gaining insurance for travel and critical	

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		illness cover. Stress, anxiety, low self-esteem, feelings of isolation and depression are all elements of an individual's condition that must be monitored and managed. **Hospital Admissions** When faced with acute issues, patients are usually admitted to hospital. This can be a challenging experience as health professionals outside of the thalassaemia/ haematology units are not aware of the condition or how to treat them. This can cause a delay in treatment which can result in serious life changing consequences. This is a national problem that as has been reported from patients throughout the UK. The unpredictable nature of thalassaemia means there is an inability to predict and plan for the future. Difficulties with aspects of personal care and moving around may be worse during days / weeks before transfusion. Patients can suffer from extreme fatigue, exhaustion, breathlessness, palpitations, bone pain (due to the bone marrow going into overdrive), headaches, lack of concentration, cognition disturbances, low mood, anxiety, depression and insomnia. Patient lives can be disrupted by becoming unwell due to infections or inflammatory flares which can last for days, weeks or months. Overall, this can negatively impact an individual's chance of having an independent life and can also affect educational, employment and social opportunities.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Thalassaemia is a life-long genetic condition that can vary on a day-to-day basis and over time it will continue to cause patients' health to deteriorate more rapidly than their healthy peers. When an individual has an infection or becomes anaemic, it can result in an exacerbation of their symptoms, causing everyday tasks to be become extremely complex and challenging. Often, this necessitates the care and support of a carer or member of their family to help them complete basic tasks. Patients can often become bedbound until their symptoms resolve. Some of the daily challenges people with thalassaemia can have are: 1. Managing of daily medication 2. Attend and cope with daily treatment- iron chelation (oral subcutaneous (over 12-24 hours) or intravenous (over 12-24 hours) and others depending on patients' specific comorbidities identified. 3. Preparing Food 4. Food shopping 5. Household chores 6. Washing and bathing 7. Dressing and undressing 8. Standing for a prolonged period of time 9. Walking/Moving around/ ability to climb stairs The treatment burden of daily medications combined with symptoms of bone and neuropathic pain can cause the individual to become fatigued on a daily basis. The logistical challenges and pressure of individuals to be responsible for and maintain their own extensive and complex treatment routine directly impacts quality of life. Individuals may be required to self-administer	

Section	Consultee/ Commentator	Comments [sic]	Action
		intravenous or subcutaneous iron chelation treatments at home and monitor their own condition. The nature of thalassaemia care and treatment has significant logistical and financial implications that include a heavy burden of travel to specialist regional centres or clinics, as well as difficulties finding insurance cover for travel and critical illness. Stress, anxiety, low self-esteem, feelings of isolation and depression are all elements of an individual's condition that must be monitored and managed. **Carers** Thalassaemia can have a major impact on carers and loved ones. Most parents are not aware of thalassaemia until they are pregnant or after the birth of their child. The birth of a child is a life changing event but receiving a diagnosis of a lifelong condition can be heart-breaking. There still is not adequate support for carers in terms of handling the diagnosis and how to manage their children's condition. Carers also suffer experience psychological issues such as anxiety, depression etc from trying to help their loved ones manage their condition. The diagnosis also changes their lives not only on an emotional perspective but also from a financial perspective as managing their loved one conditions can be a full-time job and many terminate their employment to take their loved ones to hospital appointments. Thalassaemia also affects their social lives, as planning holidays or trips become centred on the needs of the person with thalassaemia.	

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society for Haematology (professional) Endorsed by Royal College of Physicians	This section needs updating as there are inaccuracies and the burden of disease is not accurately reflected. ***'In transfusion-dependent beta-thalassaemia, haemoglobin production is reduced to such a low level that normal growth, development and quality of life can only be achieved by regular red cell transfusions from infancy.'*** This would be more accurate as follows: Thalassaemia patients will be initiated on regular transfusions life long, if there is evidence of severe anaemia causing failure to thrive (measured by failure to grow and gain weight in children) or evidence extramedullary haematopoiesis where organs such as the liver or spleen enlarge or expansion of the bone marrow causing facial or other skeletal deformities. In patients with genetic mutations in keeping with thalassaemia major this will occur within the first few years of life whereas patients with the severe thalassaemia intermedia genetic mutations may develop transfusion dependence later in life. It is important to note that although patients will survive and function on regular blood transfusion and iron chelation there is a considerable burden of disease on patients. The regular transfusion every 3 to 4 weeks and the reoccurrence of anaemia prior to the next transfusion means that patients feel reasonably well post transfusion but then develop progressive tiredness and bone pain as they approach the next transfusion. In non-splenectomised patients the haemoglobin will fall at around 15 g per week equivalent to the loss of 1.5 pints of blood in a week. This has a significant impact on patients wellbeing and functional performance. Despite transfusion and chelation being the mainstay of treatment there is considerable morbidity and mortality in the patient cohort [2]. ***'The most severe cases can lead to heart failure or liver complications.'***	Thank you. The background section is meant to be a summary. A small number of amendments have been made in line with the stakeholder's comments, but more details including of the impact of the condition on the patient and their carers can be described within the submissions and discussed by committee during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		Anaemia if untreated will cause heart failure however liver complications are not because of severe anaemia but due to iron overload from regular transfusions. Thalassaemia patients are at increased risk of thrombosis and can develop pulmonary hypertension and other complications related to thrombotic events if suboptimally transfused especially if they have been splenectomised. This is due to the poor quality red cells in the circulation in the context of anaemia. ***'Transfusion dependent beta-thalassaemia usually requires lifelong treatment with blood transfusions and medication.'*** Transfusion dependant thalassaemia will always require transfusion as this is integral to the definition as stated in wording section of the scope. ***'repeated transfusions are associated with an increased risk of bloodborne infections and graft versus host disease'*** Graft versus host disease as a consequence of repeated transfusion is exceptionally rare in the UK where directed donations from family members are not undertaken in thalassaemia patients. The statement should probably read "repeated transfusions are associated with an increased risk of iron overload and alloimmunisation, there is also a risk of a reportable Serious Hazard of Transfusion (SHOT reportable event) such incorrect blood group transfusion and transfusion transmitted infections. ***"Treatment with transfusions can cause too much iron to build up in the body and lead to complications including liver cirrhosis, endocrine complications such as diabetes, sterility, and heart failure"*** Blood transfusion will result in the accumulation of iron. Long term complications of iron overload add increasing burden of disease management for patients and include endocrine complications such asv insulin dependent diabetes, hypoparthyroidism, hypothyroidism, hypogonadism resulting in failure to enter puberty and subsequently infertility. These occur with moderate degrees of iron overload. In patients with more severe and	

Section	Consultee/ Commentator	Comments [sic]	Action
		prolonged iron overload cardiac failure and cardiac arrythmias are a common cause of serious ill health and death and late effects such as liver cirrhosis, portal hypertension and liver failure.[3] ***Chelation therapy itself is associated with adverse events including kidney failure, liver and heart toxicity.*** The term heart toxicity is incorrect. Better wording is as below: Chelation therapy has significant side effects, the commonest of which with both oral iron chelation drugs is nausea, vomiting, diarrhoea and abdominal pain. This occurs in 30% of patients on deferasirox [4] and early in the start of therapy with Deferiprone of the order of 10-20% [5]. Other serious side effects include abnormal renal function and Fanconi syndrome with deferasirox and neutropenia and agranulocytosis with deferiprone. Desferrioxamine is known to cause skin reactions at site of needle insertion, skeletal changes, hearing loss and retinal changes in high doses. [3] Health related quality of life is impacted significantly for patients and their families and often the quality of life questionnaires such as the EQ 5D are not detailed enough to identify the variation on HR-QOL during a transfusion cycle as is noted by the issues with the Luspatercept HR-QOL data presented at congresses. The impact on the patients family in relation to the inherited nature of the disorder and the burden of managing the disease is considerable with a high level of anxiety and depression in both sufferers and their families [6] Morbidity in thalassaemia population is high despite improvements in transfusion practice and monitoring[7]	

Section	Consultee/ Commentator	Comments [sic]	Action
		I would emphasis that transfusion dependent thalassaemia is life limiting in childhood without regular transfusions. It is life-limiting in early adulthood without successful iron chelation, due to the health complications that come with iron overload (e.g. heart failure, liver cirrhosis and hepatocellular carcinoma) and even with good iron chelation, continues to have a shortened life expectancy compared to that of the general population.	
	UK forum on Haemoglobin Disorders (professional)	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
	Cell and Gene Therapy Catapult (general commentator)	No comment	Thank you
	Haemoglobinopathy Clinical Reference Group, NHS England	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
	National Haemoglobinopathy Panel,	***'In transfusion-dependent beta-thalassaemia, haemoglobin production is reduced to such a low level that normal growth, development and quality of life can only be achieved by regular red cell transfusions from infancy.'***	Thank you. The background section is meant to be a summary. A small number of amendments

Section	Consultee/ Commentator	Comments [sic]	Action
	England (professional)	We suggest the following as a review of the above statement: The indication for regular blood transfusion in Thalassaemia patients includes severe anaemia causing failure to thrive or evidence extramedullary haematopoiesis where organs such as the liver or spleen enlarge or expansion of the bone marrow causing facial or other skeletal deformities. this may occur in the first few years of life in those with genetic mutations consistent with thalassaemia major and later years for those with severe thalassaemia intermedia The regular transfusion every 3 to 4 weeks and the reoccurrence of anaemia prior to the next transfusion means that patients feel reasonably well post transfusion but then develop progressive tiredness and bone pain as they approach the next transfusion. Despite transfusion and chelation (iron removal agents) being the mainstay of treatment there is considerable morbidity and mortality in the patient cohort [2] . ***'The most severe cases can lead to heart failure or liver complications.'*** Anaemia if untreated will cause heart failure however liver complications are not because of severe anaemia but due to iron overload from regular transfusions. Thalassaemia patients are at increased risk of thrombosis and can develop pulmonary hypertension and other complications related to thrombotic events if suboptimally transfused especially if they have been splenectomised. ***'Transfusion dependent beta-thalassaemia usually requires lifelong treatment with blood transfusions and medication.'*** Transfusion dependant thalassaemia will always require transfusion as this is integral to the definition as stated in wording section of the scope. ***'repeated transfusions are associated with an increased risk of bloodborne infections and graft versus host disease'*** . The statement should read "repeated transfusions are associated with an increased risk of iron overload and alloimmunisation, there is also a risk of a	have been made in line with the stakeholder's comments but more details including of the impact of the condition on the patient and their carers can be described within the submissions and discussed by committee during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		reportable Serious Hazard of Transfusion (SHOT reportable event) such incorrect blood group transfusion and transfusion transmitted infections. ***"Treatment with transfusions can cause too much iron to build up in the body and lead to complications including liver cirrhosis, endocrine complications such as diabetes, sterility, and heart failure"*** Blood transfusion will result in the accumulation of iron. Long term complications of iron overload add increasing burden of disease management for patients and include endocrine complications such asv insulin dependent diabetes, hypoparthyroidism, hypothyroidism, hypogonadism resulting in failure to enter puberty and subsequently infertility. These occur with moderate degrees of iron overload. In patients with more severe and prolonged iron overload cardiac failure and cardiac arrythmias are a common cause of serious ill health and death and late effects such as liver cirrhosis, portal hypertension and liver failure.[3] and cancer ***Chelation therapy itself is associated with adverse events including kidney failure, liver and heart toxicity.*** we suggest review to: Chelation therapy has significant side effects, the commonest of which with both oral iron chelation drugs is nausea, vomiting, diarrhoea and abdominal pain. This occurs in 30% of patients on deferasirox [4] and early in the start of therapy with Deferiprone of the order of 10-20% [5]. Fanconi syndrome with severe renal tubular defect Other serious side effects include abnormal renal function and Fanconi syndrome with deferasirox and neutropenia and agranulocytosis with deferiprone. Desferrioxamine is known to cause skin reactions at site of needle insertion, skeletal changes, hearing loss and retinal changes in high doses. [3]	

Section	Consultee/ Commentator	Comments [sic]	Action
		Health related quality of life is impacted significantly for patients and their families and often the quality of life questionnaires such as the EQ 5D are not detailed enough to identify the variation on HR-QOL during a transfusion cycle as is noted by the issues with the Luspatercept HR-QOL data presented at congresses. The impact on the patients family in relation to the inherited nature of the disorder and the burden of managing the disease is considerable with a high level of anxiety and depression in both sufferers and their families [6] **Morbidity in thalassaemia population is high despite improvements in transfusion practice and monitoring[7]**	
Population	Vertex Pharmaceuticals Ltd (company)	Vertex suggests redefining the population to better align with the proposed indication. (i.e. [redacted]).	Thank you. As the marketing authorisation has not yet been received, the population has been kept broad. This can be discussed further by committee once the marketing authorisation has been received.
	Anthony Nolan (patient)	The defiined populations is in line with the parameters of the single-arm, open-label, multi-site, single-dose Phase 1/2/3 study.	Thank you
	The Essenelle Foundation (patient)	Yes	Thank you

Section	Consultee/ Commentator	Comments [sic]	Action
	United Kingdom Thalassaemia Society (patient)	No. It is not clear whether this would be open to all individuals with transfusion dependent beta thalassaemia or if restricted only to those who do not meet the criteria for allogenic stem cell transplants or as result of secondary conditions acquired.	Thank you. The population has been amended to focus on those who do not have an HLA-matched donor. As such, allogenic stem cell transplantation has been removed as a comparator.
	British Society for Haematology (professional) Endorsed by Royal College of Physicians	The terminology for transfusion dependant thalassaemia needs to be used throughout rather than thalassaemia major. Definitions should be based on the study inclusion criteria so the same population is offered the intervention. Yes, this therapy should be considered for those with transfusion dependent thalassaemia	Thank you. The scope was intentionally focused on transfusion-dependent beta thalassaemia rather than beta thalassaemia major, also including severe forms of thalassaemia major. However, the background has now been clarified and explicitly includes haemoglobin E beta thalassaemia, as noted by a stakeholder. The definition of what constitutes transfusion-dependence can be

Section	Consultee/ Commentator	Comments [sic]	Action
			proposed by the company and discussed by committee during the development of the appraisal. The definition used in the trial has been added to the description of the trial in the section 'the technology'.
	UK forum on Haemoglobin Disorders (professional)	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
	Cell and Gene Therapy Catapult (general commentator)	The population is defined appropriately but it should be noted that the CLIMB-111 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. The trial description and population have been amended to focus on those who do not have an HLA-matched donor and allogenic stem cell transplantation has been removed as a comparator
	Haemoglobinopathy Clinical Reference	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology

Section	Consultee/ Commentator	Comments [sic]	Action
	Group, NHS England		
	National Haemoglobinopathy Panel, England (professional)	The terminology for transfusion dependant thalassaemia to replace thalassaemia major. this is evidence-based.	Please see response to British Society for Haematology
Subgroups	Vertex Pharmaceuticals Ltd (company)	The draft scope does not describe any potential subgroups, and it is not appropriate that subgroups be examined in this appraisal.	Thank you. Please note one of changes to the scope following public consultation is the inclusion of the following subgroups, as evidence permits: people with beta thalassaemia major and people with beta thalassaemia intermedia. The reason for this addition is following input from a clinical expert who noted that people with these two phenotypes may present slightly differently and have slightly different

Section	Consultee/ Commentator	Comments [sic]	Action
			complications and associated prognoses. For example, people with beta thalassaemia intermedia may not immediately be transfusion-dependent but they may have developed different complications by the time they are considered 'transfusion-dependent'. As such, there may be a differential impact on health-related quality of life and/or costs for each of these phenotypes and considering them separately in the modelling may be preferred by the committee.
	United Kingdom Thalassaemia Society (patient)	This has been mentioned within the document, however, it is important to note that in the UK, a majority of the patient population come from an Asian or South-East Asian ethnic background which is not fully represented by earlier studies in thalassaemia- who primarily focussed on the patient cohort of the time which were those coming Mediterranean backgrounds.	Thank you. The issues raised by the stakeholder have been summarised in the Equalities Impact

Section	Consultee/ Commentator	Comments [sic]	Action
		It is found that within the recent cohort of patients, overall health outcomes are poorer due to a variety of factors.	Assessment for this topic. NICE aims to advance equality of opportunity, eliminate unlawful discrimination and foster good relations between people with particular protected characteristics and society as a whole. In addition, the principles that guide the development of NICE guidance and standards includes the aim to reduce heath inequalities. During the appraisal, the committee will consider the evidence submitted by stakeholders including related to unmet need and health inequalities for people with the condition.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society for Haematology (professional) Endorsed by Royal College of Physicians	Definitions should be based on the study inclusion criteria so the same population is offered the intervention; there are no subgroups that require specific consideration. No	Thank you
	UK forum on Haemoglobin Disorders (professional)	In additional to transfusion dependent thalasseamia other forms such as HbE beta thalassaemia present unpredictable outcomes and risk of poor outcome and should be considered	Thank you. The scope background has been changed to clarify that HbE beta thalassaemia who are transfusion dependent are included
	Cell and Gene Therapy Catapult (general commentator)	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. The population has been amended to focus on those who do not have an HLA-matched donor and allogenic stem cell transplantation has been removed as a comparator.
	National Haemoglobinopathy Panel, England (professional)	Response verbatim to UK forum on Haemoglobin Disorders response	Please see response to UK forum on Haemoglobin Disorders response

Section	Consultee/ Commentator	Comments [sic]	Action
Comparators	Vertex Pharmaceuticals Ltd (company)	It is not appropriate to include stem cell transplant (SCT) as a comparator [redacted] patients with an HLA-matched related haematopoietic stem cell donor were not eligible to participate in the CLIMB-111 study. Less than 30% of patients with TDT have a matched related donor and therefore most do not have access to a potentially curative therapy.[vi] Furthermore, HSCT is not currently commissioned as a treatment for adults with thalassaemia.	Thank you. The trial description and population have been amended to focus on those who do not have an HLA-matched donor and allogenic stem cell transplantation has been removed as a comparator
	Anthony Nolan (patient)	Comparators look to be in line with standard of care	Thank you
	The Essenelle Foundation (patient)	At the moment not much is offered to those who would require this choice or option. So yes	Thank you
	United Kingdom Thalassaemia Society (patient)	Yes, However, it is important to note that allogenic stem cell transplantation is not available to the majority (approximately 90%) of the transfusion dependent beta thalassaemia population due not having a matched donor. Additionally, it is also not recommended, available or funded to individuals over the age of	Thank you. Allogenic stem cell transplantation has been removed as a comparator and the population has been focused on those who

Section	Consultee/ Commentator	Comments [sic]	Action
		18. It also brings the risk of acquiring GVHD and organ rejection complications.	do not have an HLA-matched donor.
	British Society for Haematology (professional) Endorsed by Royal College of Physicians	Allogeneic stem cell transplantation from a sibling donor is not available to most patients. The comparator should be standard of care which is transfusion and iron chelation. Yes, the clearest comparator is to those with transfusion dependent thalassaemia who do not have a suitable donor for allogenic bone marrow transplant. The treatment should ideally be considered as safe and as effective and the allogenic bone marrow transplant that is offered to those with a suitable donor. Therefore this is a good comparator group. I am not sure what best supportive care would represent in this context, if not either of the first two options.	Thank you. Allogenic stem cell transplantation has been removed as a comparator and the population has been focused on those who do not have an HLA-matched donor.
	UK forum on Haemoglobin Disorders (professional)	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
	Cell and Gene Therapy Catapult (general commentator)	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. Allogenic stem cell transplantation has been removed as a comparator and the population has been focused on those who

Section	Consultee/ Commentator	Comments [sic]	Action
			do not have an HLA-matched donor.
	Haemoglobinopathy Clinical Reference Group, NHS England	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
	National Haemoglobinopathy Panel, England (professional)	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
Outcomes	Vertex Pharmaceuticals Ltd (company)	The outcomes listed are largely appropriate, although it is not clear what is meant by 'new or worsening haematological disorders', so we suggest this is removed.	Thank you. This outcome was included in the longer-term follow-up study of this treatment (NCT04208529). As another stakeholder has noted it is relevant, it has been retained.
	Anthony Nolan (patient)	The outcome measures listed in the draft scope are considered appropriate to capturing key benefits and contrainidications of this technology.	Thank you

Section	Consultee/ Commentator	Comments [sic]	Action
	The Essenelle Foundation (patient)	Each individual patient will have different things that are important to them when it comes to maintain health but yes, they have captured what they can	Thank you
	United Kingdom Thalassaemia Society (patient)	Yes partially, however, to capture the most important health related benefits and potential risks the following outcomes should be added to the list in the draft scope. • Reduction in the use of iron chelating agents • New or worsening of non-haematological disorders • Health related quality of life of individuals living with transfusion dependent beta thalassaemia and their carers.	Thank you. New or worsening hematologic disorders and health related quality of life for people with the condition are already included as outcomes. Reduction in use of iron chelating agents has been added as an outcome. The NICE health technology evaluation manual notes that evaluations should consider all health effects for patients, and, when relevant, carers. It is not necessary to specify this level of detail in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society for Haematology (professional) Endorsed by Royal College of Physicians	Outcomes are appropriate. Yes these seem appropriate	Thank you
	UK forum on Haemoglobin Disorders (professional)	Outcomes are appropriate.	Thank you
	Cell and Gene Therapy Catapult (general commentator)	No comment	Thank you
	Haemoglobinopathy Clinical Reference Group, NHS England	Outcomes are appropriate.	Thank you
	National Haemoglobinopathy Panel, England (professional)	Outcomes are appropriate.	Thank you

Section	Consultee/ Commentator	Comments [sic]	Action
Equality	Vertex Pharmaceuticals Ltd (company)	People with thalassaemia are largely from non-white backgrounds, including South Asian, South East Asian and Middle Eastern heritage. Therefore, they are subject to a number of challenges related to their condition which manifest as health inequalities. NICE should take account of issues relating to health inequalities faced by people with TDT as it has done recently in the appraisal of crizanlizumab for sickle cell disease.vii	The issues raised by the stakeholder have been summarised in the Equalities Impact Assessment for this topic. NICE aims to advance equality of opportunity, eliminate unlawful discrimination and foster good relations between people with particular protected characteristics and society as a whole. In addition, the principles that guide the development of NICE guidance and standards includes the aim to reduce heath inequalities. During the appraisal, the committee will consider the evidence submitted by stakeholders including related to unmet need and health inequalities

Section	Consultee/ Commentator	Comments [sic]	Action
			for people with the condition.
	Anthony Nolan (patient)	Traits for thalassemia are more common in people from Mediterranean countries, like Greece and Turkey, and in people from Asia, Africa, and the Middle East. The Rh blood groups of the Mediterranean lands differ considerably from those of Northern Europe. Two main strains can be recognized, typified by the Basques with high cde(r) and the Sardinians with high CDe(Ph). This can make the collection of approriate blood groups more complicated. This has a bearing on those needing regular blood transfusions.	The issues raised by the stakeholder have been summarised in the Equalities Impact Assessment for this topic. NICE aims to advance equality of opportunity, eliminate unlawful discrimination and foster good relations between people with particular protected characteristics and society as a whole. In addition, the principles that guide the development of NICE guidance and standards includes the aim to reduce heath inequalities. During the appraisal, the committee will consider the evidence submitted by stakeholders including

Section	Consultee/ Commentator	Comments [sic]	Action
			related to unmet need and health inequalities for people with the condition.
	Genetic Alliance UK (company)	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: - the depth and breadth of inequalities (health and otherwise) experienced by people living with beta thalassaemia 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 beta thalassaemia if they are applied without due consideration and flexibility.	Thank you. The issues raised by the stakeholder have been summarised in the Equalities Impact Assessment for this topic. NICE aims to advance equality of opportunity, eliminate unlawful discrimination and foster good relations between people with particular protected characteristics and society as a whole. In addition, the principles that guide the development of NICE guidance and standards includes the aim to reduce heath inequalities. During the appraisal, the committee will

Section	Consultee/ Commentator	Comments [sic]	Action
			consider the evidence submitted by stakeholders including related to unmet need and health inequalities for people with the condition. However, the committee must follow the processes and methods set out in the NICE health technology evaluation manual and are unable to divert from these methods and processes for individual evaluations or they will risk introducing further inequalities.
	United Kingdom Thalassaemia Society (patient)	In the UK, thalassaemia affects ethnic minority populations that often receive discrimination due to having smaller numbers when compared to the general White British and Northern European populations. As a result, funding within services, treatment options and decisions to fund new therapies which would not only give individuals the choice for the first time but may have also improved their health outcomes have been negatively affected due to the comparison with the majority population. As a consequence of this., the NICE committee should acknowledge and take the racial discrimination and health inequalities faced by this cohort of	Thank you. The issues raised by the stakeholder have been summarised in the Equalities Impact Assessment for this topic. NICE aims to advance equality of opportunity, eliminate unlawful

Section	Consultee/ Commentator	Comments [sic]	Action
		individuals into consideration as they have with other ethnic minority populations and conditions with small patient numbers that have also received funding for life changing therapies and potential curative options.	discrimination and foster good relations between people with particular protected characteristics and society as a whole. In addition, the principles that guide the development of NICE guidance and standards includes the aim to reduce heath inequalities. During the appraisal, the committee will consider the evidence submitted by stakeholders including related to unmet need and health inequalities for people with the condition.
	British Society for Haematology (professional) Endorsed by Royal College of Physicians	Patients suffering with thalassaemia syndromes are from Asian and middle eastern, southern European background. This population already had significant health inequalities and should be prioritised. Thalassaemia has no disease modifying therapeutic intervention at this time and life long blood transfusion every 3 to 4 weeks and iron chelation is highly burdensome.	Thank you. The issues raised by the stakeholder have been summarised in the Equalities Impact Assessment for this topic.

Section	Consultee/ Commentator	Comments [sic]	Action
		Almost all those with transfusion dependent beta thalassaemia are non-white and there is a significant history of under resourcing and de-prioritising their care, as well as stigmatisation and prejudice. This needs to be reddressed	NICE aims to advance equality of opportunity, eliminate unlawful discrimination and foster good relations between people with particular protected characteristics and society as a whole. In addition, the principles that guide the development of NICE guidance and standards includes the aim to reduce heath inequalities. During the appraisal, the committee will consider the evidence submitted by stakeholders including related to unmet need and health inequalities for people with the condition.
	UK forum on Haemoglobin Disorders (professional)	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology

Section	Consultee/ Commentator	Comments [sic]	Action
	Cell and Gene Therapy Catapult (general commentator)	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. The issues raised by the stakeholder have been summarised in the Equalities Impact Assessment for this topic. NICE aims to advance equality of opportunity, eliminate unlawful discrimination and foster good relations between people with particular protected characteristics and society as a whole. In addition, the principles that guide the development of NICE guidance and standards includes the aim to reduce heath inequalities. During the appraisal, the committee will consider the evidence submitted by stakeholders including related to unmet need

Section	Consultee/ Commentator	Comments [sic]	Action
			and health inequalities for people with the condition.
	Haemoglobinopathy Clinical Reference Group, NHS England	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
	National Haemoglobinopathy Panel, England (professional)	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
Other considerations	Vertex Pharmaceuticals Ltd (company)	As mentioned in the equalities section, NICE should consider the impact that exa-cel may have on the health inequalities faced by patients with TDT, and capture this in its decision-making. In addition, the availability of blood can be compromised by the chronic shortage of ethnically matched blood stocks available to treat patients of ethnic-minority heritage and ensure optimal treatment outcomes. Where any treatment can completely remove the need for chronic transfusions, or even significantly reduce the volumes of blood required, this will have a positive impact on the wider healthcare system.	Thank you. The issues raised by the stakeholder have been summarised in the Equalities Impact Assessment for this topic. NICE aims to advance equality of opportunity, eliminate unlawful discrimination and foster good relations between people with particular protected

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			characteristics and society as a whole. In addition, the principles that guide the development of NICE guidance and standards includes the aim to reduce heath inequalities. During the appraisal, the committee will consider the evidence submitted by stakeholders including related to unmet need and health inequalities for people with the condition.
	The Essenelle Foundation (patient)	None	Thank you
	United Kingdom Thalassaemia Society (patient)	The health inequalities faced by the thalassaemia community should be taken into consideration. Not only do patients suffer from racial discrimination throughout the country due to originating from ethnic minority communities, having small patient numbers of results in the population being overlooked for treatment, not prioritised and services being underfunded when compared to other haemoglobinopathy conditions. Based on reports from our members and our interactions with various hospitals and clinicians patients with thalassaemia	Thank you. The issues raised by the stakeholder have been summarised in the Equalities Impact

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		are treated like second class citizens. This lack of prioritisation, often leads to individuals with thalassaemia having poorer health outcomes- this is often exacerbated in regions outside of thalassaemia specialist centres due to small patient numbers. Due to natural disasters, wars and conflict, we have seen an increase in the number of refugees with thalassaemia coming from Syria, Afghanistan, etc. As a consequence of this we expect that there will be an increase in the number of births with TDT in the near future.	Assessment for this topic. NICE aims to advance equality of opportunity, eliminate unlawful discrimination and foster good relations between people with particular protected characteristics and society as a whole. In addition, the principles that guide the development of NICE guidance and standards includes the aim to reduce heath inequalities. During the appraisal, the committee will consider the evidence submitted by stakeholders including related to unmet need and health inequalities for people with the condition.
	British Society for Haematology	None	Thank you

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	(professional) Endorsed by Royal College of Physicians		
	UK forum on Haemoglobin Disorders (professional)	Improvement in research funding for thalassaemia will allow monitoring of these therapies e.g. Health related quality of life and risk factors for poor outcome.	Thank you. Research funding is outside of the mandate of a technology appraisal.
	Cell and Gene Therapy Catapult (general commentator)	No comment	Thank you
	National Haemoglobinopathy Panel, England (professional)	We propose rein fenced research funding for thalassaemia will allow monitoring of these therapies e.g. Health related quality of life and risk factors for poor outcome	Thank you. Research funding is outside of the mandate of a technology appraisal.
Questions for consultation	Vertex Pharmaceuticals Ltd (company)	**How do you define transfusion-dependence in clinical practice?** A patient may be considered transfusion dependent if they require regular transfusions to maintain good health. This may be defined as 10 units per year of red blood cell transfusions over a period of 2 or more years. This is the definition used in the pivotal trial for exa-cel, CLIMB-111 (NCT03655678).	Thank you. The definition of what constitutes transfusion-dependence can be proposed by the company and discussed by committee during the

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		Where do you consider CTX001 will fit into the existing care pathway for transfusion-dependent beta-thalassaemia? Is the current comparator accurate? Should hematopoietic stem cell transplant be considered a comparator? Exa-cel would be used according to its anticipated marketing authorisation, [redacted] SCT should not be considered as a comparator. Furthermore, SCT is not commissioned as a treatment for adults. **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 current standard of care. **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?** There are likely significant benefits beyond the QALY that exa-cel could deliver. First, the technology has the potential to address health inequalities issues described above, and Vertex will present evidence to illustrate this. In addition to improvements in EQ-5D-5L, the CLIMB-111 study also measured other aspects of patient reported quality of life improvements using instruments not incorporated into QALY calculations; health-related quality of life (HRQoL) from baseline over time using the Functional assessment of cancer therapy-bone marrow transplant questionnaire (FACT-BMT); PRO over time assessed using pediatric quality of life inventory (PedsQL). Second, as mentioned in the comments on the background section, thalassaemia has a significant societal burden, and burden on caregivers of	development of the appraisal. However, this definition has been added to the description of the trial in the section 'the technology'. Allogenic stem cell transplantation has been removed as a comparator and the population has been focused on those who do not have an HLA-matched donor. The committee will consider the company's proposal for managed access and the extent to which there may be substantial health-related benefits beyond the QALY calculation within the company's submission or raised by other stakeholders during development.

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		those with thalassaemia. Patients undergoing regular transfusions are required to regularly attend hospital for their treatment, which is disruptive to school, university and working life. Recent research found that approximately 30% of patients are unemployed or unable to work full time owing to their condition. On average, patients spent over 15 hours a month managing their condition.[viii] Equally, patients' education and working lives are often impacted by other aspects of thalassaemia which may not be adequately captured in the QALY calculation, including fatigue and impacts on mental health.	
	United Kingdom Thalassaemia Society (patient)	**Q1. How do you define transfusion-dependence in clinical practice?** Transfusion- dependence is the requirement of regular transfusions due to the severity of the thalassaemia mutation inherited. Transfusion dependent thalassaemia can be defined as receiving 8 or more red blood cell transfusions per year[(1,6)]. **Where do you consider CTX001 will fit into the existing care pathway for transfusion-dependent beta thalassaemia? Is the current comparator accurate? Should hematopoietic stem cell transplant be considered a comparator?** Current treatment options for transfusion dependent beta-thalassaemia are restricted to blood transfusions and three types of iron chelation medications desferrioxamine (DFO), deferiprone (DFP), and deferasirox (DFX) and their risks and side-effects vary. In addition, there are some complications associated with blood transfusion such as allergic reactions, viral infections, iron overload, graft versus host disease and other complications. We believe clinical trials of CTX001 have shown the potential to provide better quality of life by reducing transfusions requirements. Furthermore, β-thalassaemia is a quantitative disorder described by a decrease in the β-globin chain production	Thank you. The population has been amended to focus on those who do not have an HLA-matched donor and allogenic stem cell transplantation has been removed as a comparator. The committee will consider the company's proposal for managed access and the extent to which there may be substantial health-related benefits beyond the QALY calculation within the company's submission or raised by

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		therefore improving haemoglobin levels is a necessary step to reduce the burden of transfusions. CTX001 relies on an autologous transplant with no need for a matched donor, works by disrupting the erythroid enhancer of the BCL11A gene in addition to stimulating the expression of foetal haemoglobin (HbF) in erythrocytes (BCL11A is a suppressor of HbF expression, disruption of the BCL11A enhancer decreases the expression of BCL11A). The current Haematopoietic stem cell transplant (HSCT) as a comparator is not entirely accurate. HSCTs are associated with significant risks and restricted to certain age (under 18 years of age) excluding a significant population of the thalassaemia community in the UK. In addition to the fact that HSCT relies on finding or the availability of a matching donor whereas CTX001 relies on an autologous transplant with no need for a matched donor. Therefore, this technology has the potential to be an alternative curative treatment providing a better quality of life and benefits. **Q3. Would CTX001 be a candidate for managed access?** Yes, NHS England with advice from the National Haemoglobinopathy Panel have had several discussions over the last three years about the managed access route and how they would refer patients to be considered. **Q4. Do you consider the use of CTX001 can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Yes, UKTS believes that the benefits that are unlikely to be included in the QALY calculation are profound.	other stakeholders during development. The issues raised by the stakeholder have been summarised in the Equalities Impact Assessment for this topic. NICE aims to advance equality of opportunity, eliminate unlawful discrimination and foster good relations between people with particular protected characteristics and society as a whole. In addition, the principles that guide the development of NICE guidance and standards includes the aim to reduce heath inequalities. During the appraisal, the committee will consider the evidence submitted by

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		As there is no validated tool to measure health related quality of life in thalassaemia, reliance on the EQ5D as a standardised tool and NICE approved measure is not appropriate in this cohort of patients. The eq5d instrument is a generic tool that does not include condition specific information. As a consequence of this, the true impact of the role thalassaemia has on the daily life of a person, life expectancy (and the differences noted between various ethnicities), and their carers are not taken into consideration. It is important to note that previously QALY calculations in thalassaemia were based on published data on a group of patients originating from the Mediterranean regions who were being treated as the majority at the time. Whilst there are some levels of homogeneity within the calculation, this data including life expectancy, does not represent the current cohort of patients living in the UK who originate from other regions of the world. Previous to 2022, accurate databases and records of causes of death, incidence and age of developing secondary conditions etc were not well documented or recorded due to no commissioning arrangement in place. **Q5. Nice is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others ….** It is important to consider that as thalassaemia and the population affected (especially in recent times) has not been considered a profitable area of political or for on career boosting agenda; research and funding to improve life expectancy and quality of life has and continues to suffer greatly.	stakeholders including related to unmet need and health inequalities for people with the condition.
	British Society for Haematology (professional)	**How do you define transfusion-dependence in clinical practice?** We consider patients as transfusion dependent if they require regular transfusions to maintain good health.	Thank you. Allogenic stem cell transplantation has

	Endorsed by Royal College of Physicians	Generally this means at least 7 transfusion episodes per annum. **Where do you consider CTX001 will fit into the existing care pathway for transfusion-dependent beta-thalassaemia? Is the current comparator accurate? Should hematopoietic stem cell transplant be considered a comparator?** We would consider this as a therapeutic intervention for patients who meet the inclusion and exclusion criteria for the License/ trial. Allogenic stem cell transplantation is not a suitable comparator as most patients do not have suitable donors who are willing or able to donate. **Would CTX001 be a candidate for managed access?** We would be very supportive of a managed access programme for this therapy. **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?** We expect there to be significant benefits outside of QALY calculations. QALY assessments are limited in their scope. The impact of reduced financial and psychological 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. Patients' ability to live and work in areas of their choice, not tied to the hospitals is unlikely to be captured adequately in any QALY calculation. None	been removed as a comparator and the population has been amended to focus on those who do not have an HLA-matched donor.. The committee will consider the company's proposal for managed access and the extent to which there may be substantial health-related benefits beyond the QALY calculation within the company's submission or raised by other stakeholders during development.

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	UK forum on Haemoglobin Disorders (professional)	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
	Cell and Gene Therapy Catapult (general commentator)	**Where do you consider CTX001 will fit into the existing care pathway for transfusion dependent beta-thalassaemia? Is the current comparator accurate? Should hematopoietic stem cell transplant be considered a comparator?** 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. **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 innovative medicines fund to facilitate patient access while further evidence is generated to reduce uncertainty. **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?** Beta-thalassaemia 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.	Thank you. Allogenic stem cell transplantation has been removed as a comparator and he population has been amended to focus on those who do not have an HLA-matched donor.. The committee will consider the company's proposal for managed access and the extent to which there may be substantial health-related benefits beyond the QALY calculation within the company's submission (including if carer health-related quality of life is included in the submission) or raised by other

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			stakeholders during development.
	Haemoglobinopathy Clinical Reference Group, NHS England	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
	National Haemoglobinopathy Panel, England (professional)	Response verbatim to British Society for Haematology response.	Please see response to British Society for Haematology
Additional comments on the draft scope	Vertex Pharmaceuticals Ltd (company)	In the draft scope NICE lists Betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia. NICE technology appraisal guidance [ID968] as 'publication date to be confirmed'. We believe this appraisal has now been formally discontinued by NICE.	Thank you. This has been removed from the scope.
	Genetic Alliance UK (company)	CTX001 is a gene therapy and therefore a novel approach to treating the cause of beta-thalassaemia rather than symptom management. There are limited treatment options for people living with beta-thalassaemia and this treatment is seen as a significant step forward in disease modifying treatment options therefore improving patient outcomes for the beta thalassaemia community.	Thank you

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

Neonatal and Paediatric Pharmacists Group

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