National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Voxelotor for treating haemolytic anaemia in people with sickle cell disease [ID1403]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness *It is important that appropriate topics are referred to NICE to ensure that NICE guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would it be appropriate to refer this topic to NICE for appraisal?*	NHS England and Improvement	Yes it is appropriate	Thank you for your comment. This appraisal has been scheduled into the work programme.
	Global Blood Therapeutics UK	Yes, GBT considers that there is a significant unmet medical need within the patient population, with sickle cell disease (SCD) posing a lifelong and progressive burden to patient health and wellbeing. Voxelotor is a novel, well tolerated and effective therapy with a disease modifying mechanism of action. By modifying the underlying pathophysiology of SCD, Voxelotor has the potential to slow down disease progression and its associated complications; thus, improving health and quality of life for affected individuals. Therefore, this appraisal should be considered a priority.	Thank you for your comment. This appraisal has been scheduled into the work programme.

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	Novartis Pharmaceuticals	Yes it is appropriate to refer this topic to NICE for appraisal as there is a high unmet need for treatments for haemolytic anaemia in sickle cell disease.	Thank you for your comment. This appraisal has been scheduled into the work programme.
	Sickle Cell Society	Of course, it would be appropriate to refer this topic to NICE for appraisal. The reason for this is that there is good evidence to show that people living with sickle cell disorder (SCD) have been underserved for decades. This is reflected in many ways, one of which is the lack of access to different options of new disease modifying treatments for SCD	Thank you for your comment. This appraisal has been scheduled into the work programme.
Wording *Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*	NHS England and Improvement	Yes	Thank you for your comment.
	Global Blood Therapeutics UK	The remit in the draft scope does not accurately reflect the proposed indication submitted to the regulatory authorities. GBT suggest: To appraise the clinical and cost effectiveness of Voxelotor within its proposed marketing authorisation for [redacted]	Thank you for your comment. The remit has been amended to reflect the wording submitted for regulatory approval.
	Novartis Pharmaceuticals	The draft remit does not appear to align with the anticipated EMA marketing authorisation of voxelotor as stated in the company press release https://ir.gbt.com/news-releases/news-release-details/european-medicines-agency-accepts-gbts-marketing-authorization, which states that the EMA has accepted a marketing authorisation application for 'voxelotor for the treatment of haemolytic anaemia in sickle cell disease'	Thank you for your comment. The remit has been amended to reflect the wording submitted for regulatory approval.

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	Sickle Cell Society	Yes	Thank you for your comment. The remit has been amended to reflect the wording submitted for regulatory approval.
Timing Issues *What is the relative urgency of this proposed appraisal to the NHS?*	NHS England and Improvement	There are few options for treating sickle cell disease so a timely guidance would be welcomed.	Thank you for your comment.
	Global Blood Therapeutics UK	There is significant unmet medical need in the patient population confirming the urgency of this appraisal. In particular, there is a need for therapies that can prevent haemolysis and anaemia which have well established links to SCD complications including stroke, leg ulcers, pulmonary hypertension and renal impairment.[1-5] Patients with SCD have limited treatment options, which currently address disease related symptoms, Voxelotor targets the root cause of SCD through inhibition of HbS polymerisation; thus, preventing sickling and the resultant haemolytic anaemia.[6] Hydroxycarbamide is the only active pharmacological therapy currently used to treat SCD in UK clinical practice and is indicated for the prevention of recurrent painful vaso-occlusive crises (VOCs); hydroxycarbamide is considered as the standard clinical management for many patients. Crizanlizumab is another pharmacological therapy indicated specifically for the prevention of VOCs that is currently being appraised by NICE for reimbursement. Other non-pharmacological managements are an important aspect of patient care, these primarily include lifestyle advice, including the avoidance of	Thank you for your comment. This appraisal has been scheduled into the work programme.

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		dehydration and infection that aims to decrease the severity of symptoms and the probability of experiencing acute sickle cell crises.[7] Voxelotor presents a novel therapeutic option to address the unmet need within the SCD treatment pathway.	
	Novartis Pharmaceuticals	Due to the high unmet need, patients would benefit from a NICE appraisal as soon as possible.	This appraisal has been scheduled into the work programme.
	Sickle Cell Society	From our perspective as a Patient Advocacy organisation, there is urgency to move forward rapidly with this proposed appraisal to the NHS. We have all been affected by the Covid19 pandemic and the resultant interruptions/delays to business operations. Nevertheless, the urgency relates to the fact that there are extremely limited disease modifying treatments available from the NHS for people who live with SCD, which has been the case in the UK for decades. As a result serious health inequalities continue for the SCD community. NICE are also considering another disease modifying treatment for SCD (Crizanlizumab) which has already been delayed and which a decision is awaited.	This appraisal has been scheduled into the work programme.
Any additional comments on the draft remit	Sickle Cell Society	There is no acknowledgement that we could see in the remit/scope about the significant burden of the SCD condition and its consequential impact on quality of life. This must not be ignored.	Thank you for your comment. The committee will consider the impact sickle cell disease has on quality of life and the background section of the scope references the significant morbidity

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			associated with the condition. The remit is a succinct statement on what the appraisal will cover and therefore this detail is not included here. No changes to the remit are needed.

Comment 2: the draft scope

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Background information	Global Blood Therapeutics UK	The background information does not reflect the full impact of SCD as it focuses primarily on sickle cell crises. Crises are but one aspect of SCD alongside chronic haemolytic anaemia (haemolysis and anaemia), each contributing individually to the acute and chronic manifestations of the disease.2,3,8-11 Furthermore, a disease background in which VOCs are the sole focus does not fully reflect the proposed positioning of Voxelotor within the treatment pathway. Voxelotor's disease modifying mechanism of action is expected to provide value to patients through the long-term health benefits realised from addressing the underlying root-cause of the disease, polymerisation of HbS, to prevent sickling, the resultant haemolytic anaemia and other sequelae of haemolysis. Excepting hydroxycarbamide, this is in contrast to currently available therapies which act downstream of HbS polymerisation to provide symptom relief without having an effect on the underlying cause of SCD.	Thank you for your comment. The background section has been updated to emphasise the role haemolysis and anaemia have in sickle cell disease. The updated wording also includes additional information on the chronic complications of sickle cell disease. Reference to the risk of stroke in children and treatment with allogenic stem cell transplant for

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		In order to capture the disease burden of SCD beyond acute crises and to more appropriately reflect the positioning of Voxelotor within this disease management landscape we have re-drafted the scope background (included under the 'additional comments' section of this table). In summary, GBT recommends making the following changes to the background: The impact on the life of the patients due to the chronic nature of SCD should be emphasised, the focus should not only be upon a single acute manifestation of SCD such as acute crises events. Comorbidities and organ damage result from the cumulative effects of red blood cell dysfunction, not just due to acute crises.1,5,12-15 HbS polymerisation and the resulting haemolysis and anaemia should be more accurately framed as drivers behind the progressive organ damage, disability, reduced HRQoL and significant decrease in life expectancy experienced by SCD patients, not just as the mechanisms by which crises can eventually occur.16 Without effective treatment, SCD is associated with relentless lifelong progression leading to these long-term complications. Chronic complications are not the only way in which SCD affects patients, with haemolytic anaemia also inhibiting patients' abilities to perform daily activities due to severe fatigue and shortness of breath associated with an insufficient oxygen availability.10 Therefore, SCD creates barriers to work and educational performance for many patients and can also increase burden for caregivers, presenting a source of productivity loss and financial burden.17 Despite the availability of hydroxycarbamide as an established clinical management, SCD still poses a burden to patients and payers which should	children has been amended. It is appreciated that sickle cell disease mainly affects people of African or African-Caribbean family background, and this has been reflected in the background of the scope. Reference to sickle cell disease as a group of inherited conditions has not been updated, as this is line with wording used in the NHS.

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		be highlighted as evidence of a need for further effective therapies: the mortality of patients with SCD still falls far behind that of the general population18,19, and there is a substantial burden to healthcare providers in the UK driven by increasing hospital admission rates for SCD, which have increased by over 50% from 2001-2010.20 In line with the proposed indication submitted in the EU market authorisation application, the background information should be limited to patients aged 12 and above. The references to increased risk of stroke in children aged 2 to 16 and the specific considerations for allogeneic stem cell transplants in children are not relevant to the proposed indication and should be removed. Whilst the background does acknowledge the increased prevalence of SCD among people of African and African-Caribbean origin, the extent to which SCD affects these ethnic minority groups above all others in the UK should be emphasised. Approximately 86% of sickle cell registrations through NHS England in 2018/2019 were for patients of African, African-Caribbean, or other Black descent, with patients of South Asian descent also representing a high proportion of the affected population.21 In addition to the health inequalities affecting ethnic minority groups, SCD has a substantial impact on absenteeism for both education and work which can further the health and economic inequalities felt by patients with SCD.22 As a final clarification GBT would like to note that SCD should not be referred to as a group of conditions but as a single disease.	
	Novartis Pharmaceuticals	There is growing understanding of the pathophysiology of vaso-occlusive crises (referred to as sickle cell crises in the draft scope). Previously, sickle	Thank you for your comment. The scope

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		shaped red blood cells were thought to be the primary cause of blockages leading to vaso-occlusive crises. However, now it is understood that vaso-occlusive crises occur due to increased cell-cell interactions between sickled red blood cells, other blood cells and the endothelial cells lining the blood vessel wall, which leads to the formation of a multi-cellular aggregate within the blood vessel lumen. • Kaul et al 2009; Available at https://pubmed.ncbi.nlm.nih.gov/18720225/ • Zhang et al 2016; Available at https://pubmed.ncbi.nlm.nih.gov/26758915/ Although red blood cell sickling is one of the main features of SCD, it is not sufficient on its own to initiate a vaso-occlusive episode. without abnormally increased intercellular adhesion between blood cells and the endothelium. The increased cell-cell interactions that play an essential role in vaso-occlusion are mediated via adhesion molecules such as P-selectin. We propose that the second paragraph of the background section of the draft scope should be updated to reflect the currently understood pathophysiology of vaso-occlusive crises.	has been amended to reflect the pathophysiology of sickle cell crises as described.
	Sickle Cell Society	See comment immediately above.	Thank you for your comment. The background section of the scope aims to provide a brief overview of the condition. While impact on quality of life has not been explicitly listed, the symptoms associated with sickle

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			cell disease and the chronic and acute complications associated with the condition have been described. The committee will consider the impact sickle cell disease has on quality of life during the appraisal.
The technology/ intervention *Is the description of the technology or technologies accurate?*	Global Blood Therapeutics UK	The technology is accurately described; however, the benefits of preventing haemoglobin polymerisation should be clarified given the novel mechanism of action: Prevention of haemoglobin polymerisation and subsequent red blood cell sickling leads to a reduction in haemolysis and associated anaemia.	Thank you for your comment. The technology section has been amended to include the mechanism of voxelotor in preventing haemolysis and anaemia.
	Novartis Pharmaceuticals	No comment	Thank you.
	Sickle Cell Society	Yes	Thank you for your comment.
Population *Is the population defined appropriately? Are*	Global Blood Therapeutics UK	GBT does not believe that the proposed population of this appraisal is appropriate.	Thank you for your comment. The population has not been changed in order to

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there groups within this population that should be considered separately?		This population is broader than the patients described in the proposed indication submitted to regulatory authorities: [redacted]	keep the population broad in the scope. The committee will consider if it is appropriate to make a recommendation for a narrower population and will only be able to make recommendations within the marketing authorisation for this technology.
	Novartis Pharmaceuticals	The population should be updated to reflect the anticipated marketing authorisation as explained above: for the treatment of haemolytic anaemia in sickle cell disease	Thank you for your comment. The population has not been changed in order to keep the population broad in the scope. The committee will consider if it is appropriate to make a recommendation for a narrower population and will only be able to make recommendations within the marketing authorisation for this technology.

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	Sickle Cell Society	Yes	Thank you for your comment. No change to the population has been made.
Comparators	Global Blood Therapeutics UK	The proposed indication for Voxelotor submitted to regulatory authorities is [redacted] Crizanlizumab is currently under appraisal by NICE for the prevention of sickle cell associated VOCs and is conditionally approved by the EMA specifically for the prevention of recurrent VOCs in SCD patients aged 16 years and older. Whereas Crizanlizumab is indicated specifically for preventing VOCs which are among the consequences of sickling, Voxelotor prevents polymerisation of haemoglobin S, the cause of sickling and tackles the consequences of haemolysis and anaemia, which may include VOCs. Also, Crizanlizumab is indicated for only SCD patients aged 16 and older, a smaller group than the expected patient population for Voxelotor. As such, GBT do not consider Crizanlizumab to be a relevant comparator in this appraisal. GBT do not consider allogeneic stem cell transplant to be a relevant comparator. The commissioning of stem cell transplant for SCD in adults is restricted by NHS England on the grounds of risk vs. benefit. Eligible patients include only those with the most severe SCD without irreversible organ damage; defined as patients with high predicted mortality (25% over a 10-year period), history of ≥3 severe pain crises or other acute complications per year, recurrent acute chest syndrome or other chronic morbidity, requirement of regular	Thank you for your comment. Crizanlizumab has been removed from the comparator list. This is because crizanlizumab has been recommended with a managed access agreement. Section 2.2.15 of NICE Health Technology Evaluations: The Manual states "Technologies that NICE has recommended with managed access are not considered established practice in the NHS and are not considered suitable comparators." Allogenic stem cell transplant has been

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		blood transfusions, intolerance to hydroxycarbamide/transfusion where treatment is indicated or where end organ damage is established.23 Adults receiving allogeneic stem cell transplant are also required to have a matched sibling donor to reduce the probability of rejection, further limiting the pool of patients eligible for transplant.23 Contemporary data from the UK and Ireland show that just 37 patients received allogeneic stem cell transplantation for any haemoglobinopathy in 2018, exemplifying the very small proportion of patients with SCD for whom transplant is deemed appropriate.24 When considering allogeneic stem cell transplant as a treatment of last resort in severe SCD only, it can be reasonably expected that patients who are considered for stem cell transplant are also fulfilling the eligibility criteria and are not being considered for other currently available treatments. As such, it is not expected that Voxelotor would displace stem cell transplant as a treatment option of last resort or substantially alter the number of patients that would ultimately receive stem cell transplant. Allogeneic stem cell transplant is not considered to be a standard medical management as it is only applicable to a very small subset of patients in UK clinical practice; thus, it is not a relevant comparator for Voxelotor. Best supportive care (BSC), hydroxycarbamide and blood transfusions are the only treatments currently used in UK clinical practice for the management of SCD symptoms and should be considered as comparators in this appraisal. BSC is the background management of SCD, focused on reducing the chances of experiencing acute symptoms and sickle cell crises through lifestyle advice (avoiding dehydration, sudden changes in temperature and infection) and optimum use of analgesics during SCD related pain crises.	removed from the comparator list, as this is likely to be used at a later point in the treatment pathway. The comparators in the scope are listed as examples of established clinical management, and it is accepted that multiple treatment options may be used in combination. No changes to the scope on this point are needed.

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		BSC, hydroxycarbamide and blood transfusions each occupy a slightly different place in the SCD treatment landscape, considered for background disease management, reduction of acute crises and aiming to increase the ratio of normal red blood cells to sickled cells, respectively. Patients may receive each of these treatments independently or in combination. As such, GBT consider these treatments/SCD managements to be more suitable as comparators when grouped under the heading of 'established clinical management' rather than each being treated as independent comparators. In addition, established clinical management is considered appropriate for treating SCD regardless of patients' prior therapy [redacted] or as continued disease management following treatment with hydroxycarbamide. Established clinical management would reflect current clinical practice where patients may receive BSC and/or hydroxycarbamide and/or blood transfusions.	
	Novartis Pharmaceuticals	Crizanlizumab is currently listed as a potential comparator, however please note that crizanlizumab and voxelotor target different underlying mechanisms and the indication/anticipated indication is thus different: • Crizanlizumab is indicated for the prevention of recurrent VOC in SCD patients aged 16 years and older • Voxelotor's anticipated EMA indication is for the treatment of haemolytic anaemia in sickle cell disease	Thank you for your comment. Crizanlizumab has been removed from the comparator list. This is because crizanlizumab has been recommended with a managed access agreement. Section 2.2.15 of NICE Health Technology Evaluations: The

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			Manual states "Technologies that NICE has recommended with managed access are not considered established practice in the NHS and are not considered suitable comparators."
	Sickle Cell Society	The comparators in the scope include Hydroxyurea. We know and there is good evidence to support this, that Hydoxyurea is not tolerated by every person with SCD. In addition, some patients/parents remain concerned about the side effects of this chemotherapy drug and as a consequence are reluctant to take it up. We believe that it is vitally important that NICE understand these nuances when using terms such as best alternative care. There is also data that shows that there is scope for better take up of Hydroxyurea in the UK. In our view lack of choice of disease modifying treatments increases the risks to patients well -being and morbidity. We are also not convinced that allogenic stem cell transplantation (which is only available for children on the NHS or via an Individual Funding Request (IFR), is a truly relevant comparator. If you accept this and our point about hydroxyurea, then the term best alternative care is tantamount to meaningless.	Thank you for your comment. It is appreciated that hydroxycarbamide (also known as hydroxyurea) may not be suitable for all people with sickle cell disease. However, as a treatment option at the point in the treatment pathway where voxelotor may be given, it is appropriate to keep it in the comparator list in the scope. The committee will discuss the relevance of comparators during the appraisal.

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			Allogenic stem cell transplant has been removed from the comparator list, as this is likely to be used at a later point in the treatment pathway.
Outcomes *Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	Global Blood Therapeutics UK	GBT consider the listed outcomes to be appropriate for capturing the potential health benefits of Voxelotor, with the exception of the following: Complications should not be limited to those arising from VOCs, all listed complications can manifest from both the acute and chronic aspects of the disease. It should also be noted that leg ulcers, chronic kidney disease and pulmonary hypertension present resource intensive complications of SCD.1,5,15,25 Suggested rewording: Complications arising from SCD (including but not limited to chronic kidney disease, pulmonary hypertension, stroke, acute chest syndrome and leg ulcers). In line with the burden of haemolytic anaemia as a manifestation of SCD, markers of haemolysis (including indirect bilirubin levels and reticulocyte percentage) should also be included in the list of outcomes that capture the potential health benefits of Voxelotor.	Thank you for your comment. The outcome 'complications arising from vasco-occlusive crises' has been amended to 'complications arising from sickle cell disease'. However, the examples of these complications have been removed from the outcomes list, in order to keep the outcomes listed broad. Markers of haemolysis has been added to the outcomes listed in the scope.
	Novartis Pharmaceuticals	The primary outcome of the pivotal phase III HOPE trial was the proportion of patients with a haemoglobin response at week 24, defined as the proportion	Thank you for your comment. The

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		of patients who had a haemoglobin change from baseline of >1 g/dL and this is in line with the anticipated EMA indication. Therefore the outcomes listed in the draft scope should be updated to reflect the main outcome from the HOPE trial and the anticipated indication. Furthermore, please note that even though the annualised incidence of vaso-occlusive crises by treatment group was a secondary outcome in the HOPE trial, there was no significant reduction in VOCs with 1500-mg voxelotor compared to placebo group, albeit the study patient population was not powered to evaluate the incidence of vaso-occlusive crises as an efficacy endpoint. (Howard et al 2021. Available at https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(21)00059-4/fulltext)	outcomes listed includes changes to haematological parameters which covers the primary outcome in the HOPE trial of proportion of people with increase in haemoglobin levels. Markers of haemolysis has also been added to the outcomes listed in the scope. Irrespective of the efficacy of voxelotor for reducing the number or severity of sickle cell crises, this remains an important outcome. No changes have been made to the scope.
	Sickle Cell Society	Yes, with the exception of not covering the key co-morbidities of SCD such stroke and acute chest syndrome.	Thank you for your comment. The outcomes list has been updated to refer to complications associated with sickle cell disease, rather than

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			from vaso-occlusive crises.
Economic analysis	Global Blood Therapeutics UK	No further comments.	Thank you.
	Novartis Pharmaceuticals	No comment	Thank you.
	Sickle Cell Society	The economic analysis should also take account of the burden of SCD on quality of life. The economic cost of NHS emergency admissions, attendances and other co-morbidities specifically associated with SCD is very significant. There is also an economic impact for individuals and families such as lost school days, educational attainment, job security and other aspects of quality of life.	Thank you for your comment. The NICE reference case states that the preferred measure of health effects is the quality adjusted life year measure which will capture quality of life and inform the economic analysis. The economic analysis will also consider all relevant associated costs. The NICE reference case states that this includes costs from an NHS and personal social services perspective.

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Equality and Diversity	Global Blood Therapeutics UK	No equality issues have been identified with the scope that could exclude or differentially impact any protected groups. However, it should be noted that sickle cell is a disease that disproportionately affects ethnic minority groups, above and beyond others in the UK.21 Patients with SCD may also be registered as disabled due to the morbidity associated with their disease including strokes, chronic kidney disease, chronic leg/foot ulcers, osteonecrosis and other mobility issues.1,15 Therefore, effective treatment for SCD has the potential to benefit these people in particular who are protected by the equality legislation. There is also a socioeconomic imbalance among SCD patients in the UK, with 58% of patients coming from the lowest income quartile, these most socio-economically deprived patients are also associated with higher rates of hospital readmission and mortality.26 Thus, investment in an effective treatment for SCD may also reduce health inequality in these low-income groups.	Thank you for your comment. The committee will consider any relevant equality issues when it makes recommendations. The equality issues raised have been formally considered in the equality impact assessment.
	Novartis Pharmaceuticals	No comment	Thank you.
	Sickle Cell Society	You continually state that NICE is committed to providing equality of opportunity, eliminate unlawful discrimination and fostering good relations between people with particular protected characteristics. Despite these statements, we believe NICE ignores and is silent on the challenges and health inequalities faced by people living with SCD. This is particularly important because SCD primarily affects people with African and/or Caribbean heritage including people with mixed race heritage as well as other ethnic groups. We firmly believe that the remit and scope should fully acknowledge this. The recent evidence from the impact of Covid19 also highlighted that black and brown communities and poorer communities were disproportionally affected by the Covid19 pandemic. Furthermore, it is evident	Thank you for your comment. The committee will consider any relevant equality issues when it makes recommendations. The equality issues raised have been formally considered in the equality impact assessment. The scope

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		that when SCD is compared with other like conditions such as Cystic Fibrosis and/or Haemophilia, both of which are smaller in size and mainly affect a different demographic, these comparable conditions are better funded and benefit from significant innovation and research in medicine development. NICE must ask itself why this is so? The evidence of SCD being underserved is there and should be taken into account in any decision making.	also references that the prevalence of sickle cell disease is highest in people with African or African-Caribbean family background.
Other considerations	Global Blood Therapeutics UK	The HOPE trial was not powered for subgroup analyses based on SCD genotype. Whilst patients of mixed genotypes were recruited including HbSS, HbSC, HbSβ+, HbSβ^0 and other variants, limited patient numbers in the HbSC and HbSβ+ genotypes make formal analyses unfeasible in these sub-populations of the trial. Limitations to the final marketing authorisation based on SCD genotype are very unlikely, with all genotypes expected to be indicated for treatment with Voxelotor. Voxelotor is considered to be efficacious across the whole population in the proposed indication; thus, GBT do not consider this to be a relevant subgroup analysis for this appraisal. Subgroup analysis for patients treated with and without concomitant hydroxycarbamide is also not relevant to this appraisal and should be removed from the scope. There was a consistent treatment benefit with respect to the primary trial endpoint (haemoglobin response rate at week 24) in HOPE for patients both with and without hydroxycarbamide use at baseline. Therefore, Voxelotor has demonstrated efficacy in patients with SCD both as a monotherapy and in combination with hydroxycarbamide. Furthermore, the EMA marketing authorisation application includes Voxelotor use [redacted] As such, the marketing authorisation for Voxelotor is unlikely to be restricted based on concomitant hydroxycarbamide use and GBT do not consider this to be a relevant subgroup analysis within this appraisal.	Thank you for your comment. The subgroups described in the scope may be considered relevant by the committee. The committee will discuss if there is evidence available for these subgroups and any other relevant considerations when making recommendations.

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	Novartis Pharmaceuticals	No comment	Thank you.
	Sickle Cell Society	We know from NHS clinical audits that there is significant non- compliance by NHS Trusts, across the country, of NICE guidance on administering pain medication when SCD patients are admitted to Accident and Emergency(A&E) departments. This speaks to an earlier point about health inequalities. Furthermore, we know from patients that they are sometimes regarded as drug seekers when they have frequent admissions via A&E, difficult (because they are advising health care professionals what works by way of treatment) and that their level of pain is not believed by health care professionals in many cases. In this respect a recent Coroner's inquest highlighted such a failure by health care professionals which resulted in the preventable death of a young man with SCD. We have no doubt that race, prejudice and discrimination are factors that contribute to these additional issues	Thank you for your comment. The committee will consider any relevant equality issues when it makes recommendations.
Innovation *Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?*	Global Blood Therapeutics UK	GBT consider Voxelotor to be innovative in the treatment of [redacted] due to the novel and disease modifying mechanism of action, and the potential for it to provide long term management of SCD in a patient population with a substantial unmet need. Voxelotor is the first and only haemoglobin polymerisation inhibitor. It binds reversibly to the alpha subunit of haemoglobin and increases their affinity for oxygen. HbS is stabilised in the oxygenated state which inhibits polymerisation, the cause of red blood cell sickling.[6,10,27] Sickled red blood cells have a shorter lifespan, have limited deformability and experience haemolysis due to impaired cell membrane function.[10] There is also targeted partitioning of Voxelotor to red blood cells only, this drug localisation results in an overall favourable safety profile with only mild	Thank you for your comment. The committee will consider the innovative nature of voxelotor when it makes recommendations.

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Do you consider that the use of the technology can result in any potential significant and 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 Appraisal Committee to take account of these benefits.		and transitory adverse events.[27,28] In addition, due to its mechanism of selectively binding to HbS molecules, affected red blood cells have a sustainable occupation of Voxelotor which can act to prevent polymerisation in all red blood cells susceptible to sickling. Voxelotor has the potential to modify the course of SCD through its novel mechanism of action and reduce the morbidity and mortality associated with SCD, these potential long term health benefits are not offered by current pharmacological treatments, which focus primarily on symptom relief in acute events associated with SCD. Voxelotor has also received the PRIME therapy designation from the EMA. PRIME is a scheme launched by the EMA to increase support for medicines that target an unmet medical need.[29] Additional accolades awarded to Voxelotor have included the Xconomy breakthrough drug of the year and the NORD rare impact award. Given the above, Volexotor can be considered an innovative treatment and represents a step-change for the treatment of SCD.	
	Novartis Pharmaceuticals	No comment	Thank you.
	Sickle Cell Society	Yes	Thank you for your comment. The committee will consider the innovative nature of voxelotor when it makes recommendations.

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Questions for consultation	Global Blood Therapeutics UK	**1. Are there any other subgroups of people in whom voxelotor is expected to be more clinically effective and cost effective or other groups that should be examined separately?** At this stage GBT do not believe there are any subgroups which should be examined separately. **2. Where do you consider voxelotor will fit into the existing NICE pathway,** sickle cell disease: acute painful episode? Voxelotor is intended as a long-term treatment for the prevention of HbS polymerisation, subsequent haemolytic anaemia and other sequelae including painful crisis. The presented treatment pathway specifically covers acute pain management as reactive treatments for when acute events occur, which does not completely cover Voxelotor's position within the SCD treatment landscape. **3. Do you consider that the use of voxelotor can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** There are several key benefits of Voxelotor that may not be captured in the economic model by the utility and QALY assessment. There will be a substantial societal benefit, where effective treatment can reduce days off work or school for patients and caregivers alike, with an indirect cost benefit to patients and employers associated with this reduction. Whilst there is limited data available on the indirect costs of SCD to social services, patients and their caregivers, there is evidence supporting a substantial loss of income due to the reduced life expectancy associated with SCD in the UK.[30]	Thank you for your comments. The subgroups listed in the scope have been retained. The relevant NICE pathway will be considered upon publication of this appraisal. Any additional benefits which are not captured by the QALY will be considered by the committee when it makes recommendations. Your comment on adoption of voxelotor has been noted.

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		Voxelotor treatment has no monitoring requirements and has demonstrated a benign and transient side-effect profile in the HOPE trial.[28] As a result, Voxelotor has no burden associated with treatment monitoring and is anticipated to help avoid blood transfusions which impose a substantial healthcare burden to patients and payers alike due to monitoring requirements, potential iron overload and alloimmunization.[31] The currently recommended pharmacological management for SCD, hydroxycarbamide, also has a requirement for frequent blood monitoring and is associated with low uptake and suboptimal adherence due to patients' safety concerns, which should be less of a limiting factor with Voxelotor treatment.[32-34] Also, as a once daily oral treatment, Voxelotor is convenient for patients to store and administer. **4. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** GBT do not consider there to be any barriers to the adoption of Voxelotor into UK clinical practice.	
	Sickle Cell Society	These have been addressed in the above sections	Thank you for your comment.
Additional comments on the draft scope	Global Blood Therapeutics UK	GBT have redrafted the background information to capture the disease burden of SCD beyond acute crises and to more appropriately reflect the positioning of Voxelotor within this complete disease landscape. The background has been redrafted to incorporate the comments submitted under section 2 of this response form:	Thank you for your comment. The background section has been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		Sickle cell disease (SCD) is the name given to the lifelong inherited condition that affects haemoglobin and red blood cells. The most common type of SCD occurs when people inherit a copy of the beta globin gene with the sickle mutation from both parents (homozygous sickle cell anaemia). Heterozygous sickle cell anaemia occurs when people inherit one copy of the beta globin gene with the sickle mutation from one parent and a different variant of the beta globin gene from the other parent. In all cases, the abnormal haemoglobin, known as haemoglobin S, tends to form polymers (or chains) with other haemoglobin S molecules. These polymers cause red blood cells to become rigid and misshapen, resembling a sickle.[34] Sickle-shaped red blood cells do not last as long in the body as normal red blood cells, with a greatly reduced half-life (12 vs. 120 days, respectively),[16] and get broken down more readily by a process known as haemolysis. Due to chronic haemolysis, people with SCD often develop anaemia as there are not enough red blood cells to carry oxygen throughout the body.[10] Episodic vaso-occlusion may also occur due to the sickled cells not flowing easily through blood vessels and causing blockages. Whilst reduced oxygen delivery is a constant effect of chronic SCD both with and without the occurrence of vaso-occlusion, blockages may lead to ischaemic injuries and excruciating pain (known as acute sickle cell crises) where insufficient oxygen is delivered to tissues. Chronic haemolysis, anaemia and vaso-occlusion all contribute individually and synergistically to progressive blood vessel injury, decrease in functional red blood cell counts and tissue damage.[2,3,8-11] These chronic manifestations of SCD cause complications including progressive organ damage, kidney disease, pulmonary hypertension, leg ulcers, acute chest syndrome and stroke, eventually leading to life-long disability and a reduced life expectancy of up to 30 years in affected patients when compared to the UK general population.[18,19,34]	

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		It is estimated that there are 15,000 people with sickle cell disease in England.[35] The prevalence of sickle cell disease varies considerably across different ethnic communities. Whilst carriers of the sickle cell gene are found in almost all ethnic groups, people of African, African-Caribbean, and other black descent are affected above and beyond all others in the UK, with approximately 86% of recent sickle cell registrations for patients within these ethnic minority groups.[21,36] The prevalence of the disease is increasing because of immigration into the UK, new births and increased survival.[37] SCD causes significant morbidity and mortality and is associated with relentless lifelong progression without effective treatment. Hydroxycarbamide can reduce both acute painful crises and acute chest syndrome (caused by reduced blood flow in the lungs) in people with recurrent painful crises and is considered as the primary pharmacological treatment option for managing the symptoms of SCD. Non-pharmacological disease management in England focuses on reducing the chances of experiencing acute symptoms and sickle cell crises by avoiding dehydration, sudden changes in temperature and infection. Sickle cell crises may be extremely painful and will often require emergency admission to hospital and pain management with paracetamol, non-steroidal anti-inflammatory drugs and opiates. Blood transfusions including exchange transfusions (where sickle red blood cells are replaced with healthy red blood cells) and simple (top-up) transfusions can help to maintain a healthy proportion of normal red blood cells to sickled red blood cells. Transfusions are usually given in response to an acute episode or as a longer-term treatment in patients with severe complications who do not respond to hydroxycarbamide, who refuse to be treated with hydroxycarbamide or who do not tolerate hydroxycarbamide.[31,38] Allogeneic stem cell transplants may be considered as a potentially curative treatment in patients with severe disease not responding or intolerant to hydroxycarbamide; however, restrictions based on severity and a requirement	

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		for matched sibling donors as well as a mortality risk of 2-5% substantially limit the pool of patients eligible for transplant in clinical practice.[23]	
	Novartis Pharmaceuticals	No comment	Thank you.
	Sickle Cell Society	No	Thank you.

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