Single Technology Appraisal

Voxelotor for treating haemolytic anaemia caused by sickle cell disease [ID1403]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Global Blood Therapeutics**

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. AOFAC Foundation
   b. Cianna's Smile
   c. Essenelle Foundation – written by patient expert Layla Lawson.
   d. Sickle Cell Society
   e. Royal College of Pathologists
   f. NHS England and Improvement

4. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group (LRIG)

5. **External Assessment Report – factual accuracy check**

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Emma Drasar, Consultant Haematologist – clinical expert, nominated by Global Blood Therapeutics
   b. Paul Telfer, Professor of Haemoglobin Disorders and Haematology – clinical expert, nominated by Global Blood Therapeutics

8. **External Assessment Group critique of company response to technical engagement** prepared by Liverpool Reviews and Implementation Group (LRIG)

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

June 2022

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		Yes	22 June 2022

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List of abbreviations

ACS	acute chest syndrome
AE	adverse events
AFT	accelerated failure time
AKI	acute kidney injury
ARCET	automated red cell exchange transfusions
ARF	acute renal failure
AS	absolute QALY shortfall
BNF	British National Formulary
CGIC	Clinical Global Impression of Change
CI	confidence interval
CKD	chronic kidney disease
CPRD	Clinical Practice Research Database
CSR	clinical study report
CUA	cost-utility analysis
DES	discrete event simulation
DHTR	delayed haemolytic transfusion reaction
EMA	European Medicines Agency
eMIT	electronic market information tool
EQ-5D	EuroQol health questionnaire 5-dimension
ESA	erythropoietin stimulating agents
ESRD	end stage renal disease
GDPR	General Practice Research Database
Hb	haemoglobin
HbA	adult haemoglobin
HbF	foetal haemoglobin
HbS	sickle β-globin haemoglobin
HbSS	homozygous sickle β-globin haemoglobin
HC	hydroxycarbamide (hydroxyurea)
HES	Hospital Episode Statistics
HRQoL	health-related quality of life
HSCT	haematopoietic stem cell transplant
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICF	informed consent form
ICU	intensive care unit
IR	incidence rate
ITT	intention-to-treat
IV	intravenous

L2+	second line and above
LDH	lactate dehydrogenase
LS	least squares
MAR	missing at random
MHRA	Medicines & Healthcare Products Regulatory Agency
mITT	modified intention-to-treat
MMRM	mixed model for repeated measures
OLE	open-label extension
PH	pulmonary hypertension
PPPY	per patient per year
PPY	per patient-year
PSS	Personal Social Service
QALY	quality-adjusted life-year
RBC	red blood cell
RTT	regular transfusion therapy
RWE	real world evidence
SAE	serious adverse event
SC	subcutaneous
SCD	sickle cell disease
SCDSM	sickle cell disease severity measure
SCT	sickle cell trait
SD	standard deviation
SE	standard error
SLR	systematic literature review
SmPC	summary of product characteristics
SMR	standardised mortality ratio
SOC	standard of care
TEAE	treatment-emergent adverse-event
TRV	tricuspid regurgitation velocity
TTD	time-to-discontinuation
TTE	time-to-event
VLU	venous leg ulcers
VOC	vaso-occlusive crisis
WTP	willingness to pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

Voxelotor received marketing authorisation from the European Medicines Agency (EMA) on 14 February 2022[1] indicated for the treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide.[2] Approval from the Medicines & Healthcare Products Regulatory Agency (MHRA) is expected to be in the same indication and is expected [redacted]

The submission focuses on part of voxelotor's proposed marketing authorisation. The proposed primary positioning for voxelotor is as a second line treatment for haemolytic anaemia in patients with SCD who are intolerant, ineligible, unwilling to take or have an inadequate response to, hydroxycarbamide. This narrower population, in comparison to the approved indication, has been chosen because:

- This positioning reflects where voxelotor will be used in clinical practice and therefore this population is of most relevance to health technology assessment (HTA) decision making. This positioning was proposed by expert UK clinicians in a modified Delphi panel exercise (Appendix U) and validated in additional meetings with individual clinical experts.
- The submission population broadly reflects the population of the pivotal trial (the HOPE study[3]). HOPE studied voxelotor vs placebo given in addition to standard of care (SOC). British guidelines recommend that all SCD patients are offered hydroxycarbamide[4], as do many guidelines around the world, and hydroxycarbamide was available in all the participating countries. For 64% of participants, SOC included hydroxycarbamide (i.e. they were taking hydroxycarbamide at baseline in the trial, see Section B.2.3 for details). In these cases, investigators and patients concluded that hydroxycarbamide was delivering inadequate efficacy and chose to participate in a trial of an investigational product. In the 36% of patients who were not taking hydroxycarbamide, it is reasonable to believe that they had either used it in the past and stopped (i.e. were unwilling or

unable to continue treatment); or had been offered hydroxycarbamide but were unwilling to take it; or had been evaluated for use of hydroxycarbamide but were considered by their physician to be ineligible. Based on the above it is reasonable to assume that the population in HOPE had an inadequate response to hydroxycarbamide or were intolerant, ineligible, or unwilling to take it, although these were not formal inclusion criteria for the trial. The population is also reflective of patients accessing voxelotor in the UK through EAMS.[5] Patients receiving regular blood transfusions were not included in HOPE as it would have confounded the primary endpoint; the implications of this for generalisability are discussed in Section B.2.12.

- This population captures the cost-effectiveness of voxelotor in a population with high unmet need. As noted by the EMA, most SCD patients are treated with hydroxycarbamide and/or crizanlizumab, which are indicated for the prevention of vaso-occlusive crises (VOC), although hydroxycarbamide is recommended by British Society of Haematology guidelines to be offered as first line treatment for all SCD patients.[4] The EMA note that there is a high unmet need for medicines to treat haemolytic anaemia, which is experienced to various degrees by all SCD patients.[6]

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with sickle cell disease (adults and paediatric patients aged 12 years or older).	Patients requiring second-line treatment after hydroxycarbamide, i.e. adults and paediatric patients aged 12 years or older with SCD who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective.	This positioning reflects where voxelotor will be used in clinical practice and therefore is of most relevance to HTA decision making. This positioning has also been validated by UK clinical experts (see Appendix U), who have confirmed that voxelotor would be used as a second line treatment after hydroxycarbamide in the NHS, consistent with BSH guidelines that hydroxycarbamide should be offered to all SCD patients. This rationale is further elaborated in the text preceding this table.
Intervention	Voxelotor	Voxelotor	As NICE scope
Comparator(s)	Established clinical management without voxelotor including: • hydroxycarbamide • blood transfusions (exchange and top-ups) • best supportive care.	Established clinical management (termed standard of care [SOC]) without voxelotor in second line treatment of haemolytic anaemia in patients who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective. This includes supportive care and also hydroxycarbamide and/or blood transfusions (exchange and top-up) for a proportion of patients.	Current second line treatment of haemolytic anaemia in SCD comprises supportive treatment, and blood transfusions for a proportion of patients. In addition, a proportion of patients obtain some clinical benefit from hydroxycarbamide and remain on hydroxycarbamide treatment. The comparator for this submission is therefore as stated in the adjacent column. The second-line position in therapy adopted for the submission means that hydroxycarbamide alone is not a relevant comparator.

Outcomes	The outcome measures to be considered include: • changes to haematological parameters (haemoglobin levels) • number and severity of sickle cell crises • complications arising from sickle cell disease • markers of haemolysis • mortality • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • changes to haemoglobin level • Impact of Hb, VOCs and Hb*VOC (interaction) on the following complications: acute renal failure (ARF), Arrythmias, Cardiomegaly, chronic kidney disease (CKD), end-state renal disease (ESRD), Gallstones, Heart Failure, Leg Ulcer, Osteomyelitis, Osteonecrosis, Pulmonary hypertension, Priapism, Sepsis, Stroke, VOC (as defined in HOPE, that is, joint endpoint which includes uncomplicated and complicated to ACS/Pneumonia) • "Impact" is measured by: 1) Proportion of patients experiencing each complication by the end of the simulation; 2) Incidence rate (events per person per year) for each complication • mortality • adverse effects of treatment • health-related quality of life	While statistically significant differences in favour of voxelotor were observed in other haematological parameters (markers of haemolysis), to avoid the potential for double counting and due to data limitations, only Hb benefit is considered and not markers of haemolysis. Sickle cell crises, SCD complications and mortality are modelled through the effect of treatment on Hb.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective	Cost-effectiveness will be evaluated in accordance with the NICE reference case: • The cost-effectiveness of treatments will be expressed in terms of incremental cost per quality-adjusted life year as per NICE TA guidelines • The time horizon for estimating clinical and cost effectiveness will be over a lifetime horizon to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective	GBT believes that voxelotor is eligible for the application of a severity modifier to the willingness to pay threshold, on the basis that it is an innovative treatment that addresses high unmet need in a medically severe rare disease with few treatment options, in a patient population that suffers from health and socio-economic inequalities. SCD is a life-long genetic condition which may be clinically impactful from an early age.[7] it is progressive and is associated with a wide range of acute and chronic complications, progressive organ damage, a severe quality of life impact on both patients and families, and a 20-30-year reduction in life expectancy even under modern treatment.[8] Voxelotor is a disease-modifying therapy that acts on the underlying molecular basis of SCD and thus is likely to improve both short- and long-term outcomes. [redacted] (see Section B.3.6 for further discussion).

Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • subgroups defined by combination treatment with/without hydroxycarbamide • subgroups defined by genotypes of sickle cell disease	The submission population is a subgroup of the licensed indication, i.e. second line treatment (patients who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective). Transfusion-dependent patients will also be considered, as a subgroup of the overall submission population. The subgroups described in the SCOPE will not be modelled.	**Genotype**: Voxelotor's marketing authorisation is not restricted by SCD genotype. Voxelotor is considered to be efficacious across the whole submission population; thus, GBT does not consider this to be a relevant subgroup analysis. In addition, the HOPE trial was not powered for subgroup analyses based on SCD genotype. Whilst patients of various genotypes were recruited including HbSS, HbSC, HbSβ+, HbSβ0 and other variants, limited patient numbers in the HbSC and HbSβ+ genotypes make formal analyses unfeasible in these sub-populations. **Hydroxycarbamide**: Subgroup analysis for patients treated with and without concomitant hydroxycarbamide is not considered relevant. There was a consistent treatment benefit in HOPE for patients both with and without stable hydroxycarbamide use at baseline. Therefore, voxelotor has demonstrated efficacy both as a monotherapy and in combination with hydroxycarbamide. [redacted] is not restricted based on concomitant hydroxycarbamide use, reinforcing the view that this is not a relevant subgroup analysis. However, the patient population from HOPE has been stratified by HC use for the purposes of modelling (see Section B.3.3.1.1)

Special considerations including issues related to equity or equality		Special considerations: 1. The decision problem disproportionately affects patients from ethnic minorities, who already suffer from health and socioeconomic inequalities (see Section B.1.4). Therefore, issues of equity and equality are relevant to this submission. 2. SCD is a severe rare disease with high unmet medical need and therefore the higher severity modifier should be applied (see Economic Analysis row above).	As described in the adjacent column.

B.1.2. Description of the technology being appraised

Details of the technology being appraised in this submission are summarised in Table 2. The Summary of Product Characteristics and EPAR are attached in Appendix C.

Table 2 Technology being appraised

UK approved name and brand name	Voxelotor (Oxbryta®)
Mechanism of action	Voxelotor is a haemoglobin S (HbS) polymerisation inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to red blood cells (RBCs). By increasing the affinity of Hb for oxygen, voxelotor demonstrates dose-dependent inhibition of HbS polymerisation. Voxelotor inhibits RBC sickling and improves RBC deformability. The impact of the anti-polymerisation effect is to reduce measures of haemolysis (indirect bilirubin) with a concomitant decrease in percent reticulocyte count and an increase in Hb consistent with improvement in haemolytic anaemia.[2] Polymerisation of HbS is the initial pathological event responsible for all symptoms of SCD. The earliest pathological changes detectable in normal care are haemolysis and anaemia. Because voxelotor inhibits the initial pathophysiological event in SCD, it is a disease modifying therapy.
Marketing authorisation /CE mark status	Voxelotor received marketing authorisation from the European Medicines Agency (EMA) on 14 February 2022.[1] Approval from the Medicines & Healthcare Products Regulatory Agency (MHRA) is expected to be in the same indication and is expected [redacted] Voxelotor was granted orphan drug status (EU/3/16/1769) as a medicinal product for the treatment of an orphan condition in accordance with Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on 18/11/2016. This was maintained on 17/12/2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Voxelotor is indicated by the EMA for the treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide.[2] [redacted]
Method of administration and dosage	The recommended dosage of voxelotor is three x 500 mg film-coated tablets taken orally once daily with or without food. Voxelotor can be administered alone or in combination with hydroxycarbamide.[2]
Additional tests or investigations	No additional tests or monitoring are required by patients receiving voxelotor.

List price and average cost of a course of treatment	List price: Oxbryta (voxelotor) One bottle containing 90 x 500mg tablets: [redacted] Average treatment cost: [redacted] per patient per year
Patient access scheme (if applicable)	[redacted]

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

B.1.3.1.1. *Pathophysiology*

SCD is a rare, chronic, progressive, life-threatening inherited disorder of haemoglobin (Hb) that begins in infancy and may be clinically impactful from an early age. Hb is the component of red blood cells (RBCs) that carries oxygen from the lungs to the organs and tissues, where oxygen is released. Normal adult Hb (HbA) is formed by two α-globin subunits and two β-globin subunits. The β-globin subunits are encoded by the *HBB* gene. A single nucleotide substitution in this gene results in the HbS variant (sickle β-globin or βs).[7] SCD occurs in individuals with two copies of the HbS gene (or one HbS plus another abnormal Hb variant). Individuals with one normal Hb (HbA) and one HbS gene are defined as having sickle cell trait (SCT; not usually associated with clinical symptoms), but do not have SCD.[7,9]

HbS reversibly polymerises (forms long chains) under conditions of low oxygen. This causes RBCs to distort into a rigid sickle shape, returning to their normal shape upon reoxygenation. However, continual sickling and unsickling lead to irreversibly sickled RBCs, which then break up in a process known as haemolysis (Figure 1). Haemolysis releases the cell contents into the blood, causing damage to the vascular system.[8-11]

HbS polymerisation results in a cascade of pathological events (Figure 1), starting with RBC sickling and haemolysis and leading to haemolytic anaemia, blood vessel damage (vasculopathy) and vaso-occlusion (including VOCs). This results in reduced oxygen delivery to the tissues, and chronic sterile inflammation caused by the presence of free cell contents in the blood.[10,11]

Together, these pathologies cause a range of acute and chronic severe complications, including progressive organ damage and associated symptoms and comorbidities. This results in significantly reduced health-related quality of life, a reduction in life expectancy of around 30 years even in high-income countries,[8] and a severe burden on families and carers. SCD patients are a severely underserved

population with very limited treatment options available. The disease process is summarised in Figure 1; the action of voxelotor is also shown.

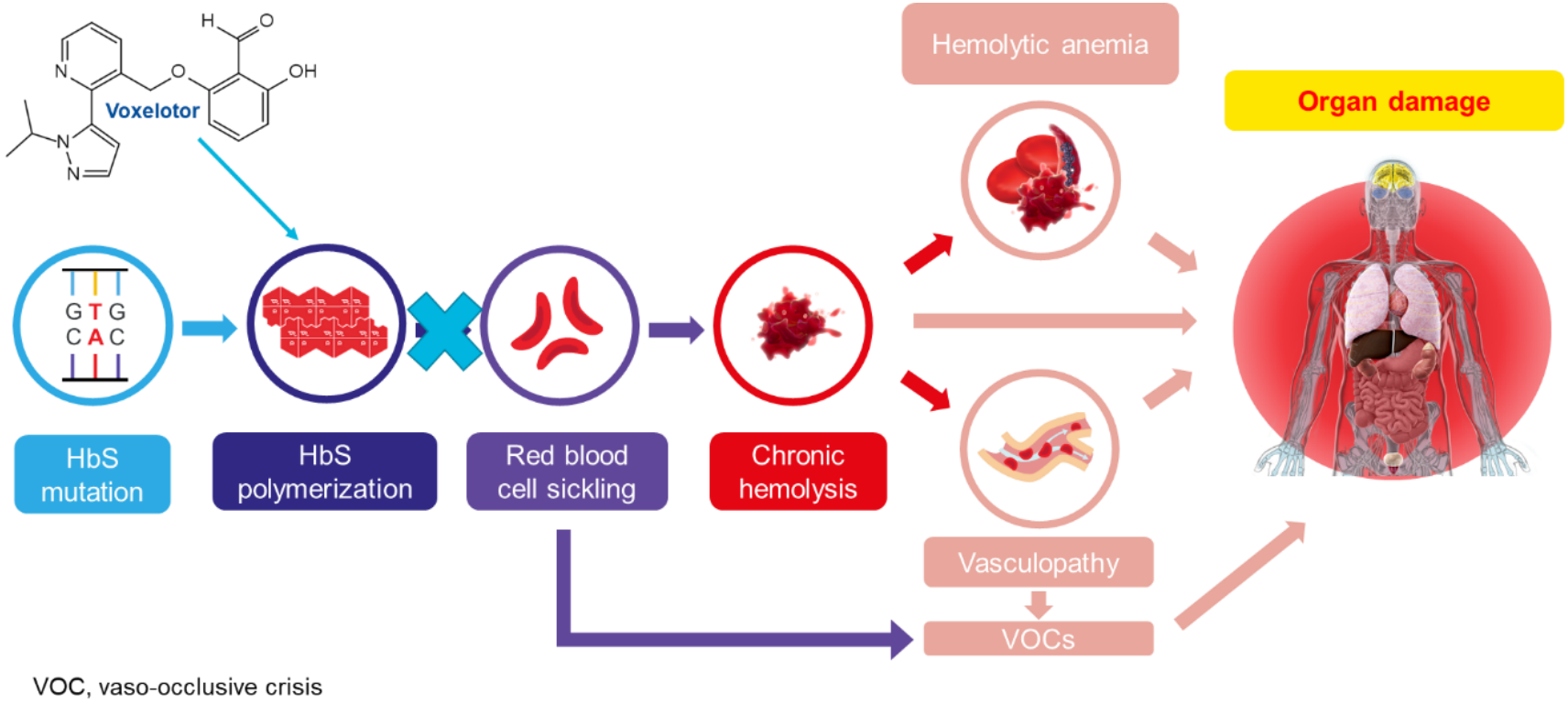


Figure 1. Disease process in SCD and action of voxelotor

B.1.3.1.2. *Haemolytic anaemia and its association with adverse outcomes*

Chronic haemolytic anaemia (i.e. low Hb levels caused by haemolysis) is a major characteristic of SCD experienced by all patients to various degrees, and an important driver of SCD pathology.[1,11] Sustained haemolytic anaemia causes progressive deterioration in tissue and organ function, through chronic reduction in oxygen supply and via inflammation and vascular damage caused by the products of haemolysis.[10,11] This leads to progressive symptoms resulting from organ failure.[12] The clinical presentation of SCD-related organ damage is described in Section B.1.3.1.4.

Haemolysis and the resulting haemolytic anaemia are associated with a range of adverse outcomes in SCD:

- Lower Hb levels are associated with increased risk of vascular complications of SCD, including stroke, leg ulcers, pulmonary hypertension, priapism, and renal failure.[10] The Cooperative Study of Sickle Cell Disease (CSSCD; N=4082) found low steady-state Hb concentration to be the most powerful predictor of first stroke in SCD patients: relative risk [RR] was 1.85 per 1 g/dL decrease in Hb for infarctive stroke [$p < 0.001$] and 1.61 per 1 g/dL decrease in Hb for haemorrhagic stroke [$p < 0.013$].[13]

- Analysis of a cohort of 182 paediatric patients at a centre in Italy found a significant inverse correlation between Hb and middle cerebral artery (MCA) and terminal internal carotid artery (TCA) velocities by transcranial Doppler ultrasound (TCD). Univariate analysis showed significant inverse correlation between abnormal/conditional TCDi results and Hb considered as a continuous variable (OR: 0.484, $P<0.001$). The correlation between TCDi results and Hb remained significant in multivariate analysis. High TCD velocities are an indication to start disease-modifying treatments or consider disease-curative options in children with SCD. The study supports the beneficial effect of higher Hb levels in reducing time-averaged maximum mean velocities.[14]

- Lower Hb levels are associated with increased mortality. An analysis of 3,764 patients from the CSSCD showed increased mortality in SCD in patients with

lower Hb levels; SCA patients with Hb ≤ 7.1 g/dL had an increased risk of death compared with all other patients (2.8 vs 1.1 deaths per 100 person–years, p=0.003, analysis carried out in patients aged ≥20 years).[15] A systematic review and meta-analysis by Ataga et al. also found that Hb was significantly lower (0.6 g/dL) in patients who were reported as having subsequently died compared with those who were not.[16]

- A systematic review and meta-analysis by Ataga et al. found that mean Hb was significantly lower in SCD patients with cerebrovascular disease (0.4 g/dL), increased transcranial Doppler velocity in cerebral arteries (0.6 g/dL), albuminuria (0.6 g/dL), elevated estimated pulmonary artery systolic pressure (0.9 g/dL), and in patients that subsequently died (0.6 g/dL). A modelled Hb increase of ≥1 g/dL resulted in a 41-64% reduction in the risk of negative clinical outcomes.[16]

- An analysis of patients with SCD in the CPRD/HES databases in England by Telfer et al. found that an increase in Hb of 1 g/dL was associated with a statistically significant reduction in risk for 6 common EOD outcomes and clinical complications (leg ulcer, pulmonary hypertension, chronic kidney disease, end-stage renal disease, acute chest syndrome and stroke).[17]

- A large-scale longitudinal analysis of data from 17,034 patients with SCD in the Symphony health claims database in the US found that higher Hb levels were significantly associated with reduced odds of developing end-organ damage (chronic kidney disease, pulmonary hypertension or stroke).[18]

Symptoms of anaemia itself include fatigue, weakness, tachycardia, dizziness and confusion. Fatigue in particular is a major burden for many people with SCD.[19]

The evidence for the relationship between Hb levels and outcomes in SCD is discussed in Section B.3.3.3.1.

B.1.3.1.3. *Epidemiology*

SCD is a severe, rare inherited disorder that predominantly affects people of African, Caribbean, Middle Eastern or South Asian descent, where malaria is more prevalent and the same genetic mutation that causes SCD provides a protective benefit

against malaria.[7,20,21] It affects approximately 1 in every 2000 live births in England, making it one of the most common genetic diseases.[21] In 2018/2019, 299 babies were identified as having SCD by the NHS screening for sickle cell disease and thalassaemia programme.[22] In addition, new cases enter the population via migration. Approximately 12,500–15,000 people are living with SCD in England.[21]

SCD is a life-shortening disease. Infant mortality due to SCD has declined and more people with SCD are surviving into adulthood due to improvements in supportive care.[21] However, a 2017 review published in New England Journal of Medicine states that SCD still reduces life expectancy by approximately 30 years even with the best available treatment.[8] Data from a centre in the UK showed an estimated median lifespan of 67 years in patients with SCD.[23]

B.1.3.1.4. *Clinical presentation*

SCD is a chronic, progressive disease characterised by a wide range of symptoms and complications resulting from irreversible organ damage (see Figure 2). Presentation and clinical course vary between individuals.[8,19] While some experience a milder clinical course, the most severe form causes significant morbidity and mortality.[8,19] This submission is concerned with patients who require second-line treatment for their SCD owing to the severity of their condition. Complications associated with SCD can begin in the first year of life and accumulate with age. As survival has improved due improvements in supportive care, there has been increasing recognition of the consequences of repeated sickling and chronic haemolysis for multiple organ systems.[24] There is therefore an urgent need for new treatments that can modify the course of the disease and prevent or slow the development of irreversible damage.

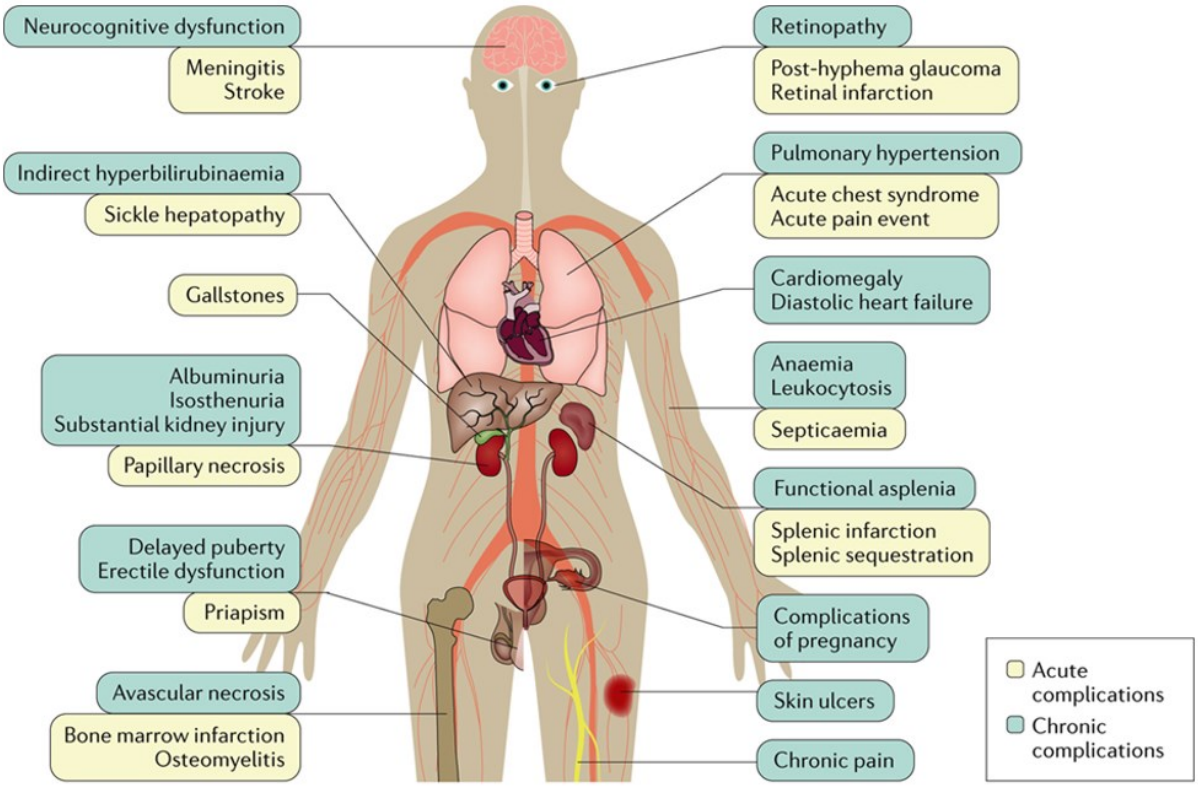


Figure 2 Sites of organ damage and clinical complications of SCD

Source: Kato 2018[7]

Organ damage

Organ damage is associated with low Hb levels[16] (see Sections B.1.3.1.2 and B.3.3.3 for details) and occurs regardless of VOC frequency.[25] Seven-year follow-up of a cohort of 104 adult SCD patients (median age 33 years) at an academic medical centre in the Netherlands, beginning in 2006, found that 62% developed a new SCD-related complication during the period. There was no relationship between rate of hospital admission for VOCs and the development of any form of organ damage except for iron overload and acute chest syndrome (ACS). Seven patients died from SCD-related causes: one each from ACS, multi-organ failure, renal failure and stroke, and three from liver failure.[25] Chronic organ complications develop insidiously and become the main cause of morbidity and mortality in adults with SCD in their thirties and beyond.[9] In a large US based observational study, 48% of SCD patients had documented irreversible organ damage when in their fifth decade.[26]

There is therefore an urgent need for disease-modifying treatments that act early in the cascade of pathology to prevent haemolysis, haemolytic anaemia and the

downstream effects that result in organ damage. Common manifestations of SCD-related organ damage are described below.

Cardiopulmonary complications

- Patients with SCD experience a range of cardiovascular problems, including cardiomegaly, heart failure and arrythmias. Anaemia, resulting in increased cardiac output, and iron overload (from blood transfusions) are key factors in the development of cardiac complications in SCD.[27]

- At least 6-10% of adults with SCD develop pulmonary hypertension (PH) as a result of cardiopulmonary damage.[28] PH causes chest pain, fatigue, dizziness and fainting, and reduced exercise tolerance caused by progressive breathlessness on exertion.[19] PH is associated with increased mortality in SCD: one study found 5-year survival was 63% in SCD patients diagnosed with PH, compared with 85% in SCD patients in the same cohort who did not have PH.[10]

Cerebrovascular disease

- By 45 years of age, one in four adults with SCD will have had a stroke.[13]

- Cerebral vascular injury and neuro-ischemic damage are leading causes of death and morbidity in children and adults with SCD.[7] Silent cerebral infarctions (SCI; i.e. strokes without noticeable symptoms) are also common, estimated to be present in 29.5% of patients with HbSS or HbSβ^o genotype.[29] SCI contribute to cognitive deficits in SCD,[30] which can negatively affect education and employment.

Renal disease

- SCD has important effects on the structure and function of the kidney, as the physiological conditions in the renal tissue promote RBC sickling.[31] This leads to both acute kidney injury and chronic kidney disease resulting from a range of pathologies, collectively known as sickle cell nephropathy. In their 2015 review, Nath and Hebbel refer to a “steady, age-dependent accrual of adverse renal sequelae shortens the average lifespan of patients with SCD” and note

that approximately 16-18% of overall mortality in patients with SCD is attributable to kidney disease.[31]

Liver disease

- Liver disease is an important cause of morbidity and mortality in patients with SCD, where it is known as sickle hepatopathy.[32] Liver disease can arise from sickling and consequent hypoxia within the liver, from the effects of multiple transfusions, or from the sequelae of gallstones, which are common in SCD. Clinical manifestations can be both acute and chronic, and some patients progress to cirrhosis and end-stage liver disease; cirrhosis has been reported in up to 30% of SCD patients in autopsy series.[32]

Leg ulcers

- Leg ulcers are a painful and often disabling complication of SCD and may take months to years to heal.[33] It is estimated that between 26% and 75% of SCD patients will experience leg ulcers during their lifetime.[34]

Skeletal damage

- SCD is associated with skeletal complications including osteomyelitis (bone infection) and osteonecrosis (death of bone cells), caused by inadequate blood supply to the bone.[35] Osteonecrosis (also known as avascular necrosis) causes progressive bone degeneration and affects up to 50% of people with SCD.[36] It can result in chronic pain, impairment and disability.[19] It is most common in the head of the femur but can occur elsewhere and often affects multiple joints.[19] People with SCD are at higher risk of requiring hip replacement and typically require it at a younger age than in the general population; a systematic review of total hip arthroplasty (hip replacement) in SCD found that mean age at the time of the procedure ranged from 23.8 to 37 years.[37]

Chronic pain

- An estimated 30% to 40% of adolescents and adults with SCD live with chronic pain; a prospective study of 232 SCD patients aged 16+ years, followed for up to 6 months as part of the PiSCES study, found that 29.3% experienced pain on more than 95% of days.[38,39] Many patients require

opioids to deal with SCD-related pain, with potential for adverse effects, stigma and dependency.[40]

- Priapism (a painful, persistent, unwanted erection of the penis) is estimated to affect 35-90% of males with SCD during their lifetime. First episodes usually occur before age of 20.[19] While most episodes are self-limiting, sustained episodes require emergency treatment in order to prevent permanent erectile dysfunction.[19]

Bacterial infections

- Immune deficiency in early childhood results in a life-long increased susceptibility to bacterial infection. Bacteraemia and sepsis are common complications of SCD.[41] Improving the prevention of sepsis is a key goal in the NHS England Second Sepsis Action Plan.[42]

Vaso-occlusive crises (VOC)

VOC, also known as sickle cell crises, are acute painful events caused by vaso-occlusion (blockage or narrowing of blood vessels). Nearly all people with SCD will experience a VOC during their lifetime, but their frequency varies. In a study of 8,521 SCD patients, using US Medicaid data, the average number of VOC episodes reported during the first-year follow-up period was 2.79, with a rate of 3.31 VOCs per person-year. However, during this period, 52.3% of patients did not have any VOC episodes, 1.7% had 1, 6.7% had 2 and 26.3% had >2 VOC episodes.[43] Vora et al. analysed two cohorts of patients from specialist SCD centres in the UK over 1-year periods in 2019-2021 and found that 47.5% in one cohort and 73.9% in the other cohort had no recorded VOCs that were either hospital-treated or required prescribed analgesia. This may have been partially due to patients self-managing, particularly during the pandemic. However, taken together these data confirm that while VOCs are an important feature of SCD, they are only one of a range of manifestations and occur infrequently for many patients. Furthermore, as reported above, frequency of VOCs is not predictive of degree of organ damage, and organ damage still occurs in patients who rarely experience VOCs.[25]

B.1.3.1.5. *Burden of SCD on health-related quality of life*

The symptomatic burden of SCD and SCD-related comorbidities has a significant impact on health-related quality of life (HRQoL).[44-46] An analysis of 230 patients in the PiSCES study found that greater somatic symptom burden has a significantly negative impact on all subscales of the SF-36 questionnaire.[46] Health state utility, measured with EQ-5D, is reduced as the disease progresses, with the lowest scores seen in those with organ damage.[47] Appendix V contains testimonies from patients with SCD in the UK detailing the wide-ranging effects of living with SCD on all aspects of their lives.

GBT conducted a multinational survey entitled Sickle Cell Health Awareness, Perspectives and Experiences (SHAPE), to better understand the experience of SCD patients, their carers and healthcare professionals (HCPs).[48] The sample from the UK was 200 patients, 30 carers and 30 HCPs.[49] Patients reported that the symptoms with the greatest impact on their lives were, in order, VOCs, fatigue/tiredness, and low mood/feeling depressed.[49] HCPs in the overall sample reported the great impact that SCD has on multiple areas of patients' lives. For patients aged ≥18 years, 63% of HCPs believed that SCD 'greatly impacts' overall wellbeing. 'Great impact' was reported on long-term health prospects (60%), optimism about the future (58%), ability to attend school/work (49%), self-esteem (50%) and mental health (55%).[50]

SCD exerts a significant burden on mental health. The emotional and psychological impact of SCD on patients and families adds to the lifelong progressive burden of the disease caused by clinical symptoms.[51,52] The prevalence of depression in SCD patients was reported at 28% and 39% in the PiSCES [53] and SWAY[54] studies, respectively, and prevalence of anxiety in the SWAY study was 38% (including 6.5% with an anxiety disorder).[54]

Patients with SCD often experience stigma and discrimination, which negatively impacts HRQoL, psychological well-being, and healthcare experience.[55] This was confirmed by the No One's Listening report 2021, published by the All-Party Parliamentary Group on Sickle Cell and Thalassemia and the Sickle Cell Society.[56] They found that patients are regularly treated with disrespect, not believed or

listened to, and not treated as a priority by healthcare professionals, partially as a result of low awareness and insufficient training in SCD.

B.1.3.1.6. *Burden of SCD on education, employment and productivity*

SCD disproportionately affects disadvantaged communities, and its effects magnify existing inequalities.[54,57] Symptoms, fatigue and frequent medical visits associated with SCD negatively affect both education and careers for patients and their carers, making it difficult for people to achieve their full potential and reinforcing socioeconomic inequalities. In a large multinational survey (SWAY), working people with SCD had missed an average of 7 hours of working over 7 days; 53% reported reducing their working hours and 32% were dismissed from a job due to SCD.[54] A study conducted for GBT in SCD patients with high unmet need (as defined by at least 3 SCD confirmed secondary care interactions [inpatient or outpatient] within a year). Total productivity loss due to healthcare admissions, attendances, consultations, and non-hospitalised sickness for patients with SCD and high unmet need was £[redacted] (mean £[redacted] and median £[redacted] per patient year). Members of the cohort who were found to have end organ damage (EOD) had [redacted] the median number of days of productivity loss as members of the cohort with no EOD (mean [redacted] and [redacted] per patient year respectively). This equated to £[redacted] and £[redacted] of lost productivity per patient year, measured using mean wages for the UK. There was also substantial loss of future income.[58]

SCD also negatively affects educational participation. In children and adolescents with SCD, academic attainment and school completion years are lower those of their peers and siblings.[57] Interest and performance at school is negatively impacted by increased absence in many children with SCD.[54] Neurocognitive deficits caused by strokes and silent cerebral infarctions can also affect education and employment.[30]

B.1.3.1.7. *Burden on carers*

As SCD begins in infancy and needs to be managed into adulthood, informal caregiving, predominantly provided by family, is vital to SCD management. Carers experience stress and negative impact on physical and mental health and family functioning.[59] In the SHAPE survey, caregivers (N=207) felt that most areas of their lives - particularly their ability to attend and succeed at school or work (56%) and their own overall wellbeing (53%) and mental health (52%) - were impacted by caring

for someone with SCD.[48] In addition, a study of HRQoL in carers of people with SCD in the UK was carried out on behalf of GBT (see Appendix S for report). Caring for somebody with SCD was found to negatively impact HRQoL, as measured using the generic preference-based QoL measure (EQ-5D-5L) and a caregiver-specific QoL measure (CarerQol-7D). The mean EQ-5D-5L utility score was [redacted], whilst the CarerQol-7D score was [redacted]

Caring (e.g. looking after patients when sick, attending medical visits, visiting patients in hospital) affects carers' ability to work, which in turn negatively affects socio-economic status. A survey of 43 carers for SCD patients in the UK using the WPAI:SHP Questionnaire (see Appendix S) found that average missed work hours per year was [redacted] resulting in a yearly mean productivity loss of £[redacted].[60] The carer burden is a particular issue in SCD, where families are more likely to live in poverty or be single parent households.[61,62] Additionally, as SCD is inherited, several family members are often affected.[54]

B.1.3.2. Clinical pathway of care and position of voxelotor

B.1.3.2.1. *Guidance*

There are no comprehensive NICE guidelines for the treatment of SCD. Current NICE guidelines are limited to the management of acute painful SCD episodes in hospital.[63] NICE have also released guidance relating to automated red blood cell exchange (ARCET)[64] and crizanlizumab.[65] The following UK-based guidelines on treating SCD are available:

- Sickle Cell Society (2018), UK standard for the Clinical Care of Adults with SCD in the UK.[19]
- Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline.[4]
- British Society of Haematology: Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects;[66] Part II: indications for transfusion.[67]
- NICE Clinical Knowledge Summaries: Sickle Cell Disease.[21]

B.1.3.2.2. *Current treatment of SCD*

The goals of management of SCD are to improve survival, reduce acute and chronic complications, and improve quality of life.[19] People with SCD should receive care from a multidisciplinary team, including health and social care provision, community nursing care, primary health care and secondary/tertiary care in specialist centres.[19] Lifestyle advice and supportive care (e.g. vaccinations, prophylactic antibiotics, analgesia, management of comorbidities) are an important management aspects. Many patients require chronic use of opioids to manage their pain, with the potential for adverse effects, dependency and stigma.[40] Some patients also receive blood transfusions as part of supportive care, either occasionally or on a regular schedule (see below).

Treatment options beyond supportive care are limited and consist of hydroxycarbamide, blood transfusions and (as a last resort for selected patients with suitable donors) allogeneic stem cell transplantation. Crizanlizumab has also recently been recommended by NICE subject to a Managed Access Agreement, and is indicated specifically for the prevention of VOCs.[65] [68] There are currently no pharmacological therapies apart from voxelotor (by the EMA) that are indicated for the treatment of haemolytic anaemia in SCD. In its approval of voxelotor the EMA noted that there is a high unmet need for haemolytic anaemia treatments.[6]

Hydroxycarbamide

Hydroxycarbamide (also known as hydroxyurea) is currently the only pharmacological treatment approved specifically for SCD that is routinely available in the UK. It was originally developed as an oral antineoplastic drug and a ribonucleotide reductase inhibitor.[4] Its mechanism of action in SCD is not fully understood; however, it increases levels of foetal Hb (HbF) in the blood.[4] It has been proven to decrease mortality and ACS incidence and RBC transfusion need over a 2-year follow-up.[69-71] In SCD it is indicated for the prevention of vaso-occlusive crises in patients over 2 years of age.[72]

Due to the variable pharmacokinetics and narrow therapeutic window, treatment with hydroxycarbamide requires regular monitoring of blood counts; the BSH recommends full blood count and reticulocyte count after initiation, after every dose increment and at least every 8-12 weeks for the entirety of treatment.[4] The aim is to

optimise the percentage of HbF without causing excessive bone marrow suppression.[4] Monitoring of hepatic and renal function is also required, and monitoring imposes a significant burden to both clinicians and patients.[73]

The BSH recommends that the benefits of hydroxycarbamide should be discussed on an ongoing basis with all parents of children with SCD and all adults and adolescents to enable informed joint decision-making. They recommend that it should be offered to all children aged >42 months, adolescents and adults with SCD in view of the impact on reduction of mortality.[4] Despite this, clinical expert opinion accepted by NICE during the appraisal of crizanlizumab indicates that only approximately 30% of SCD patients who have recurrent VOCs are currently receiving hydroxycarbamide in the UK, though exact usage is uncertain and varies between centres.[74] Clinical experts consulted by the company for the appraisal of voxelotor, via a modified Delphi panel process (see Appendix U), estimated that [redacted]% of patients in the 2L patient population are taking hydroxycarbamide. Maximum tolerated dose is determined by effects on blood count,[4] and some patients cannot reach an effective dose due to bone marrow toxicity. There may be a reluctance among some clinicians to prescribe hydroxycarbamide to patients who they feel will not be compliant with monitoring, and some patients are reluctant to use it because of perceived safety issues around carcinogenicity and fertility.[4,75,76]

Blood transfusions

Blood transfusions are an important treatment modality in SCD, but should only be offered to patients when the benefits outweigh the risks (see below for information on risks).[67] Transfusions can be given ad hoc in response to acute episodes, or on a regular, predefined schedule as part of an ongoing treatment plan (patients receiving regular planned transfusions will be termed transfusion-dependent in the remainder of the submission). The British Society of Haematology recommends that regular transfusions should be considered for ameliorating severe SCD in patients for whom hydroxycarbamide has failed to prevent recurrent ACS or painful episodes, or for whom hydroxycarbamide is contraindicated or unacceptable.[67] Regular transfusions are also recommended for primary or secondary prevention of SCD-related stroke in patients considered to be at high risk.[67] Regular transfusions can be either simple or exchange:[67]

- Simple transfusions, also called top-up transfusions, involve the infusion of RBCs only, without the removal of any of the patient's blood.[19]

- Exchange transfusions involve removing some of the patient's blood and replacing it with donor RBCs and saline solution; plasma, platelets and white cells are returned to the patient.[19,64] Exchange transfusion reduces iron overload compared with simple transfusions,[64] but exposure to an increased number of donor units means it increases the risk of subsequent alloimmunisation.[77] Automated red blood cell exchange transfusion (ARCET) requires access to specialised equipment (an apheresis machine such as Spectra Optia.[64]) Access to apheresis machines is restricted to tertiary centres and is not uniform across the UK. The machines are also used in other specialties, and specialties may have to compete for machine time. Patients often have to travel long distances for treatment,[56] involving expense, inconvenience and absence from work or education. The transfusion typically takes 2 hours,[66] with additional time for work-up. Some patients need to be fitted with central venous access or other indwelling venous access devices, which is associated with high rates of infection and thrombosis in SCD patients.[19] Transfusion methods are compared in Table 3.

Table 3. Comparison of different transfusion modalities (all time approximate)

	Modality		
Feature	**Simple transfusion (top-up)**	**Manual exchange**	**Automated exchange**
Staffing and training	Basic	Moderate	High
Frequency	3-4 weeks	3-4 weekly	4-8 weekly
Length of procedure	4-6 hours	2-4 hours (up to 4-8 h if acute exchange in a previously untransfused patient)	2 hours
Units of red cells	2-3	3-6	8-10
Iron loading (long term use only)	High	Moderate	Minimal

Adapted from: Sickle cell Society (2018)[19]

Burden and risk of transfusions

Blood transfusions are burdensome for patients and health services and carry risks of transfusion reactions, alloimmunisation and iron overload.

- Alloimmunisation occurs when antibodies to donor RBC antigens are formed, eliciting an immune response to the donated blood. This reduces the number of compatible donors for future transfusions, and increases the risk of delayed haemolytic transfusion reaction (DHTR).[19,77] Severely affected patients can no longer receive transfusions, and currently have no other treatment options.

- DHTR involves immune-mediated haemolysis in response to transfusion and can be life-threatening; it occurs in 4-11% of transfused patients, but this value may be higher as DHTR is often confused with symptoms of VOC.[66,77,78]

- Iron overload is a significant clinical issue in SCD.[79] The additional iron introduced by transfusion cannot be excreted and progressively accumulates in the tissues, leading to organ damage and endocrine complications and in severe cases, organ failure.[79-81] Patients may require iron chelation therapy to remove accumulated iron to prevent organ toxicities.[19,81] British Society of Haematology guidelines state that SCD patients are at risk of iron overload if they receive regular top-up transfusion, manual exchange transfusions or automated apheresis with progressive rise in serum ferritin.[81] They recommend that these patients are monitored for serum ferritin levels, with liver and cardiac MRI assessments in specified circumstances. It is recommended that patients on top-up transfusions should start iron chelation therapy after 10–12 transfusions or when serum ferritin reaches >1000 µg/l on two occasions. The risk of iron overload is reduced with automated RBC exchange transfusions. The BSH recommends that SCD patients on exchange transfusions are offered iron chelation on an individualised basis according to the type of exchange and the severity of existing overload.[81]

Crizanlizumab

Crizanlizumab has recently been recommended by NICE for prevention of recurrent VOC in SCD patients aged 16 or older, as part of a managed access scheme.[65] This decision is due to be reviewed in January 2025. Crizanlizumab is effective at reducing VOCs, but due to its mechanism of action it showed no significant effect on Hb or haemolytic markers in the pivotal trial (SUSTAIN).[82] It has a different indication (for the prevention of recurrent VOCs in sickle cell disease patients aged 16 years and older)[68] from voxelotor and is expected to be used in a different subset of

patients, i.e. those for whom the treatment focus is primarily reducing the number of VOCs. Furthermore it is not currently routinely used in clinical practice, and is not listed as a comparator in the NICE scope for the submission (see Section B.3.2.1 for details).

Allogeneic stem cell transplant

The only curative treatment for SCD is allogeneic haematopoietic stem cell transplantation (HSCT), which is the replaces the patients' haematopoietic stem cells and bone marrow with those of a healthy donor.[83] Before the donor cells are introduced, the patient must undergo conditioning with high-dose chemotherapy to destroy the bone marrow. Allogeneic HSCT is associated with procedural mortality, treatment-related morbidity caused by graft versus host disease, and infertility.[84,85] In adults, NHS England restricts HSCT to patients with a matched sibling donor, and who have severe SCD that is associated with reduced survival, chronic morbidity, or where current treatments are not effective.[83] Only a minority of potentially eligible patients have a matched sibling donor, and only approximately 36 patients treated per year. Allogeneic HSCT is not part of routine clinical practice in adults and is not listed by NICE as a comparator in the submission scope.

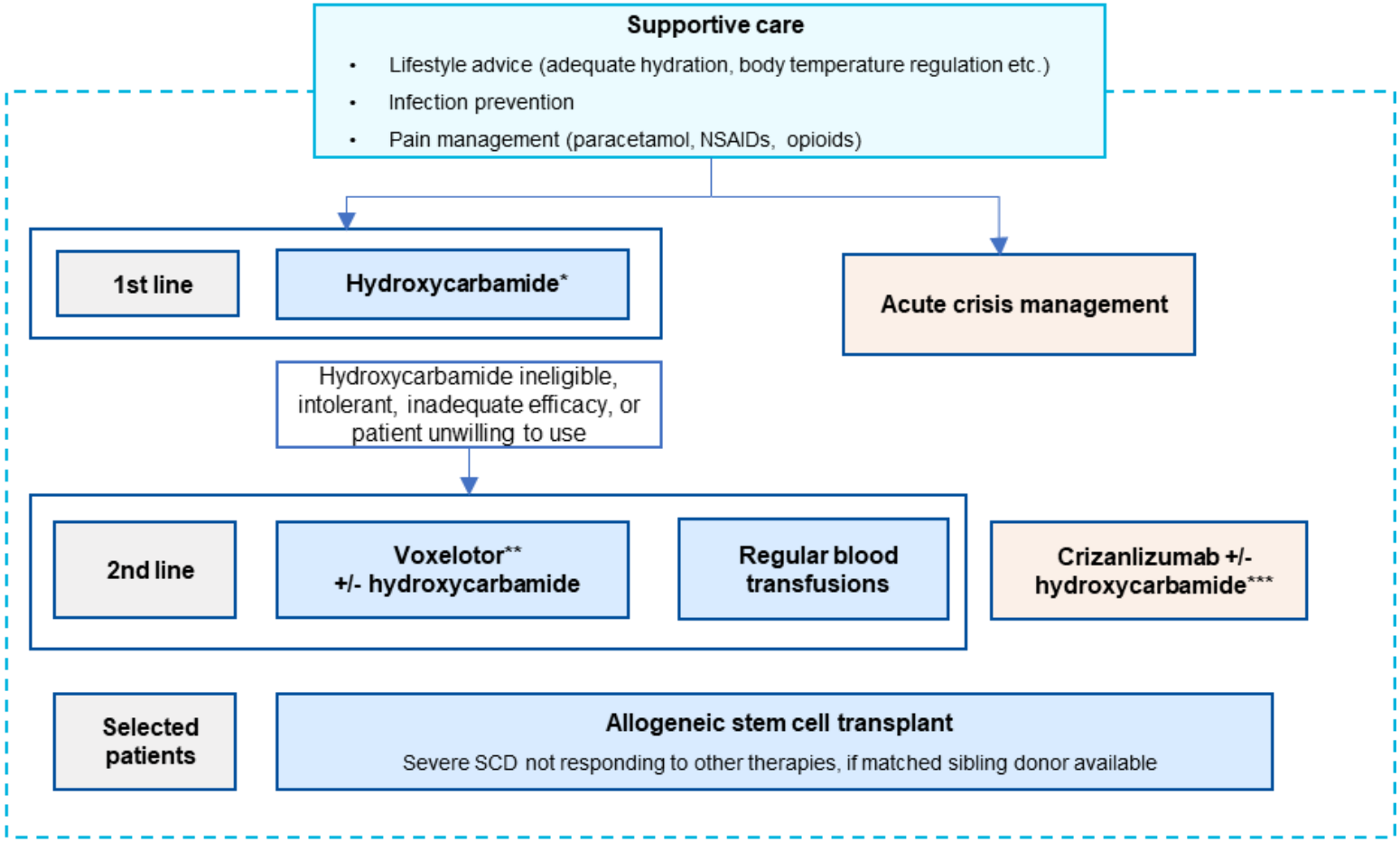
Positioning of voxelotor

The proposed position for voxelotor is as second line treatment for haemolytic anaemia in adults and paediatric patients 12 years of age and older, i.e. for patients who are intolerant, ineligible or have an inadequate response to hydroxycarbamide, or are unwilling to receive hydroxycarbamide. An additional subgroup comprising patients within this population who are transfusion-dependent will also be considered as a scenario. Voxelotor may be used as a monotherapy or in combination with hydroxycarbamide, as per the SmPC.[2]

As noted by the EMA, there is a high unmet need for medicines to treat haemolytic anaemia, which is experienced to various degrees by all SCD patients.[6] Hydroxycarbamide is recommended as first line therapy for all patients,[4] but many require an alternative or additional treatment option if hydroxycarbamide is not adequately effective or is unsuitable or cannot be tolerated. Regular blood transfusions, while effective for many patients, are burdensome for patients and health services and are associated with significant clinical risks (see section above).

- Voxelotor is the only treatment to address the underlying molecular basis of SCD, i.e. the polymerisation of Hb. It is associated with a rapid and sustained increase in Hb and a decrease in haemolysis in patients with or without background hydroxycarbamide use,[3] and therefore offers the possibility of improved management for patients who are inadequately treated with, or cannot use, hydroxycarbamide. Voxelotor is expected to be an alternative to regular transfusions in selected patients. Based on its mechanism of action and emerging data on organ damage benefits such as leg ulcers, voxelotor can be considered a disease modifying therapy.

The position of voxelotor within the treatment pathway is shown in Figure 3.



* Hydroxycarbamide is not licensed for haemolytic anaemia in the UK or Europe, but is used as part of routine SCD care

** Voxelotor may be taken as a monotherapy or in combination with hydroxycarbamide; voxelotor is indicated for the treatment of haemolytic anemia in SCD

*** Crizanlizumab is indicated for the prevention of recurrent crises

Figure 3 Positioning of voxelotor in the treatment pathway

B.1.4. Equality considerations

NICE Principle 9 states that NICE aims to reduce health inequalities, both in relation to protected characteristics in the Equality Act 2010 and the requirement in the Health and Social Care Act 2012 to give 'due regard' to reducing inequalities.[86] People with SCD are protected under the Equality Act 2010 on the grounds of disability (SCD is a chronic health condition). In addition, the great majority of people with SCD are from ethnic minorities (people of African, Caribbean, Middle Eastern or South Asian descent),[21] and race is a protected characteristic under the Equality Act 2010. Therefore there are equality considerations associated with issuing guidance on the use of voxelotor, as these groups will be disproportionately affected.

As well as the impact on groups who have protected characteristics under the Equality Act, NICE also considers those affected by health inequalities associated with socioeconomic factors or other forms of disadvantage.[86,87] These factors are relevant in the case of SCD as SCD disproportionately affects more disadvantaged populations. Nearly half (48%) of patients hospitalised for SCD in England are from the most socioeconomically deprived 20% of the population, and the least socially economically deprived 20% account for just 5% of SCD admissions (2017/18 data).[62,88]

Inequalities experienced by people with SCD were highlighted by the No One's Listening report 2021, published by the All-Party Parliamentary Group on Sickle Cell and Thalassemia and the Sickle Cell Society.[56] The report noted that, while care in specialist haemoglobinopathy services is generally seen as good, elsewhere in the NHS "patients too often receive sub-standard care" and that community care "is generally inadequate or non-existent", leading to unnecessary hospital admissions. The report also notes inadequate investment in SCD care, research and new treatments. A contrast was drawn between levels of provision and research for equivalent diseases such as cystic fibrosis and haemophilia. One haematologist is quoted in the report as saying that services for haemophilia and cystic fibrosis "provide a benchmark for holistic comprehensive care and sickle services generally fall below this standard". The level of research and availability of new treatments in

SCD were also highlighted as comparing poorly with cystic fibrosis, cancer and other diseases. Racism was considered to be a contributing factor in these inequalities.

The COVID-19 pandemic has highlighted the healthcare inequalities affecting ethnic minority populations such as those affected by SCD, including higher rates of chronic diseases and lower life expectancy in these groups even before the pandemic.[89,90]

Voxelotor is the first treatment to address the underlying molecular basis of SCD by inhibiting HbS polymerisation and thereby reducing sickling, haemolysis, haemolytic anaemia and the subsequent cascade of pathology that produces the life-limiting symptoms and complications of SCD. Making voxelotor available through the NHS would provide an important new treatment option for SCD patients in England and Wales. Decisions around the availability of SCD treatments primarily affect people from ethnic minorities who have a chronic life-long health condition, many of whom are also socio-economically disadvantaged and subject to health inequalities. These issues were acknowledged by NICE in its evaluation of crizanlizumab.[65]

B.2 Clinical effectiveness

Key points

- Voxelotor 1500 mg once daily is associated with a rapid and sustained rise in Hb in SCD patients ≥12 years of age, regardless of age, sex, race, geographic region, VOC history, baseline hydroxycarbamide use and anaemia severity:
  - Improvements to Hb concentration occurred within 2 weeks and were sustained through 72 weeks and beyond.[3,91,92]
  - Voxelotor reduces clinical measures of haemolysis.[3,91]
- All patients with leg ulcers treated with voxelotor 1500 mg (5 of 5) had their leg ulcers improve or resolve, compared with 63% (5 of 8) in the placebo group.[93]
- Real-world evidence has shown statistically significant reductions in RBC transfusions, VOCs, opioid usage, use of iron chelators, markers of kidney disease, ACS and VOC-related and all-cause hospitalisations after voxelotor use.[93-96]

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in line with NICE requirements to identify all relevant clinical evidence relating to the treatment of SCD patients. Searches were initially conducted on 30 July 2021, updated on 27 October 2021 and updated again on 05 April 2022. Searches were designed to capture randomised and non-randomised controlled clinical trials. In total, 61 publications relating to 21 unique studies were identified for inclusion in this SLR, of which 8 were RCTs and 13 were non-randomised studies. Full details of the review, including the PRISMA diagram and a description of all relevant studies informing the model, are given in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

The SLR identified two clinical trials where the clinical effectiveness of voxelotor was assessed in adult and adolescent SCD patients: GBT440-024[97] and GBT440-031 HOPE trial[98]. The evidence to support the clinical effectiveness of voxelotor in this submission was derived from the HOPE trial, a phase 3, randomised, double-blind, placebo-controlled trial. GBT440-024[99] was a phase 2, open-label extension to a

phase 1 trial, and was not used in the economic modelling because it was not an RCT and was superseded by the HOPE Phase 3 trial. Subsequent to the completion of the SLRs, an open-label extension (OLE) to the HOPE trial GBT440-034 was presented at the American Society of Hematology (ASH) 2021 conference. Outcomes are described but not used in the economic modelling.

Table 4. Clinical effectiveness evidence

<table>
<tr><td>Study</td><td colspan="5">GBT440-031: HOPE</td></tr>
<tr><td>Study design</td><td colspan="5">Phase: III
Enrolment: 449 participants (274 randomised)
Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Double (Participant, Investigator)
Primary Purpose: Treatment</td></tr>
<tr><td>Population</td><td colspan="5">Patients, aged 12–65, with confirmed SCD</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Voxelotor (1500 mg; 900 mg) vs. Placebo, on a background of best clinical standard of care*</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">None</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>X</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>X</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">Pivotal trial for direct comparative evidence of the efficacy of voxelotor vs placebo.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">Primary Endpoint:
• Number of patients with an increase in Hb >1g/dL from baseline at week 24
Secondary Endpoints:
• Change from Baseline in Hb at Week 24
• Change and percentage change from Baseline in haemolysis measures, including unconjugated bilirubin, reticulocyte percentage, absolute reticulocytes, and LDH at Week 24
• Incidence of severe anaemic episodes (Hb < 5.5 g/dL)
• Annualised IR of VOC
Exploratory Endpoints:
• Change from Baseline in Hb at Week 48 and Week 72</td></tr>
</table>

	• Change and percentage change from Baseline in haemolysis measures, including unconjugated bilirubin, reticulocyte percentage, absolute reticulocytes, and LDH, at Week 48 and 72 • **EQ-5D-5L** • CGIC
All other reported endpoints	• Time to first VOC • Time to first ACS or pneumonia • Time to first RBC transfusion • Rate of opioid use as recorded in the eDiary • SCDSM • School and/or work attendance as recorded in the eDiary
* Standard of care included all approved therapies for SCD. This included pain control, hydroxycarbamide, L-glutamine, and blood transfusions (except for regular planned blood transfusions; patients receiving regular planned transfusions were not eligible).[100] ACS: acute chest syndrome; CGIC clinical global impression of change; EQ-5D-5L: EuroQol health questionnaire; Hb: haemoglobin; IR: incidence rate; LDH: lactate dehydrogenase; RBC: red blood cell; SCD: sickle cell disease; SCDSM: sickle cell disease severity measure VOC: vaso-occlusive crisis	

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

Clinical evidence in the submission is taken from the HOPE phase 3 trial: from the peer reviewed study publications (Vichinsky et al. 2019[3] and the long-term follow-up publication by Howard et al. 2021[91]), the clinical study report [100], and proceedings from scientific congress presentations, including the HOPE trial open-label extension (OLE) and real world evidence (RWE).[94,96,101-104]

B.2.3.1. Trial design

The GBT440-031: HOPE trial was a randomised, double blind, placebo-controlled Phase III trial (NCT03036813). It was conducted at 60 sites in 12 countries (UK, Canada, the USA, France, Italy, Netherlands, Turkey, Egypt, Lebanon, Oman, Kenya and Jamaica), including 7 sites in the UK. The trial enrolled people aged 12–65 years with confirmed SCD, a Hb concentration of 5.5–10.5 g/dL at baseline and between one and ten VOC in the previous year. Two doses were studied up to 72 weeks; the dose of voxelotor taken forward to applications for marketing

authorisation as the recommended dose was 1500 mg/day. Concurrent hydroxycarbamide was allowed if the patient had achieved a stable dose for at least 90 days immediately prior to the trial. Key exclusion criteria included patients who were receiving regular transfusions, had received a transfusion in the past 60 days, or had been admitted to hospital in the previous 14 days for a VOC. These were excluded due to the anticipated confounding effect on Hb- and VOC-related endpoints.

The primary objective of the HOPE trial was to demonstrate the efficacy of voxelotor compared with placebo in inducing a Hb response (increase >1g/dL) from baseline to week 24 in patients with SCD.[3] Secondary endpoints were the change in Hb concentration at week 24, percentage change in baseline haemolysis measures from baseline to week 24, annualised incidence rate of VOC and the incidence of severe anaemic episodes (< 5.5.g/dL).

The trial design is outlined in Figure 4, and methodology is summarised in Table 5.

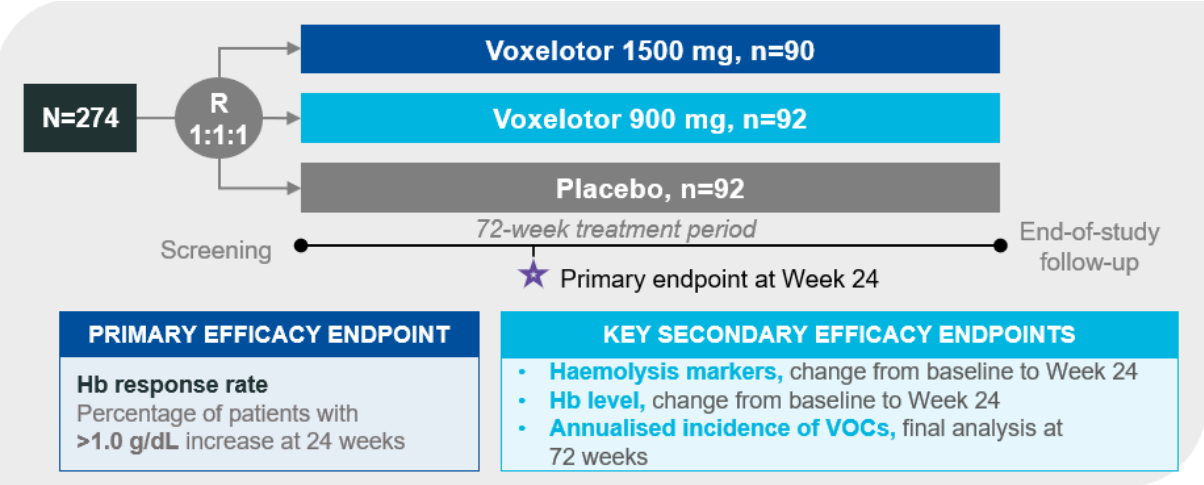


Figure 4. HOPE trial design

Table 5. Summary of study design and methodology.

Trial Descriptor	Details
Indication	Sickle cell disease
Title	A Phase 3, double-blind, randomised placebo-controlled, multicenter study of voxelotor administered orally to patients with sickle cell disease
NCT number	NCT03036813

Expected enrolment (actual)	240 (274)
Interventions	Voxelotor (1500 mg; 900 mg) vs. Placebo
Status	Completed
Endpoint measures	Primary endpoint: Number of patients with an increase in Hb >1 g/dL from baseline to week 24 Secondary endpoints: Percentage change in unconjugated bilirubin from baseline to week 24 Percentage change in the absolute reticulocyte from baseline to week 24 Percentage change in reticulocytes % of total RBC from baseline to week 24 Percentage change in lactate dehydrogenase from baseline to week 24 Number of VOC events from baseline to week 72
Phase	Phase 3
Study design	Allocation: Randomised Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment
Key inclusion criteria **(Full list of criteria available in the CSR)**	Age 12 to 65 years Confirmed SCD (homozygous Hb S, sickle Hb C disease, Hb Sβ-thalassemia, or other) Have experienced at least 1 episode of VOC in the past 12 months; defined as a previously documented episode of ACS or acute painful crisis (for which there was no explanation other than VOC) that required prescription or health-care professional–instructed use of analgesics for moderate to severe pain. Hb ≥5.5 and ≤10.5 g/dL during screening For patients taking HC, the dose of HC (mg/kg) had to be stable for at least 3 months prior to signing the informed consent form (ICF)
Key exclusion criteria **(Full list of criteria available in the CSR)**	More than 10 VOCs within the past 12 months that required a hospital, emergency room or clinic visit. Patients who are receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) or have received a RBC transfusion for any reason within 60 days of signing the ICF. Hospitalised for sickle cell crisis or other vaso-occlusive event within 14 days of signing the ICF. Hepatic dysfunction characterised by alanine aminotransferase (ALT) > 4 × upper limit of normal. Severe renal dysfunction (estimated glomerular filtration rate at the Screening visit; calculated by the central laboratory) < 30 mL/min/1.73 m^2 or on chronic dialysis.

	Receipt of erythropoietin or other hematopoietic growth factors within 28 days of signing ICF or anticipated need for such agents during the study. Females who were breastfeeding or pregnant.
Interventions	Patients were randomised in a 1:1:1 ratio to receive voxelotor 1500 mg, voxelotor 900 mg, or placebo.
Concomitant medications	All approved treatments for SCD were permitted in the HOPE study protocol, including pain control, HC, L-glutamine and blood transfusions. Other concomitant medications specifically permitted by the protocol included penicillin, folic acid, and codeine, as these are medications commonly used by SCD patients.
ACS: acute chest syndrome; CSR: clinical study report; Hb: haemoglobin; HC: hydroxycarbamide; ICF: informed consent form; ITT: intention-to-treat; PRO: patient reported outcomes; RBC: red blood cell; SCD: sickle cell disease; VOC: vaso-occlusive crisis Sources: CSR[100], Vichinsky (2019)[3]	

B.2.3.2. Baseline patient characteristics

Patients were randomly assigned in a 1:1:1 ratio to receive a once-daily oral dose of 1500 mg of voxelotor, 900 mg of voxelotor, or placebo. Stratification factors included hydroxycarbamide use (yes or no), geographic region (North America, Europe, or other), and age (adolescent [12 to 17 years] or adult [18 to 65 years]).

Baseline characteristics across the three treatment groups were generally well balanced. Patients were predominantly Black (66.8%), and there was a somewhat higher proportion of female (58%) patients than male (42%). Over half of participants (58.7%) were from Europe and North America (20.4% and 38.3% respectively). The majority of patients (75.2%) had a HbSS SCD genotype, and more than half (58%) had experienced ≥2 VOCs in the 12 months prior to screening, the other 42% had experienced 1 VOC in the 12 months prior to screening (Table 6).

Table 6 Demographic and baseline characteristics HOPE trial.

Characteristic	Voxelotor 1500 mg (N = 90)	Voxelotor 900 mg (N = 92)	Placebo (N = 92)
Age (years)			
Mean (SD)	27 (11.7)	28 (11.8)	28 (11.5)
Median (Range)	24 (12-59)	24 (12-59)	28 (12-64)
12 to < 18 Years	14 (15.6)	15 (16.3)	17 (18.5)
18 Years or older	76 (84.4)	77 (83.7)	75 (81.5)
Sex			
Male	32 (35.6)	41 (44.6)	42 (45.7)
Female	58 (64.4)	51 (55.4)	50 (54.3)

Race			
Arab/Middle Eastern	20 (22.2)	20 (21.7)	20 (21.7)
Asian	1 (1.1)	1 (1.1)	0
Black	59 (65.6)	61 (66.3)	63 (68.5)
White	12 (13.3)	7 (7.6)	5 (5.4)
Other*	2 (2.2)	5 (5.4)	6 (6.5)
Region			
North America	34 (37.8)	36 (39.1)	35 (38.0)
Europe	19 (21.1)	19 (20.7)	18 (19.6)
Other	37 (41.1)	37 (40.2)	39 (42.4)
Sickle cell genotype			
HbSS	61 (67.8)	71 (77.2)	74 (80.4)
HbSC	3 (3.3)	2 (2.2)	2 (2.2)
HbSβ^0 thalassemia	18 (20.0)	13 (14.1)	11 (12.0)
HbSβ^+thalassemia	7 (7.8)	2 (2.2)	3 (3.3)
Other Sickle Cell Syndrome Variant	1 (1.1)	4 (4.3)	2 (2.2)
No of VOCs in past 12 months			
1	35 (38.9)	41 (44.6)	39 (42.4)
2–10	55 (61.1)	51 (55.4)	53 (57.6)
Patients receiving hydroxycarbamide at baseline			
no. (%)	58 (64)	63 (68)	58 (63)
Baseline laboratory values			
Haemoglobin (g/dL)			
Mean (SD)	8.6 (1.10)	8.3 (1.08)	8.6 (1.06)
Median (Range)	8.7 (5.9,10.8)	8.3 (5.9, 10.8)	8.6 (6.1, 10.5)
Reticulocyte Percentage			
Mean (SD)	10.5 (4.97)	11.7 (5.35)	11.0 (4.85)
Median (Range)	9.6 (3.1, 24.9)	11.5 (2.9, 23.6)	10.9 (2.4, 24.9)
Absolute Reticulocytes (10^9/L)			
Mean (SD)	299.0 (123.44)	322.1 (141.68)	318.3 (130.27)
Median (Range)	290.3 (60.0, 705.0)	326.0 (92.0, 671.5)	312.5 (89.5, 636.5)
Indirect Bilirubin (µmol/L)			
Mean (SD)	45.3 (44.29)	44.2 (34.16)	50.3 (43.19)
Median (Range)	28.4 (9.0, 262.1)	31.5 (7.2, 172.6)	34.2 (5.7, 259.1)
Lactate Dehydrogenase (U/L)			
Mean (SD)	385.1 (150.61)	432.9 (179.06)	439.2 (188.70)
Median (Range)	340.8 (185.5, 865.0)	391.8 (179.5, 1210.0)	393.8 (161.5, 1151.0)
HbF (%)			
Mean (SD)	9.3 (6.29)	9.9 (7.47)	10.4 (10.96)
Median (Range)	8.3 (0.3, 28.8)	8.6 (0.3, 30.7)	7.4 (1.2, 86.4)

HbF: foetal haemoglobin; HbSβ^0: Haemoglobin Sβ^0; HbSβ$^+$: Haemoglobin Sβ$^+$; HbSC: Haemoglobin SC; HbSS: homozygous haemoglobin S; SD: standard deviation; VOC: vaso-occlusive crisis

* Other includes Egypt, Jamaica, Kenya, Lebanon, and Oman. Turkey was grouped with Europe.

Sources: EMA EPAR[1]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1. Analysis sets

Intention to treat: Primary efficacy analysis was based on an intention-to-treat (ITT) analysis of all patients who were randomised. Patients were analysed based upon the treatment group assigned at randomisation. Select efficacy endpoints were analysed based on the modified ITT (mITT) population, i.e., patients who were randomised to a treatment group and received at least 1 dose of study medication.

Per-protocol: A per-protocol analysis set was used to assess the robustness of the analysis of Hb response. The per-protocol analysis used observed data without imputation, and specifically included only patients who completed 24 weeks of study drug and did not initiate hydroxycarbamide treatment post-randomisation.

Safety analysis set: The safety population was comprised of all patients who received at least 1 dose of study medication. Subjects were analysed based upon the study drug they received. This was the primary population for safety analyses.

B.2.4.2. Summary of statistical analyses

The primary endpoint of the HOPE trial was to demonstrate the efficacy of voxelotor compared with placebo in inducing a Hb response (increase >1g/dL) from baseline to week 24 in patients with sickle cell disease.[3] Secondary endpoints were:

- Percentage change in baseline haemolysis measures from baseline to week 24 (Unconjugated bilirubin, absolute reticulocyte, percentage reticulocytes, lactate dehydrogenase)
- Annualised incidence rate of VOC.

Statistical analyses in the HOPE trial are summarised in Table 7.

Table 7. Summary of statistical analyses HOPE trial.

Statistical methods	Details
Sample size calculation	For the primary analysis of Hb response rate comparing voxelotor 1500 mg with placebo, the study with a sample size of 274 subjects (approximately 90 subjects per treatment group) had > 95% power to detect a targeted treatment difference of 30%, assuming a 10% Hb response rate in the placebo group and using Fisher's exact test with a 2-sided α of 0.0481.
Primary efficacy endpoint	The primary efficacy endpoint of Hb response (>1 g/dL) compared baseline Hb concentration with the mean Hb concentration at week 20 and 24. Additional per-protocol analysis was conducted using only observed data of patients who did not initiate HC (i.e. observed results without imputation). Hb response was analysed using an exact Cochran-Mantel-Haenszel general association test. Treatment doses were compared with placebo whilst stratifying for baseline HC use, age group, and geographic region. The primary analysis of Hb response rate was to compare voxelotor 1500 mg with placebo. The test hypotheses are as follows: H_0: $p_v = p_c$ vs H_a: $p_v \neq p_c$ where p_v is the Hb response rate in the voxelotor 1500-mg group and p_c is the Hb response rate in the placebo group.
Additional Hb analysis	Change from Baseline in Hb over time was analysed using a mixed-effects model for repeated measures (MMRM). A single model was used to fit data through week 72. The fixed-effects terms included treatment, study visit, treatment by visit interaction, HC use at Baseline, age group, and geographic region. The adjusted mean (least-squares mean) change from Baseline in Hb estimated from the MMRM, with the estimated standard error (SE) and 95% confidence interval (CI), were presented.
Change in haemolysis measures	Percentage change from baseline over time in unconjugated bilirubin, absolute reticulocytes, reticulocyte percentage, and LDH were analysed with an MMRM. A single model was fit for each haemolysis measure using final study data through Week 72. For each haemolysis measure, the adjusted mean (LS mean) change from Baseline at each visit (including Weeks 24, 48, and 72) was estimated, as well as the difference in the adjusted means between treatment groups, based on the MMRM analysis.
Vaso-occlusive crisis events	This was modelled using a negative binomial model with the independent variable of treatment group and adjusted for the stratification factors used for randomisation. Additional risk factors, including number of VOC occurrences during the 12 months prior to study participation, were also explored.
Exploratory endpoints	Kaplan-Meier methods were used to summarise time-to-event endpoints, including time to first VOC, time to first ACS or pneumonia, and time to first RBC transfusion. Rate of opioid use, rate and reasons for RBC transfusion, PRO, CGIC and EQ-5D-5L data were summarised descriptively by treatment group.

	The proportion of school and/or work attendance days were modelled via analysis of variance (ANOVA). The model included fixed-effects terms of treatment group HC use, age group, and geographic region.
Missing data	**Hb response**: Patients missing values at either timepoint (week 20 or 24) was missing the non-missing value was used; non-responder imputation was used if: values were missing for both time points, HC treatment was initiated (from baseline to week 24) or RBC transfusion was received within 8 weeks of Hb assessment. **Hb and haemolysis change from baseline:** Missing data due to subject dropout: For the primary method of analysis of this, missing at random (MAR) was assumed and no imputation was done. Subjects initiating HC post-randomisation were to be discontinued from the study. As such, only assessments prior to HC initiation were used in this analysis. Missing haemolysis data due to VOC or VOC hospitalisation: For the primary method of analysis, MAR was assumed, and no imputation occurred. Sensitivity analysis explored the imputation rule for missed assessments by assigning the haemolysis measurement from the last assessment. Regardless of whether data were missing, for subjects who received a transfusion on or 8 weeks (primary analysis) or 12 weeks (sensitivity analysis) before the endpoint visit, the most recent result prior to the transfusion was used. **VOC:** For the rate of VOC, the analyses did not make any adjustments due to missing data.
ACS: acute chest syndrome; CGIC clinical global impression of change; EQ-5D-5L: EuroQol health questionnaire; Hb: haemoglobin; HC: hydroxycarbamide; ICF: informed consent form; ITT: intention-to-treat; MAR: missing at random; PRO: patient reported outcomes; RBC: red blood cell; VOC: vaso-occlusive crisis Sources: CSR[100], Vichinsky (2019)[3]	

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from HOPE, a phase 3 trial. The quality assessment of HOPE performed as part of the systematic literature review is provided in Appendix D.

B.2.6. Clinical effectiveness results of the relevant trials

Key points

- Significantly more patients treated with voxelotor 1500 mg had Hb response (a >1g/dL increase in Hb) at week 24 (primary endpoint), compared to placebo:
  - 51.1% (95% CI 41, 61) vs 6.5% (95% CI 1, 12; p<0.001) in the ITT analysis[1,3]

- 59% ([redacted]) versus 9% ([redacted]) in the per-protocol analysis.[3,100]

- Patients in the voxelotor 1500 mg group had an adjusted (least square [LS]) mean change in Hb from baseline to 24 weeks of 1.1 g/dL (95% CI, 0.9, 1.4), compared with -0.1 g/dL (95% CI, −0.3, 0.2) in the placebo group (P< 0.001).[3]

- Improvements to Hb occurred within 2 weeks and were sustained through 72 weeks.[3,91] Data from the OLE (see Section B.2.6.8) shows durability of Hb response in patients treated with voxelotor 1500 mg.

- A consistent improvement in Hb was observed across subgroups including age, sex, race, geographic region, VOC history, baseline hydroxycarbamide use and anaemia severity.[100]

- Voxelotor 1500 mg was associated with a significant improvement in markers of haemolysis (indirect bilirubin, change in % reticulocytes) at 24 and 72 weeks compared with placebo.[3,91]

- Patients receiving voxelotor 1500 mg had a lower annualised incidence rate of VOC over 72 weeks (2.4, 95% CI 1.8, 3.1) than placebo (2.8, 95% CI 2.2, 3.6).[91] The trial was not powered for this outcome and the difference was not statistically significant.[3]

- Significantly more patients experienced moderately or very much improved clinical global impression of change with voxelotor (73.6%) compared to placebo (47.1%) after 72 weeks.[100]

- All patients treated with voxelotor 1500 mg with leg ulcers (5 of 5) had their leg ulcers improve or resolve, by week 72, compared with 63% (5 of 8) in placebo group.[93]

- Real-world evidence has shown that after initiating treatment with voxelotor patients experience fewer VOCs (-23%, P<0.001), fewer hospitalisation events (VOC-related [-34%, P<0.001] and all-cause [-37%, P<0.001]), require fewer RBC transfusions (-52%, P<0.001) and have lower iron chelation (-46%, P<0.001), opioid (-13%, P<0.001) and erythropoietin-stimulating agents (ESA) use (-28%, P<0.001).[95,96]

B.2.6.1. Primary endpoint: Hb response

An increase in Hb of > 1 g/dL was chosen as the primary endpoint as validated natural history studies indicated that an increase in Hb concentrations significantly decreases the rate of multiorgan failure and death.[3] An increase in Hb of 1 g/dL is equivalent to the intended effect of one unit of transfused blood.[105]

Hb response was achieved by 51.1% (95% CI 41, 61) of patients in the voxelotor 1500 mg group at week 24, versus 6.5% (95% CI 1, 12) in the placebo group (ITT analysis). This was a statistically significant difference (P<0.001).[1,3]

The per-protocol analysis was supportive of the ITT analysis: 59% ([redacted]) of patients in the voxelotor 1500 mg group achieved a Hb response versus 9% ([redacted]) in the placebo group at week 24.[100]

Table 8. Proportion of patients with Hb response (increase of >1 g/dL Hb) at week 24 - ITT population

	Voxelotor 1500 mg N = 90	**Voxelotor 900 mg N = 92**	**Placebo N = 92**
Response, n (%)	46 (51.1 [95% CI 41, 61])	30 (32.6)	6 (6.5 [95% CI 1, 12])
Hb: haemoglobin; ITT: intention to treat			

Source: EMA EPAR[1], Vichinsky 2019 [3]

B.2.6.2. Secondary and exploratory endpoints for Hb

B.2.6.2.1. *Change from Baseline in Hb*

Patients in the voxelotor 1500 mg group had an adjusted (least square [LS]) mean change in Hb from baseline to 24 weeks of 1.1 g/dL (95% CI, 0.9, 1.4), compared with -0.1 g/dL (95% CI, −0.3, 0.2) in the placebo group (P< 0.001).[3] Mean change from baseline is shown as a waterfall plot in Figure 5.

Changes in Hb were observed within 2 weeks and were maintained throughout treatment with voxelotor through to week 72 (Table 9 and Figure 6).[3,91]

Improvements in Hb in patients treated with voxelotor were consistent across patient subgroups stratified by baseline hydroxycarbamide use and anaemia severity at week 24.[3] LS mean change in Hb for patients receiving concomitant hydroxycarbamide and patients without concomitant hydroxycarbamide from baseline to week 24.

Table 9. Hb change from baseline, ITT population

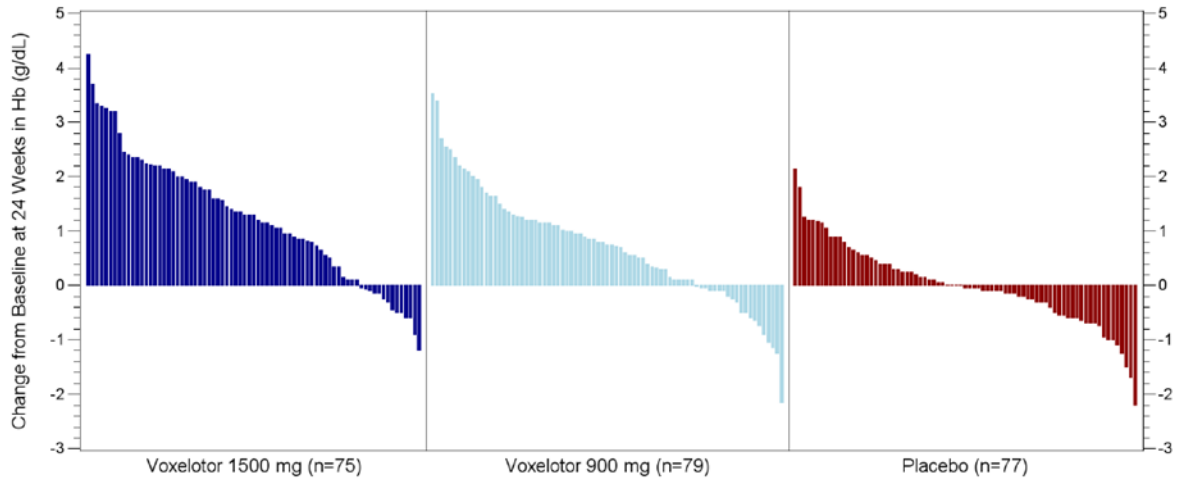
	Voxelotor 1500 mg N = 90	Voxelotor 900 mg N = 92	Placebo N = 92
Week 24*			
LS mean (SD)	1.13 (0.132)	0.58 (0.130)	-0.10 (0.132)
95% CI	[redacted]	[redacted]	[redacted]
Week 48†			
LS mean (SD)	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
Week 72†			
LS mean (SD)	1.02 (0.149)	0.54 (0.143)	0.02 (0.148)
95% CI	[redacted]	[redacted]	[redacted]

CI: confidence interval; Hb: haemoglobin; HC: hydroxycarbamide LS: least squares

* Secondary endpoint

†Exploratory endpoint

Sources: CSR[100], Howard (2021)[91], EMA EPAR[1]



Source: Vichinsky 2019[3]

Figure 5 Change from Baseline in Hb at Week 24 (per-protocol analysis)

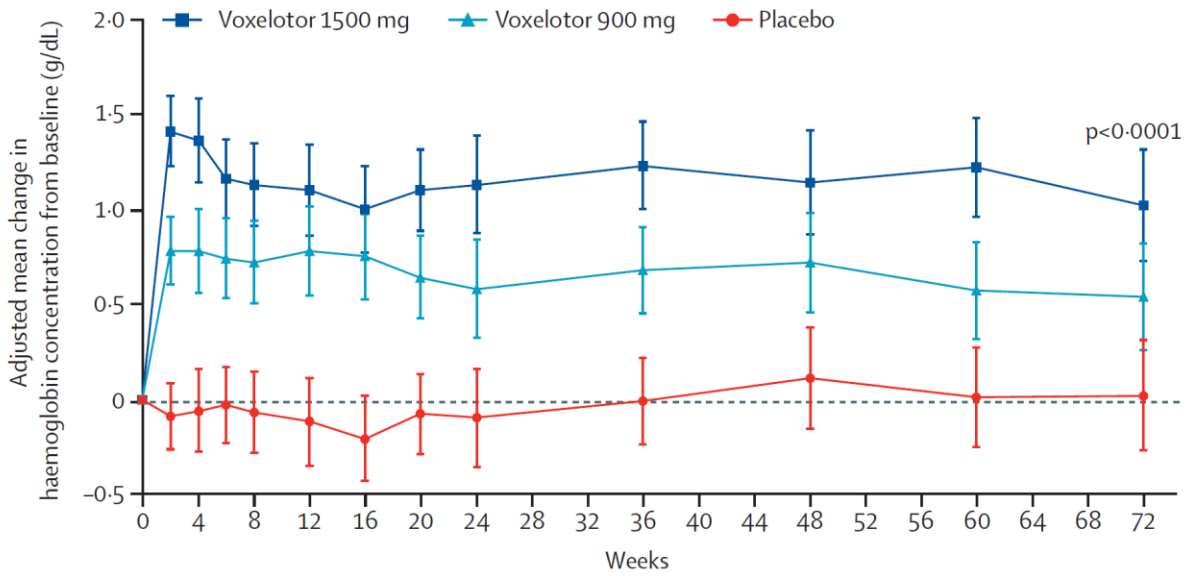


Figure 6 LS Mean change in Hb from baseline to week 72

Source: Howard (2021)[91]

B.2.6.2.2. *Incidence of severe anaemic episodes (Hb <5.5 g/dL) and acute anaemic episodes (Hb decrease > 2g/dL)*

The incidence of severe anaemic episodes (Hb <5.5 g/dL) on treatment was low across all groups (voxelotor 1500 mg [n = [redacted], voxelotor 900 mg [n = [redacted] and placebo [n = [redacted]) groups.[100] Post-hoc analysis showed the annualised incidence rate of acute anaemic episodes (decrease of Hb >2 g/dL from baseline) was three times lower in the voxelotor 1500 mg group than placebo at week 72 0.05 vs 0.15, respectively.[91] Acute anaemic episodes affected [redacted] patients treated with voxelotor 1500 mg and [redacted] patients in the placebo arm.[100]

B.2.6.3. Secondary and exploratory endpoints for haemolysis

B.2.6.3.1. *Change and percentage change from Baseline in haemolysis measures*

Patients in the voxelotor 1500 mg group showed a statistically significant (P<0.001) reduction in two haemolytic markers versus placebo at week 24: indirect bilirubin (LS mean change -29.1% vs -3.2%) and percentage of reticulocytes (least squares [LS] mean change -19.9% vs 4.5%).[3] Significant reductions in indirect bilirubin (P<0.001) and percentage of reticulocytes (P<0.05) were maintained in the voxelotor 1500 mg group to 72 weeks, in exploratory analysis.[1] Measures of absolute reticulocyte count and LDH improved (decreased) versus placebo in the voxelotor 1500 mg group at week 24 but the differences were not statistically significant.[3]

The LS mean percent change in markers of haemolysis from baseline at week 24, 48 and 72 are presented in Table 10. Figure 7 summarises the LS mean percent change in markers of haemolysis from baseline to week 24.

Table 10 LS mean change in haemolysis markers from baseline

	Percentage change from baseline, LS mean (95% CI)		
	Voxelotor 1500 mg N = 90	**Voxelotor 900 mg N = 92**	**Placebo N = 92**
LS mean percent change in indirect bilirubin (%)			
Week 24	−29.1 (−35.9, −22.2)**	−20.3 (−27.1, −13.6)**	−3.2 (−10.1, 3.8)
Week 48	−26.2 (−34.2, −18.3)**	−17.9 (−25.5, −10.3)**	3.4 (−4.5, 11.3)
Week 72	−23.9 (−33.5, −14.3)**	−15.2 (−24.4, 6.0)*	2.7 (−7.0, 12.3)
LS mean percent change in percentage of reticulocytes (%)			
Week 24	−19.9 (−29.0, −10.9)**	−1.3 (−10.3, 7.7)	4.5 (−4.5, 13.6)
Week 48	−3.6 (−15.1, 7.8)	5.5 (−5.5, 16.5)	1.8 (−9.5, 13.0)
Week 72	−7.6 (−18.5, 3.3)*	3.5 (−7.1, 14.0)	11.0 (0.2, 21.8)
LS mean percent change in absolute reticulocytes (%)			
Week 24	−8.0 (−18.1, 2.1)	5.1 (−4.9, 15.2)	3.1 (−7.0, 13.2)
Week 48	10.0 (−2.5, 22.4)	15.1 (3.2, 27.1)	0.8 (−11.5, 13.0)
Week 72	3.4 (−9.2, 15.9)	14.7 (2.5, 26.9)	9.1 (−3.3, 21.5)
LS mean percent change in LDH (%)			
Week 24	−4.5 (−11.9, 2.8)	1.4 (−5.9, 8.7)	3.4 (−4.0, 10.9)
Week 48	−4.8 (−10.2, 0.7)	−7.4 (−12.6, −2.2)*	2.1 (−3.3, 7.5)
Week 72	−1.1 (−7.5, 5.3)	−5.6 (−11.8, 0.5)*	3.8 (−2.5, 10.0

CI: confidence interval; LDH: lactate dehydrogenase; LS: least square

* P<0.05 (vs placebo)

** P<0.001 (vs placebo)

Sources: Vichinsky (2019)[3] (week 24) and EMA EPAR[1] (week 48 and 72)

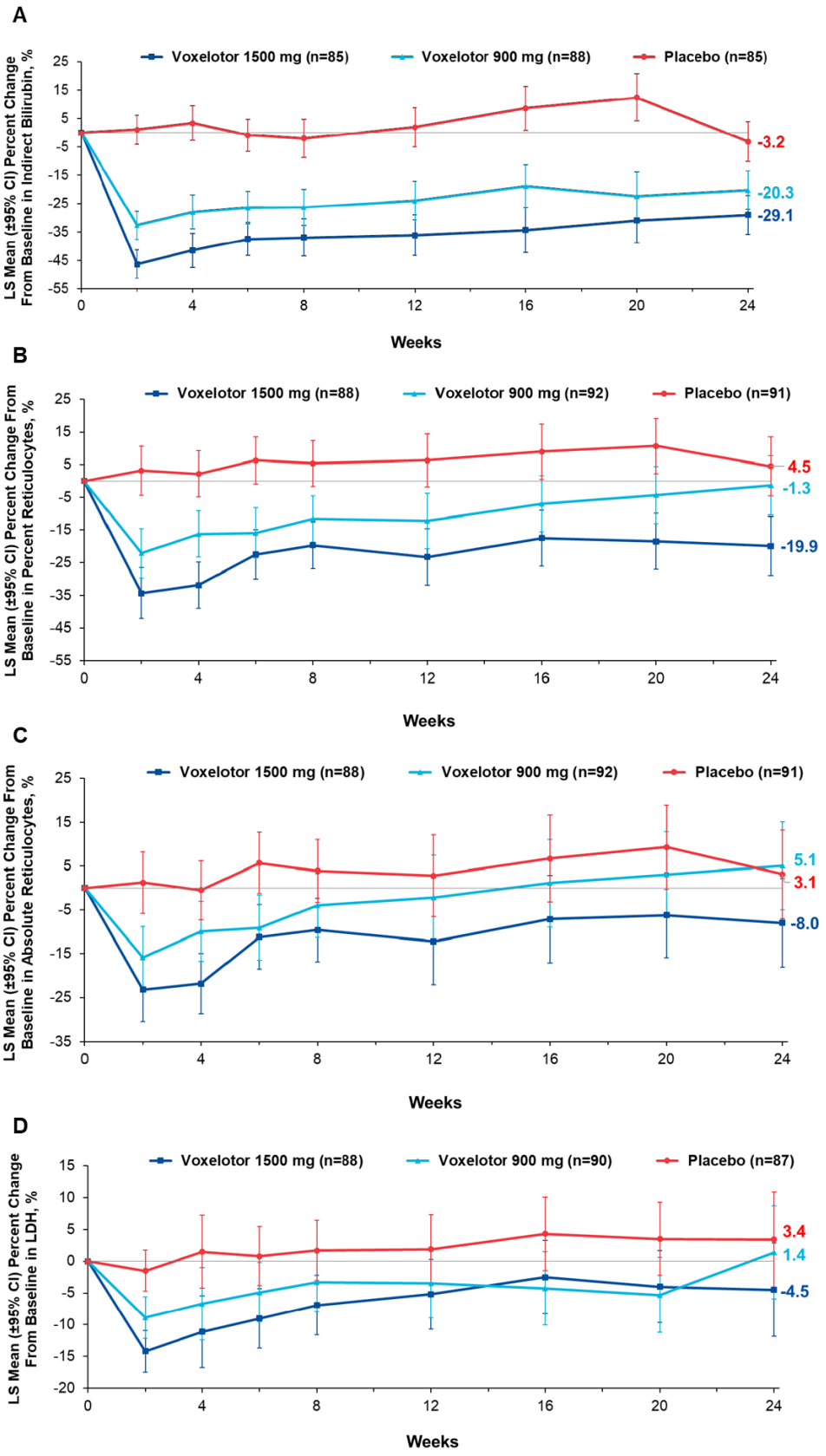


Figure 7 Percentage change from baseline to week 24 in markers of haemolysis

A) Indirect bilirubin level, B) percent reticulocytes, C) absolute reticulocytes, D) lactate dehydrogenase. Source: Vichinsky (2019)[3]

B.2.6.4. Secondary and exploratory endpoints for vaso-occlusive crisis

B.2.6.4.1. *Annualised incidence rates of vaso-occlusive crisis*

Patients treated with voxelotor had numerically lower annualised adjusted incidence rate of VOC (the number of crises per person-year) than in the placebo group (2.37 vs 2.79; Table 11); however, the trial was not powered to assess this outcome, and these differences were not statistically significant.[1]

The proportion of patients who experienced a VOC event during the study was numerically lower in the voxelotor 1500 mg group compared to the placebo group (69.3% vs 76.9%; Table 11). The total number of VOC events was also numerically lower in the voxelotor than in the placebo group (219 vs 293); however differences were not statistically significant.[1]

Table 11 Summary of on-treatment VOC events – mITT population

	Voxelotor 1500 mg N = 88	**Voxelotor 900 mg N = 92**	**Placebo N = 91**
Patients with any VOC event; n, (%)	61 (69.3)	64 (69.6)	70 (76.9)
Total number of VOC events	219	251	293
Adjusted annualised incidence rate events/year (95% CI)*	2.37 (1.84, 3.07)	2.40 (1.87, 3.07)	2.79 (2.19, 3.56)
CI: confidence interval VOC: vaso-occlusive crisis mITT modified intention to treat analysis only includes patients who received treatment *adjusted for baseline HC use, age and geographic region Source: EMA EPAR[1]			

B.2.6.5. Other exploratory endpoints

Time to first ACS or pneumonia and time to first RBC transfusion were assessed as exploratory outcomes.

B.2.6.5.1. *Acute chest syndrome*

The median time to event was not reached for time to first ACS in any treatment group due to events occurring in fewer than 50% of patients. ACS was reported in 15 patients in the voxelotor 1500 mg arm and 13 patients in the placebo arm ([redacted] events, respectively Table 12).[100]

B.2.6.5.2. *Red blood cell transfusion*

The median time to event was not reached for time to first RBC transfusion in any treatment group due to events occurring in fewer than 50% of patients. Similar proportions of patients in the voxelotor 1500 mg group and placebo group (36% vs 36%; Table 12) underwent RBC transfusions during the study. Most transfusions occurred as a result of a VOC.[91]

Table 12. Summary of other exploratory endpoints

	Voxelotor 1500 mg	Voxelotor 900 mg	Placebo
Acute chest syndrome or pneumonia (mITT)			
N	[redacted]	[redacted]	[redacted]
Patients with any ACS event n, (%)	[redacted]	[redacted]	[redacted]
Total number of ACS events	[redacted]	[redacted]	[redacted]
Adjusted annualised incidence rate events/year (95% CI)*	[redacted]	[redacted]	[redacted]
RBC Transfusions (ITT)			
N	90	92	92
Patients receiving a transfusion n, (%)	32 (36)	33 (36)	33 (36)
Total number of transfusions	[redacted]	[redacted]	[redacted]
Adjusted annualised incidence rate events/year (95% CI)*	[redacted]	[redacted]	[redacted]

ACS: acute chest syndrome; RBC: red blood cell

*adjusted for baseline HC use, age and geographic region

Source: CSR[100] Howard (2021)[91]

B.2.6.6. HRQoL-related endpoints

Using the HRQoL measure Clinical Global Impression of Change (CGIC), a single-item, seven-point scale and clinician-reported outcome that evaluates a patient's global functioning according to the clinician's judgement, a significantly greater proportion of patients in the voxelotor 1500 mg group (74% [p=0.0057]) were rated as "very much improved" or "moderately improved" compared with the placebo group (47%) at week 72 (shown in Table 13).[91]

There were no meaningful changes from baseline in HRQoL as assessed by EQ-5D in patients receiving voxelotor (1500 mg or 900 mg) or placebo at either week 24 or week 72 (shown in Table 13).[91]

Patients reported similar scores for disease severity according to the Sickle Cell Disease Severity Measure (SCDSM) in all treatment groups. At week 24 there was no appreciable change from baseline in any of the treatment groups (shown in Table 13). The mean baseline values indicate that the average score for each of the 9 SCDSM items for up to 35 days preceding baseline was “not severe” for pain. Therefore, as a group, the patients may have been insufficiently symptomatic at baseline to demonstrate a treatment effect on symptoms. Overall, SCDSM data are difficult to interpret due to low baseline scores and high variability in symptom scores.

Table 13. Summary of HRQoL and SCDSM

	Voxelotor 1500 mg N = 90	**Voxelotor 900 mg N = 92**	**Placebo N = 92**
Clinical Global Impression of Change (CGIC), Moderately or Very Much Improved n/N (%)			
Week 24	[redacted]	[redacted]	[redacted]
Week 72	39/58 (73.6)	32/58 (55.2)	39/53 (47.1)
EQ-5D-5L Index, Mean (SD)			
Baseline	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]
Change from baseline to week 24	[redacted]	[redacted]	[redacted]
Change from baseline to week 72	[redacted]	[redacted]	[redacted]
EQ-5D-5L VAS, Mean (SD)			
Baseline	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]
Change from baseline to week 24	[redacted]	[redacted]	[redacted]
Change from baseline to week 72	[redacted]	[redacted]	[redacted]
Sickle Cell Disease Severity Measure (SCDSM), Mean (SD)			
Baseline	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Change from baseline to week 24	[redacted]	[redacted]	[redacted]

Source: EMA EPAR[1], CSR[100]

B.2.6.7. Post-hoc analyses

Leg ulcers

Post hoc analysis of the incidence of leg ulcers and their outcomes in enrolled patients across the 72-week treatment period in HOPE, showed that all patients with leg ulcers (5 of 5) in the voxelotor 1500 mg group, and 89% (8 of 9) in the voxelotor 900 mg group, had their leg ulcers improve or resolve by week 72, compared with 63% (5 of 8) in the placebo group (Figure 8).[93]

Incidence of leg ulcers was collected under the classification of on-study SCD complications. A limited number of patients had leg ulcers at Baseline: 4 in the voxelotor 1500-mg group (2 mild and 2 moderate severity), 6 in the voxelotor 900-mg group (3 mild and 3 moderate severity), and 3 in the placebo group (all mild severity).[2,93] During the 72-week treatment period, nine additional patients developed new leg ulcers (Figure 8): one was in the voxelotor 1500 mg group (mild severity), three were in the voxelotor 900 mg group (two mild, one moderate), and five were in the placebo group (three mild, two moderate).[2,93] The total incidence of active leg ulcers in the HOPE study population was 8% (22 of 274).[93]

The results of this analysis suggest that voxelotor presents a potential clinical benefit for SCD patients with leg ulcers, although it is limited by the low incidence and prevalence of leg ulcers in the trial.[93]

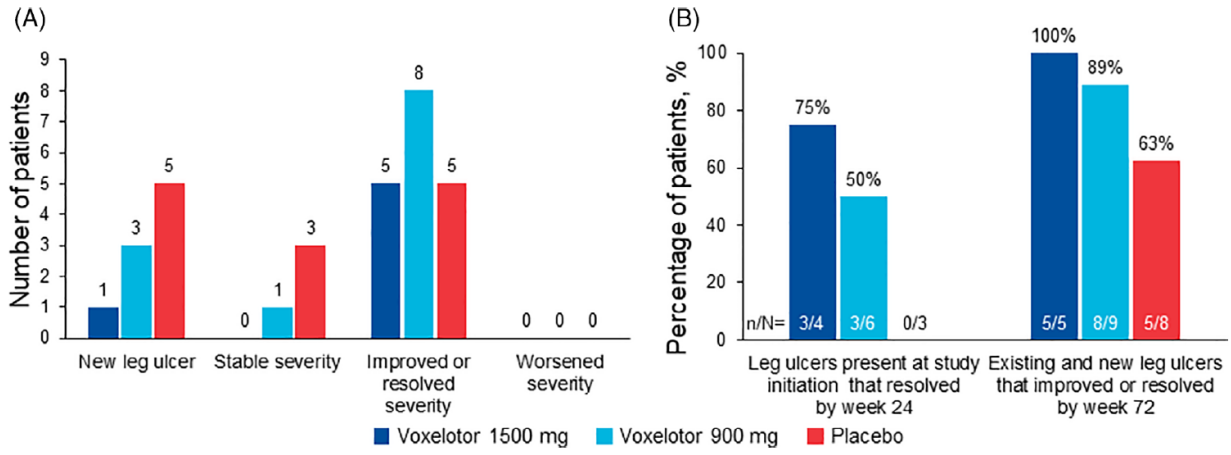


Figure 8. Change in leg ulcer severity across treatment groups during the 72-week treatment period

Source: Minniti (2021)[93]

B.2.6.8. HOPE open-label extension

Patients who completed the phase 3 HOPE trial (i.e completed 72 weeks of treatment) were eligible to enrol in the multicentre HOPE open-label extension (OLE) study (NCT03573882), the objective of which is to assess the long-term safety and efficacy of voxelotor in SCD. Patients receive treatment as long as they continue to receive clinical benefit and/or until they have access to voxelotor through commercialisation or a managed access program.[92] All patients, including those who previously received placebo or voxelotor 900 mg, received voxelotor 1500 mg as ongoing treatment.[92] Of the 199 patients who completed the HOPE trial, 178 (89.4%) were enrolled and dosed in the OLE. Median age at enrollment was 25 years (15.7% adolescents, 84.3% adults). At the cutoff date, the median duration of voxelotor exposure in the OLE was 69.9 weeks (range: 1.9-102.0 weeks), with 78 patients treated for ≥72 weeks. Of these 78 patients, 52 had previously received voxelotor in the randomized part of the study, for a combined exposure duration of ≥144 weeks.[92] The key endpoints of the OLE are:[92]

- Hb level: change from baseline
- Haemolysis markers: change from baseline
- Safety and tolerability: adverse events during the OLE

B.2.6.8.1. *Patient characteristics*

Table 14 Patient characteristics, OLE study

	Prior treatment group in HOPE trial			All patients treated in OLE
	Placebo (N = 62)	**Voxelotor 900 mg (N = 58)**	**Voxelotor 1500 mg (N = 58)**	**Voxelotor 1500 mg (N = 178)**
Age,[a] median, years	27	24	25	25
Age group,[a] n (%)				
Adolescent, 12-17 years	11 (17.7)	6 (10.3)	11 (19.0)	28 (15.7)
Adult, ≥18 years	51 (82.3)	52 (89.7)	47 (81.0)	150 (84.3)
Duration of exposure, weeks				
Median	68.6	67.9	72.9	69.9
Range (min, max)	(4.6, 102.0)	(1.9, 98.3)	(12.1, 100.6)	(1.9, 102.0)
≥72 weeks, n (%)	26 (41.9)	21 (36.2)	31 (53.4)	78 (43.8)

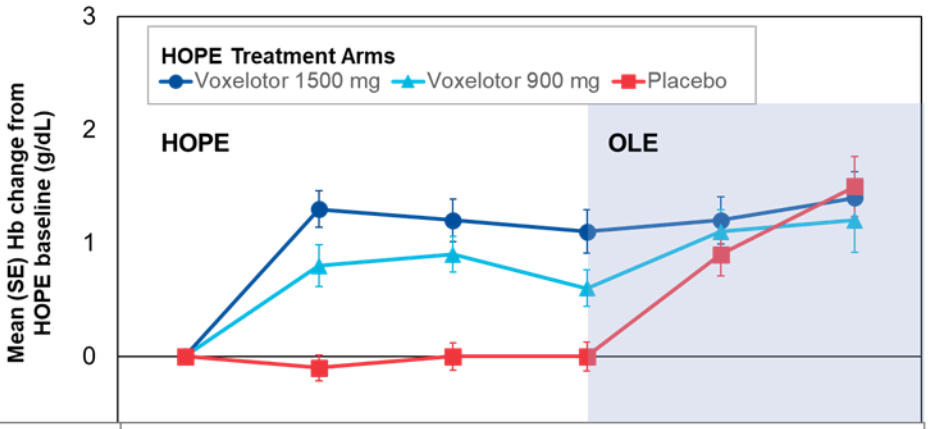
Of the 78 patients who were treated for ≥72 weeks, 52 had previously received voxelotor in the randomised part of the study, for a combined exposure duration of ≥144 weeks.

[a]Age at time of enrolment in the OLE.

OLE, open-label extension. Source: Achebe (2021)[106]

B.2.6.8.2. *Change from baseline Hb*

Patients who received placebo in HOPE had an improvement in Hb over time, a 1.3 g/dL increase from OLE baseline to OLE Week 48; this magnitude of effect was consistent with the HOPE trial results. In addition, patients who received voxelotor in HOPE experienced durability of response in the OLE[92,106] (Figure 9).



Treatment arm: HOPE → OLE (n)	Day 1 HOPE	Week 24 HOPE	Week 48 HOPE	Day 1 OLE	Week 24 OLE	Week 48 OLE
Voxelotor 1500 mg → voxelotor 1500 mg	58	56	56	53	44	37
Voxelotor 900 mg → voxelotor 1500 mg	58	56	56	55	43	35
Placebo → voxelotor 1500 mg	62	55	56	52	44	35

Data presented for OLE are based on an interim data cut (December 31, 2020).

Baseline values for the HOPE data were calculated as the mean values of the data collected at screening and on the day of randomisation. Baseline values for OLE data were the last values collected on or prior to the first dose in the OLE. Hb values within 8 weeks after a red blood cell transfusion were imputed as the last value before the transfusion. Hb values obtained after initiation of HC post-randomisation were excluded for patients without HC use at baseline.

[a]The mean difference reported is based on participants with data at both baseline and week 48 of the OLE.

Hb: haemoglobin; OLE: open-label extension; SE: standard error.

Figure 9. Change in Hb response from HOPE study baseline to OLE week 48

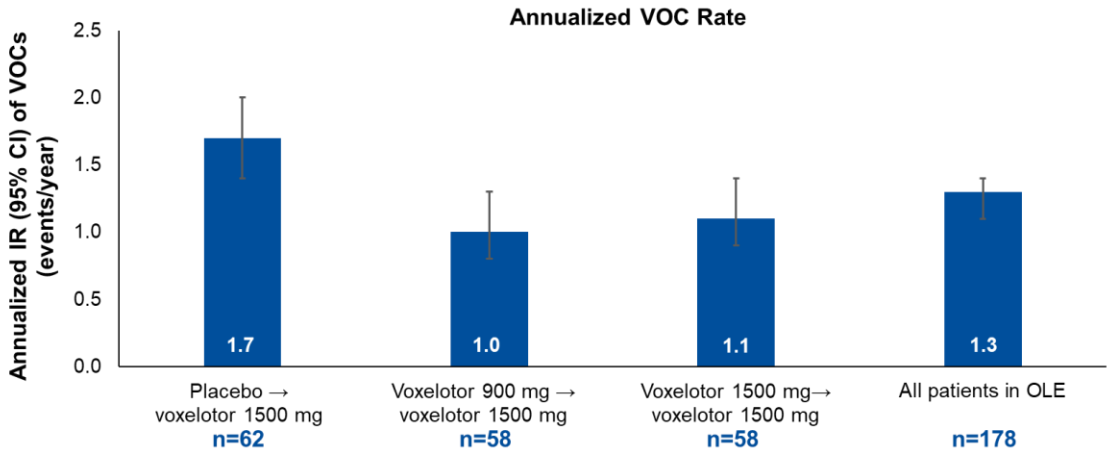
Source: Achebe (2021)[106]

B.2.6.8.3. *Change from baseline in haemolysis markers*

Patients who received placebo in HOPE had an improvement in haemolysis markers when they switched to voxelotor in the OLE trial, indirect bilirubin and percentage of reticulocytes, with mean percent changes from OLE baseline to Week 48 OLE of -39.5% and -28.6%, respectively.[92 106]

B.2.6.8.4. *Annualised incidence rate of vaso-occlusive crisis*

Patients receiving voxelotor in HOPE OLE had low annualised VOC rates across all former HOPE treatment arms, at 1.3 (95% CI: 1.1-1.4) events per year across all patients, detailed in Figure 10.



Data presented for OLE are based on an interim data cut (December 31, 2020).

For each patient, summary includes time from informed consent to earliest of last dose, withdrawal of consent, or data cut date.

IR: incidence rate; OLE: open-label extension; VOC: vaso-occlusive crisis.

Figure 10. Annualised VOC rates in the HOPE OLE trial

Source: Achebe (2021)[92 106]

B.2.6.9. Real world evidence

Voxelotor has been approved in the US since November 2019, and evidence from real-world clinical practice there provides additional evidence for the clinical effectiveness of voxelotor and supports the findings from the HOPE study.

The most comprehensive source of real-world evidence is an analysis of the Symphony Health Solutions Integrated Dataverse Database (hereafter referred to as the Symphony database). This is a large nationally representative provider-centric repository of US healthcare data that includes demographic information (e.g. age, sex) from medical claims (e.g. diagnoses and procedures), pharmacy claims (e.g. dosing and filling of drugs), and laboratory data for selected persons.[96] Medical and pharmacy claims are sourced from adjudication networks, service bureaus, and pharmacy organisations serving patients participating in commercial health plans as well as public insurance programs (e.g. Medicaid and Medicare).[96] In a published analysis, data were analysed from patients aged ≥12 years with SCD who had initiated treatment with voxelotor between November 2019 and June 2021. Patients with ≥1 year's data before the index date (date of the first voxelotor claim for each patient) were included in the analyses.[96] Annualised rates per patient-year (PPY) for transfusions, VOCs, and VOC-related and all-cause hospitalisations were compared

for the 3 months before voxelotor initiation versus the period after voxelotor initiation.[96] Analyses of individual endpoints are described below.

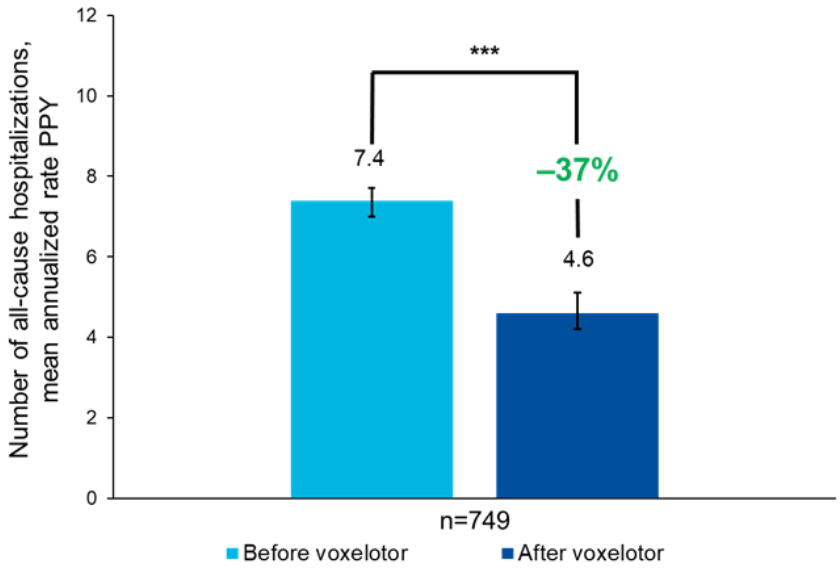
The Symphony database confirms that voxelotor increases Hb in real-word practice, consistent with the HOPE trial.[96] Hb data were not available for most patients, but Hb responses were evaluated for a subset of 74 patients who had at least 1 Hb value measured in both the pre-index and post-index periods. Of these, 60.8 % had a change in Hb >1 g/dL at any time during follow-up.[96] The increase in mean Hb concentration between pre- and post-index values was 1.1 g/dL.

The published analysis of Symphony presented below is not used in the economic evaluation for this submission; instead, a bespoke TTE analysis was conducted (see Appendix Q). Patients in the Symphony database were weighted using matching-adjusted indirect comparison methods to the HES/CPRD dataset (see Section B.3.3.1.3).

B.2.6.9.1. *Hospitalisations*

Patients in the Symphony database who had been hospitalised in the 3 months before initiating voxelotor (N = 749) had a 37% reduction (*P*<0.001) in the mean annualised rate of all-cause hospitalisations during the post-index period, from 7.4 to 4.6 hospitalisations per patient-year (Figure 11).[96]

There was a 34% reduction (*P*<0.001) in the number of VOC-related hospitalisations during the post-index period in patients with ≥ 1 VOC-related hospitalisations in the 3 months before initiating voxelotor (N=609), from 7.2 to 4.8 hospitalisations per patient-year (Figure 12).[96]



***P<0.001.

Data presented are based on an interim data cut (June 2021).

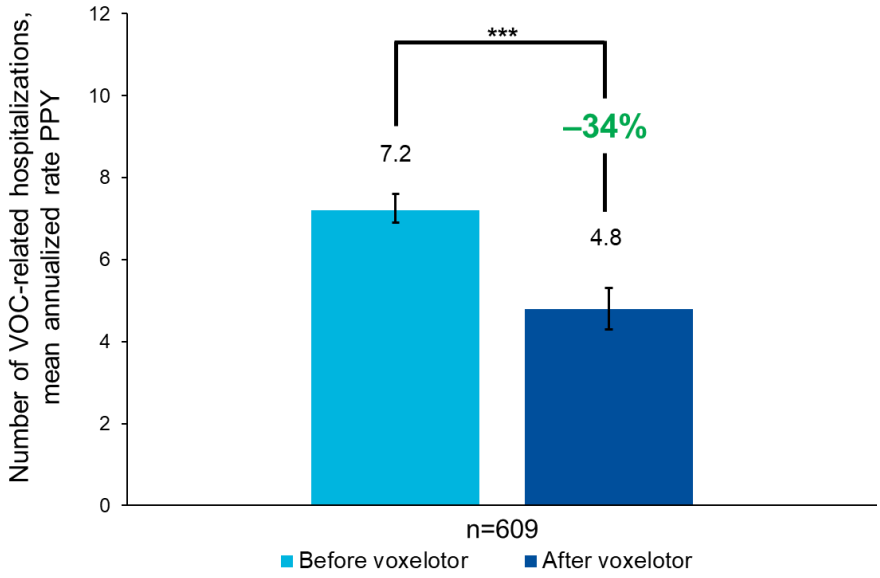
Error bars are 95% CIs. 95% CIs were obtained from bootstrapping.

“Before” refers to the 3-month period before the first voxelotor administration. “After” refers to the period from the index date (date of the first voxelotor claim for each patient) to the end of follow-up.

PPY: per patient-year.

Figure 11. Mean annualised rate of all-cause hospitalisations PPY for patients hospitalised in the 3 months before initiating voxelotor

Source: Shah (2021)[96]



***P<0.001.

Data presented are based on an interim data cut (June 2021).

Error bars are 95% CIs. 95% CIs were obtained from bootstrapping.

"Before" refers to the 3-month period before the first voxelotor administration. "After" refers to the period from the index date (date of the first voxelotor claim for each patient) to the end of follow-up.

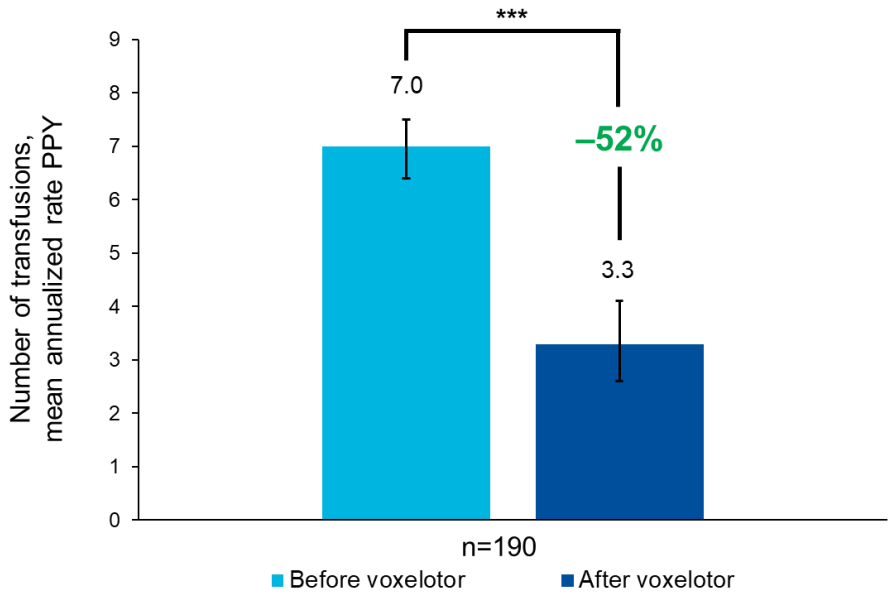
PPY: per patient-year; VOC: vaso-occlusive crisis.

Figure 12. Mean annualised rate of VOC-related hospitalisations PPY for patients with ≥1 VOC-related hospitalisation in the 3 months before initiating voxelotor

Source: Shah (2021) [96]

B.2.6.9.2. *Red blood cell transfusions*

Patients in Symphony with recent transfusions (≥ 1 transfusion in 3 months before voxelotor initiation, N = 190),) had a 52% reduction (P<0.001) in the mean annualised rate of transfusion during the post-index follow-up period after initiating voxelotor, from 7.0 to 3.3 per patient-year (Figure 13).[96]



***P<0.001.

Data presented are based on an interim data cut (June 2021).

Error bars are 95% CIs. 95% CIs were obtained from bootstrapping.

"Before" refers to the 3-month period before the first voxelotor administration. "After" refers to the period from the index date (date of the first voxelotor claim for each patient) to the end of follow-up.

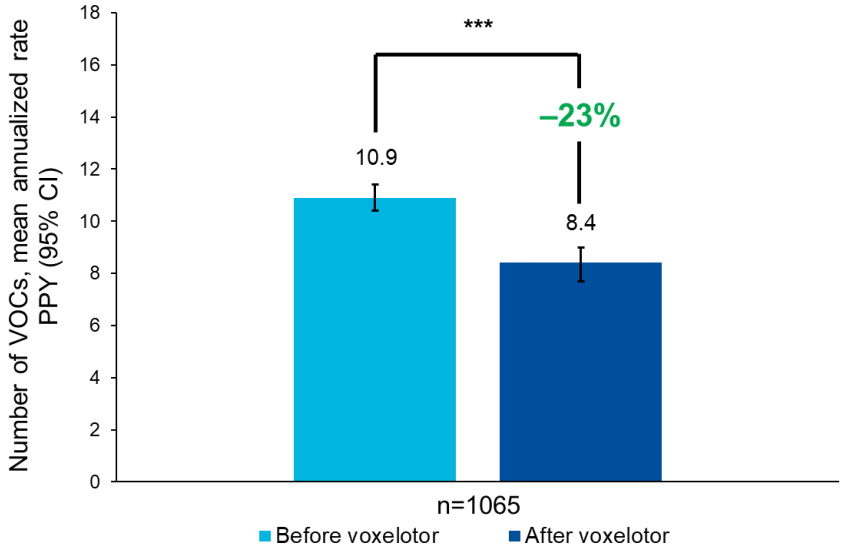
PPY: per patient-year.

Figure 13. Mean annualised rate of transfusion PPY for patients with ≥1 transfusion in the 3 months before initiating voxelotor

Source: Shah (2021)[96]

B.2.6.9.3. *VOC events*

Voxelotor was associated with a significant reduction in VOC events in the Symphony analysis. Patients with ≥1 VOC in the 3 months before initiating voxelotor (N = 1,065) had a 23% reduction (P<0.001) in the annualised incidence rate of VOCs in the post-index period, from 10.9 to 8.4 VOCs (Figure 14).[96]



***P<0.001.

Data presented are based on an interim data cut (June 2021).

Error bars are 95% CIs. 95% CIs were obtained from bootstrapping.

"Before" refers to the 3-month period before the first voxelotor administration. "After" refers to the period from the index date (date of the first voxelotor claim for each patient) to the end of follow-up.

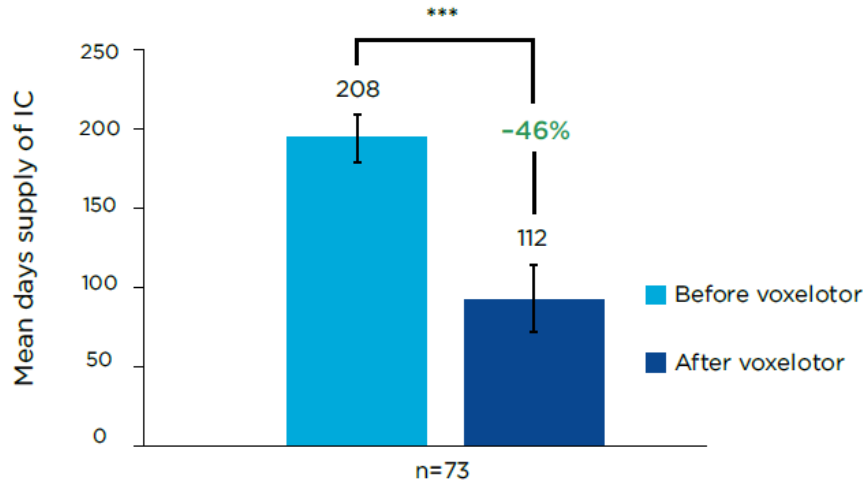
PPY: per patient-year; VOC: vaso-occlusive crisis.

Figure 14. Mean annualised rate of VOCs PPY for patients with ≥1 VOC in the 3 months before initiating voxelotor

Source: Shah (2021) [96]

B.2.6.9.4. *Use of iron chelation utilisation*

Analysis of the Symphony database showed a significant reduction (-46%; *P*<0.001) in mean days' supply of iron chelation during the post-index period after voxelotor treatment in patients with iron chelation use in the 3 months before initiating voxelotor (N = 73), from 208 to 112 mean days' supply (Figure 15).[96] Of these patients, 43 (56%) did not have any iron chelation usage in the post-index period (*P*<0.001).[96] Reducing the use of iron chelation lowers the treatment burden for patients and saves costs to the health service.



***P<0.001.

Data presented are based on an interim data cut (June 2021).

Error bars are 95% CIs. 95% CIs were obtained from bootstrapping. “Before” refers to the 3-month period before the first voxelotor administration.

“After” refers to the period from the index date to the end of follow-up.

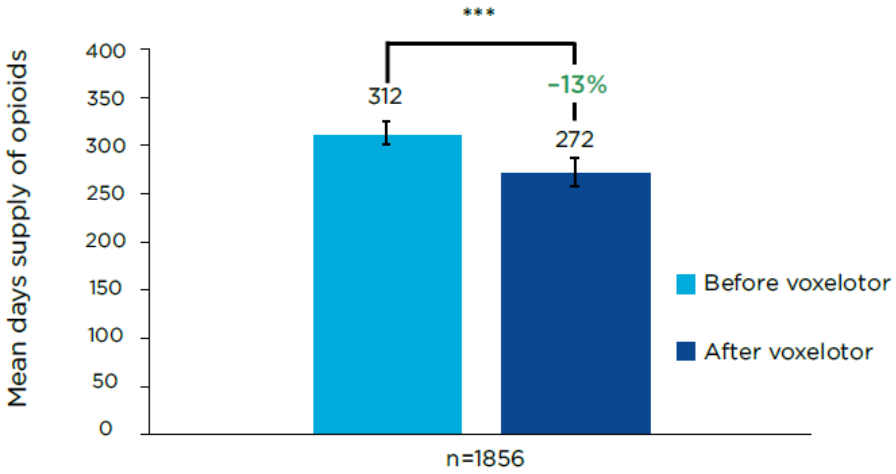
IC: iron chelation.

Figure 15. Mean days’ supply of iron chelation for patients with iron chelation use in the 3 months before initiating voxelotor

Source: Shah (2021)[96]

B.2.6.9.5. *Opioid prescriptions*

Patients in Symphony with opioids prescribed in the 3 months before initiating voxelotor (N = 1,856), had a significant reduction (-13%; *P*<0.001) in mean days’ supply of opioids during the post-index period, from 312 to 272 mean days’ supply of opioids (Figure 16).[96] A reduction in opioid use suggests an improvement in pain, which would be expected to result in an improvement in HRQoL.



***P<0.001.

Data presented are based on an interim data cut (June 2021).

Error bars are 95% Cis. 95% Cis were obtained from bootstrapping. “Before” refers to the 3-month period before the first voxelotor administration.

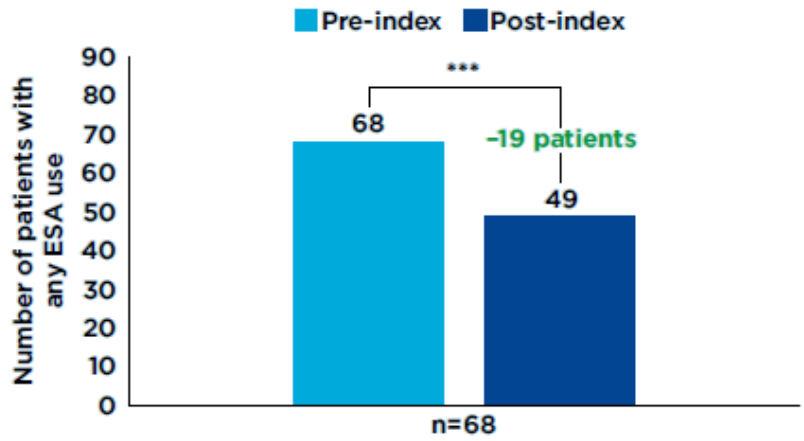
“After” refers to the period from the index date to the end of follow-up.

Figure 16. Mean days supply of opioids for patients with opioids prescribed in the 3 months before initiating voxelotor

Source: Shah (2021)[95,96]

B.2.6.9.6. *Use of erythropoietin-stimulating agents (ESA)*

The number of patients in Symphony with any use of ESA fell from 68 to 49 in the 3 months after initiating voxelotor compared with the 3 months before, a reduction of 28% (*P*<0.001; Figure 17.[95] Reducing the use of ESAs lowers the treatment burden for patients and saves costs.



***P<0.001.

ESA: erythropoietin-stimulating agent

Figure 17. Change in ESA use for patients with any ESA use in the 3 months pre-index

Source: Shah (2021)[95]

B.2.6.9.7. *Chronic kidney disease*

Preliminary data from five SCD patients with stage 1-3 chronic kidney disease (CKD) treated with voxelotor in the US suggests that voxelotor may offer benefits in kidney function.[107] Patients treated with voxelotor showed haematological improvements (increased Hb concentration and reduced haemolytic markers). A reduction in albuminuria, a marker of CKD used to define stage 1-2 CKD, was observed in all five patients (-25%; -12% to -33%). Conversely, albuminuria increased in an age- and sex-matched cohort of SCD patients (34% -34% to 101%).

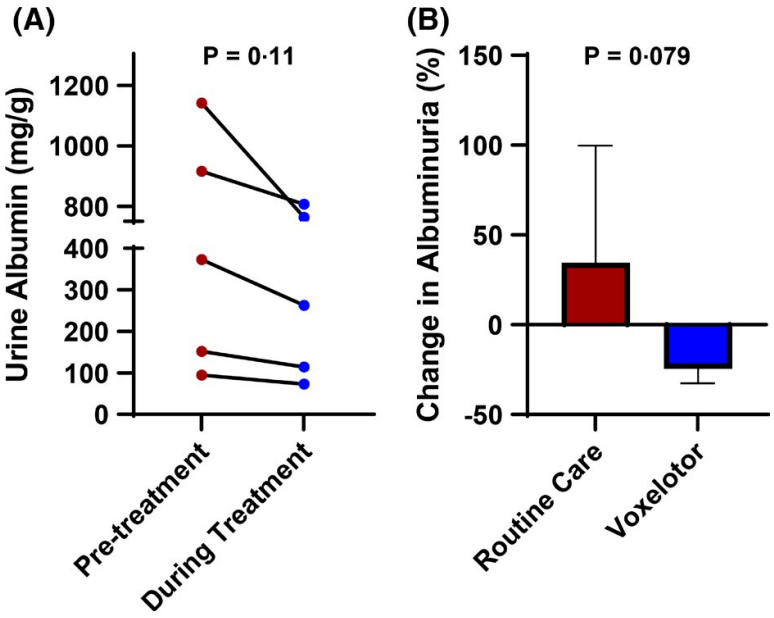


Figure 18 A) Urine albumin pre- and during treatment with voxelotor in SCD patients with CKD B) Percentage change in albuminuria in SCD patients with CKD treated with voxelotor and an age- and sex- matched cohort

B.2.7. Subgroup analysis

The following pre-specified subgroups were analysed to evaluate the impact of various characteristics on study endpoints:

- Age group (adolescents [12 to <18 years], adults [18 to 65 years])
- Sex (male, female)
- Race (Black or African American, Arab/Middle Eastern)
- Geographic region (Europe, North America, Other)
- Baseline hydroxycarbamide use (yes, no)
- Baseline VOC history (1, > 1)

- Baseline Hb (5.5 to < 7 g/dL, ≥ 7 g/dL)

Voxelotor 1500 mg showed a consistent treatment benefit vs placebo for Hb response rate across all subgroups at Week 24 (Figure 19). The benefits of voxelotor 1500 mg were consistent across all subgroups for all endpoints explored. Subgroup analyses for other endpoints are described in Appendix E.

	Placebo		Voxelotor 1500 mg	
	N	Response Rate[a]	N	Response Rate[a]
ITT (Groups 1 and 2)	92	6.5%	90	51.1%
Age				
12 to <18 years	17	5.9%	14	57.1%
18 to 65 years	75	6.7%	76	50.0%
Sex				
Male	42	9.5%	32	56.3%
Female	50	4.0%	58	48.3%
Race				
Arab or Middle Eastern	20	5.0%	20	55.0%
Black or African American	63	4.8%	59	52.5%
Geographic Region				
North America	35	11.4%	34	52.9%
Europe	18	0%	19	36.8%
Other	39	5.1%	37	56.8%
VOC History (prior 12 months)				
1 episode	39	5.1%	35	60.0%
≥2 episodes	53	7.5%	55	45.5%
Baseline HU Use				
No	34	8.8%	32	43.8%
Yes	58	5.2%	58	55.2%
Baseline Hb				
<7 g/dL	7	14.3%	7	57.1%
≥7 g/dL	85	5.9%	83	50.6%

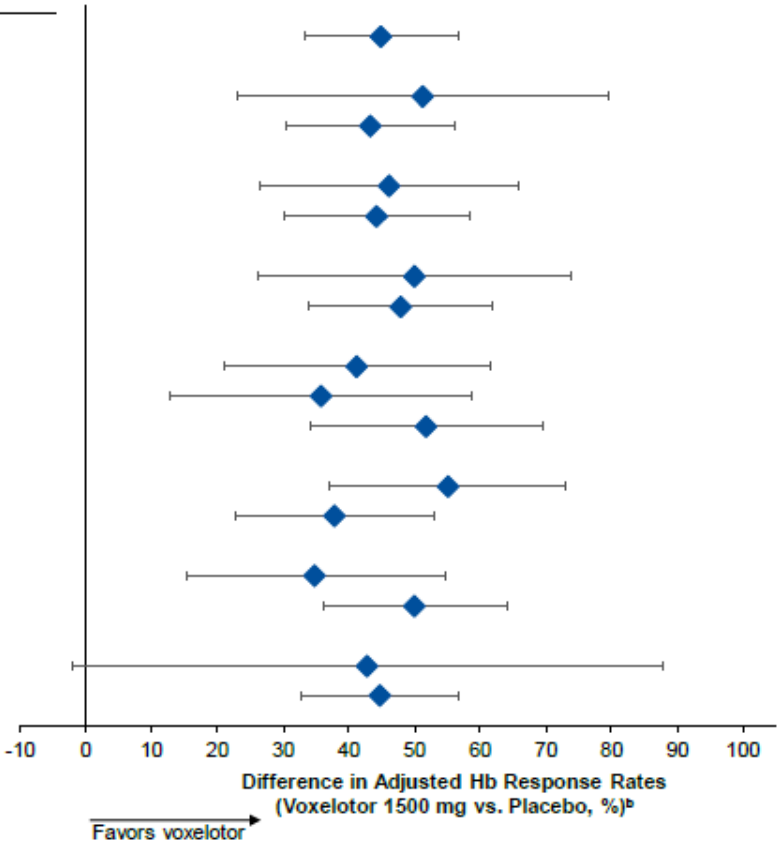


Figure 19. Hb response at week 24 by subgroup (voxelotor 1500 mg vs placebo)

Source: EMA EPAR[1]

B.2.8. Meta-analysis

Not applicable.

B.2.9. Indirect and mixed treatment comparisons

Not applicable.

B.2.9.1. Uncertainties in the indirect and mixed treatment comparisons

Not applicable.

B.2.10. Adverse reactions

Key points

- In the phase 3 HOPE trial, the proportion of patients with non-SCD-related treatment-emergent AEs (TEAEs) that occurred or worsened on treatment was similar across the voxelotor and placebo groups.[3]
- The majority of non-SCD-related TEAEs had a maximum severity of grade 1–2.[3]
- Incidence of any Grade ≥3 AEs was also similar in the voxelotor (26.1% at 24 weeks, 32.9% at 72 weeks) and placebo (26.4% at 24 weeks, 37.4% at 72 weeks) groups.[1]
- Incidence of SCD-related treatment-emergent AEs was also similar across the voxelotor and placebo groups.[3]
- TEAEs that occurred with higher incidence (by ≥ 5 percentage points) in at least 1 voxelotor group vs placebo were primarily gastro-intestinal (i.e., diarrhoea, nausea, upper abdominal pain).[3]
- Discontinuation of voxelotor due to treatment-emergent AEs was low (9.1%, vs 4.4% with placebo at 24 weeks, 12.5% vs 7.7% at 72 weeks).[3,91]
- There was no evidence of impaired oxygen delivery or hypoxia resulting from the increased oxygen affinity of Hb afforded by voxelotor.[3,108]
- The safety profile in the OLE was consistent with the findings from the HOPE trial, and no new safety signals were identified with exposure through a combined 144 weeks of treatment.[92 106]

B.2.10.1. Treatment exposure

The median duration of exposure was [redacted] weeks (range: [redacted] weeks) in the voxelotor 1500-mg group, [redacted] weeks (range: [redacted] weeks) in the voxelotor 900-mg group, and [redacted] weeks (range: [redacted] weeks) the placebo group.

Table 15. Summary of treatment exposure

	Voxelotor 1500 mg n (%) N = 88	**Voxelotor 900 mg n (%) N = 92**	**Placebo n (%) N = 91**
Duration of exposure (weeks)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
min, max	[redacted]	[redacted]	[redacted]
Study drug exposure/adherence (%)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
min, max	[redacted]	[redacted]	[redacted]
Source: CSR[100]			

B.2.10.2. Patient disposition and overall adverse events

Overview

Voxelotor was generally well tolerated throughout the treatment period (up to 72 weeks) and the incidence of AEs and serious AEs (SAE) was similar in groups receiving voxelotor and placebo.[91] The severity of events was comparable in both groups, and the majority of non-SCD related TEAEs were of grade 1-2 (placebo: 53%; voxelotor 1500 mg: 64%).[91]

Patient disposition is shown in Table 16. Discontinuations due to TEAEs occurred in 12.5% receiving voxelotor 1500 mg, 8.7% receiving voxelotor 900 mg and 7.7% of patients in the placebo group. The low incidence of discontinuations suggests that TEAEs are generally manageable.[91,100]

Dose modifications due to an AE (dose reduction or dosing interruption) were required in 47.7% of patients who received voxelotor 1500 mg compared with 32.6% of patients who received voxelotor 900 mg and 36.3% of patients who received

placebo. The majority of dose modifications were dosing interruptions, and the rate was comparable across treatment groups, with sickle cell anaemia crises being the most common cause.[1]

Table 16 Patient disposition and reasons for discontinuation, ITT population

	Voxelotor 1500 mg n (%)	**Voxelotor 900 mg n (%)**	**Placebo n (%)**
Randomised (ITT) population	90	92	92
Subjects Treated (mITT and Safety Populations)	88 (97.8)	92 (100)	91 (98.9)
Completed Study*	63 (70.0)	70 (76.1)	66 (71.7)
Early Discontinuation From Study	27 (30.0)	22 (23.9)	26 (28.3)
Primary Reason for Study Discontinuation, (n, %)			
Adverse Event	11 (12.2)	6 (6.5)	6 (6.5)
Withdrawal of Consent	6 (6.7)	12 (13.0)	10 (10.9)
Discretion of the Investigator	1 (1.1)	2 (2.2)	1 (1.1)
Subject is Lost to Follow-Up	1 (1.1)	1 (1.1)	0
Subject is Noncompliant	5 (5.6)	1 (1.1)	3 (3.3)
Pregnancy	0	0	1 (1.1)
Other	3 (3.3)	0	5 (5.4)
Completed Assigned Treatment (72 weeks)*, n (%)	63 (70.0)	68 (73.9)	66 (71.7)
Early Treatment Discontinuation, n (%)	27 (30.0)	24 (26.1)	26 (28.3)
Primary Reason for Treatment Discontinuation, n (%)			
Adverse Event	11 (12.2)	8 (8.7)	7 (7.6)
Withdrawal of Consent	6 (6.7)	10 (10.9)	9 (9.8)
Discretion of the Investigator	1 (1.1)	2 (2.2)	1 (1.1)
Subject is Lost to Follow-Up	0	1 (1.1)	0
Subject is Noncompliant	6 (6.7)	1 (1.1)	3 (3.3)

Pregnancy	0	0	1 (1.1)
Other	3 (3.3)	2 (2.2)	5 (5.4)
Duration of Follow-Up (weeks)			
N	90	92	92
Mean (SD)	59.5 (22.55)	63.2 (22.34)	61.1 (1.60)
Median (range)	72.1 (0.1, 88.6)	72.5 (4.9, 86.0)	72.1 (0.1, 87.1)

ITT: Intent-to-Treat; mITT: modified Intent-to-Treat; SD: standard deviation.

* Includes subjects who completed the End-of-Treatment Visit for Study GBT440-031 and subsequently enrolled in the open-label extension (Study GBT440-034).

Source: EMA EPAR[1]

Non-SCD related adverse events

The proportion of patients experiencing a non-SCD related TEAE at any point (baseline to week 72) was comparable between patients receiving voxelotor 1500 mg and placebo (96.6 % vs 90.1%;Table 17).[1] The majority of non-SCD related TEAE were grade 1 or 2 and were not considered to be related to treatment The rate of SAEs was also similar between the voxelotor 1500 mg, voxelotor 900 mg and placebo groups (28.4%, 21.7% and 25.3%;Table 17).[1] SAEs considered related to voxelotor occurred in 3.4% (3/88) of patients receiving voxelotor 1500 mg, these included headache, drug hypersensitivity and pulmonary embolism.[1]

The most common non-SCD-related TEAEs in the voxelotor 1500mg group were headache, diarrhoea, arthralgia; the most common in the placebo group were headache, pain in extremities and pain.[1] TEAE that occurred more frequently with voxelotor treatment (i.e. ≥5% greater incidence with voxelotor compared with placebo) than in the placebo group were primarily AEs relating to the gastrointestinal system (these are denoted with a * in Table 18) and were, in most cases were self-limiting and transitory.[1,100]

Table 17. Summary of non-SCD related treatment-emergent adverse events

	Voxelotor 1500 mg N = 88 n (%)	**Voxelotor 900 mg N = 92 n (%)**	**Placebo N = 91 n (%)**
non-SCD-related TEAE			
Patients with ≥ 1	85 (96.6)	86 (93.5)	82 (90.1)
Grade ≥ 3	29 (32.9)	30 (32.6)	34 (37.4)
Serious	25 (28.4)	20 (21.7)	23 (25.3)
Leading to discontinuation	9 (10.2)	7 (7.6)	6 (6.6)
non- SCD-related treatment-related TEAEs			
Patients with ≥1	35 (39.8)	30 (32.6)	24 (26.4)
Serious	3 (3.4)	4 (4.3)	2 (2.2)

SCD: sickle cell disease; TEAE: treatment-emergent adverse events

Source: EMA EPAR[1]

Table 18. Summary of non-SCD related treatment-related adverse events in ≥10% of patients

	Voxelotor 1500 mg n (%)	**Voxelotor 900 mg n (%)**	**Placebo n (%)**
Headache*	28 (31.8)	20 (21.7)	23 (25.3)
Diarrhoea*	20 (22.7)	17 (18.5)	10 (11.0)
Arthralgia*	19 (21.6)	14 (15.2)	13 (14.3)
Nausea*	17 (19.3)	17 (18.5)	9 (9.9)
Back Pain	15 (17.0)	13 (14.1)	12 (13.2)
Pain	15 (17.0)	15 (16.3)	18 (19.8)
Abdominal pain*	13 (14.8)	13 (14.1)	10 (11.0)
Pyrexia*	13 (14.8)	12 (13.0)	7 (7.7)
Rash	13 (14.8)	13 (14.1)	10 (11.0)
Upper respiratory tract infection*	13 (14.8)	22 (23.9)	14 (15.4)
Fatigue	12 (13.6)	13 (14.1)	12 (13.2)
Pain in extremity	12 (13.6)	20 (21.7)	19 (20.9)
Vomiting	11 (12.5)	13 (14.1)	15 (16.5)
Non-cardiac chest pain	10 (11.4)	13 (14.1)	10 (11.0)
Urinary tract infection	9 (10.2)	6 (6.5)	13 (14.3)
Abdominal pain upper	8 (9.1)	14 (15.2)	6 (6.6)
Cough	8 (9.1)	6 (6.5)	10 (11.0)

* Incidence ≥5% higher with voxelotor treatment vs placebo

Source: EMA EPAR[1]

SCD-related adverse events

The incidence of SCD-related TEAEs was also comparable between the voxelotor 1500 mg, voxelotor 900 mg and placebo groups. The incidence of SAEs and discontinuations were also similar between treatment arms (Table 19).

Sickle cell anaemia with crisis was the most common SCD-related adverse event accounting for 79.1%, 76.1% and 75.0% of events in the voxelotor 1500 mg, voxelotor 900 mg and placebo groups, respectively (Table 20).[1] The occurrence of events were well distributed throughout the study and not considered to be related to increases in Hb following initiation of treatment with voxelotor. post-hoc analysis of VOC events showed that patients treated with voxelotor 1500 mg achieving the highest Hb concentrations (≥12 g/dL) had the lowest incidence of VOCs, and the incidence of VOCs decreased in-line with increasing Hb levels.[109]

Table 19. Summary of SCD related treatment-emergent adverse events

	Voxelotor 1500 mg N = 88 n (%)	**Voxelotor 900 mg N = 92 n (%)**	**Placebo N = 91 n (%)**
SCD-related TEAE			
Patients with ≥ 1	69 (78.4)	69 (75.0)	73 (80.2)
Grade ≥ 3	50 (56.7)	52 (56.5)	52 (57.1)
Serious	46 (52.3)	48 (52.2)	48 (52.7)
Leading to discontinuation	3 (3.4)	3 (3.3)	2 (2.2)
SCD-related treatment-related TEAEs			
Patients with ≥1	5 (5.7)	3 (3.3)	5 (5.5)
Serious	4 (4.5)	1 (1.1)	1 (1.1)

SCD: sickle cell disease; TEAE: treatment-emergent adverse events
Source: EMA EPAR[1]

Table 20. SCD-related treatment-emergent adverse events

	Voxelotor 1500 mg N = 88 n (%)	**Voxelotor 900 mg N = 92 n (%)**	**Placebo N = 91 n (%)**
Sickle cell anaemia with crisis	67 (76.1)	69 (75.0)	72 (79.1)
Priapism (male patients only)	4/31 (12.9)	6/41 (14.6)	1/42 (2.4)
Osteonecrosis	0	0	1 (1.1)
Acute chest syndrome or pneumonia	16 (18.2)	15 (16.3)	13 (14.3)
SCD: sickle cell disease; TEAE: treatment-emergent adverse events Source: EMA EPAR[1]			

B.2.10.2.1. *Safety data from open label extension study*

Additional safety data from the OLE of the HOPE trial, showed that 83.7% of patients in the OLE (149/178) experienced a non-SCD-related TEAE, however most were grade 1 or 2 in severity. The most commonly reported TEAEs were arthralgia, headache, pain, nausea, and pain in extremity, as detailed in Table 21.[92]

Eleven patients (6.2%) had an AE that led to treatment discontinuation, 4 of which were considered related to voxelotor. No TEAEs consistent with lack of tissue oxygenation were observed.[92] The safety profile in the OLE was consistent with the findings from the HOPE trial, and no new safety signals were identified with exposure through a combined 144 weeks of treatment. [92] [106]

Table 21. Common non-SCD-related AEs (occurring ≥10% of patients)

	Prior treatment group in HOPE trial			All patients treated in OLE
	Voxelotor 1500 mg N = 58 n (%)	**Voxelotor 900 mg N = 58 n (%)**	**Placebo N = 62 n (%)**	**Voxelotor 1500 mg N = 178 n (%)**
Arthralgia	5 (8.6)	7 (12.1)	15 (24.2)	27 (15.2)
Headache	5 (8.6)	6 (10.3)	12 (19.4)	23 (12.9
Pain	5 (8.6)	5 (8.6)	11 (17.7)	21 (11.8)
Nausea	2 (3.4)	5 (8.6)	13 (21.0)	20 (11.2)
Pain in extremity	7 (12.1)	6 (10.3)	7 (11.3)	20 (11.2)
Diarrhoea	2 (3.4)	6 (10.3)	10 (16.1)	18 (10.1)
Upper respiratory tract infection	9 (15.5)	2 (3.4)	7 (11.3)	18 (10.1)
SCD: sickle cell disease; TEAE: treatment-emergent adverse events Source: Achebe (2021) [92] [106]				

B.2.11. Ongoing studies

There are a number of ongoing clinical trials relating to voxelotor in sickle cell disease in patients aged ≥12 years. These are shown in Table 22. Trials expected to provide additional evidence in the 12 months following submission (i.e. to June 2023) are indicated by shading.

Table 22. Ongoing clinical trials relating to voxelotor in sickle cell disease patients aged ≥12 years.

Study	Aims	Primary outcomes	Status
GBT440-034 (NCT03573882)[110]	An open label extension of the HOPE study to assess the long-term safety and efficacy of voxelotor in SCD.	• Number of participants with treatment-related adverse events as assessed by Common Terminology Criteria for Adverse Events v4.03 over a 5-year time frame. • Frequency of sickle cell-related complications over a 5-year time frame.	Active, not recruiting; completion expected October 2024.
GBT440-029 (NCT04247594)[111]	A dose escalation trial to assess the safety of titrating doses of voxelotor from 1500 mg to 3000 mg and in	• Treatment-emergent adverse events, over a time frame of approximately 200 days.	Completed.

	doses >1500 mg without up-titration.		
GBT440-4R1 RETRO (NCT04930328)[112]	A retrospective real-world study assessing clinical outcomes, HRQoL and healthcare resource utilisation in SCD patients treated with voxelotor.	All outcomes have a time frame of 1 year before and 1 year after the first dose of Oxybryta. • Change from pre-Oxbryta treatment period in haemoglobin. • Other outcomes include change in various pharmacokinetic markers, incidence of hospital events and adverse events of interest.	Active, not recruiting; completion expected 31 May 2022.
GBT440-007: HOPE Kids (NCT02850406)[113]	To assess the efficacy and safety of voxelotor in paediatric patients (12–17 years) with sickle cell disease.	• Pharmacokinetic profile of voxelotor including maximum concentration and total drug concentration from pre-dose to Day 15. • Change in haemoglobin and cerebral blood flow from Baseline to Week 24 and Week 48, respectively. • Treatment-emergent adverse events and serious adverse events from Baseline to Week 48.	Recruiting; completion expected December 2022.
GBT440-039 ActIVe (NCT04400487)[114]	To evaluate the effect of voxelotor on daily physical activity and sleep quality, with patients with SCD and chronic moderate anaemia.	All outcomes below have a time frame using Baseline, Week 10-12, and Week 22-24. • Change in total daily physical activity. • Change in total nocturnal sleep time. • Change in wake time after sleep onset. • Other outcomes included change in various pharmacokinetic markers that measure sleep efficiency	Active not recruiting, completion expected February 2023.
GBT440-044 (NCT05228834)[115]	To evaluate the treatment effect of voxelotor on neurocognitive function in paediatric patients (8-18 years).	• Change in the executive abilities composite score from Baseline to Week 12.	Recruiting, completion expected October 2023.
HEMOPROVE (NCT05199766)[116]	To evaluate the biological activity of Voxelotor on the reduction of intra vascular haemolysis measured by plasma haemoglobin.	• Evaluation of the biological activity of voxelotor on the change of intra vascular haemolysis measured by decrease of plasma haemoglobin from Baseline at Week 48.	Not yet recruiting, completion expected January 2024.

GBT440-043 (NCT05228821)[117]	To evaluate the impact of voxelotor treatment on cerebral blood flow in adult and adolescent participants (12-30 years).	• Change in cerebral blood flow from baseline to Week 12.	Not yet recruiting, completion expected April 2025.
GBT440-038 Paediatric OLE (NCT04188509)[118]	An OLE for paediatric patients (up to 18 years) with SCD who have participated in voxelotor clinical trials.	• Treatment emergent adverse events and serious adverse events throughout the entire study. • Sickle cell disease-related complications throughout the entire study.	Enrolling by invitation. Completion expected January 2026
GBT440-032 HOPE Kids 2 (NCT04218084)[119]	To assess the effect of voxelotor on the transcranial doppler ultrasound measurements in SCD participants aged 2-15 years.	• Transcranial Doppler Ultrasound measurement with a 24 week time frame.	Recruiting, completion expected March 2026.
GBT440-4R2 PROSPECT (NCT04930445)[120]	A prospective observational registry study designed to evaluate the effect of voxelotor in SCD patients in a real-world setting in the US.	All outcomes have a time frame of 1 year before and 1 year after the first dose of Oxybryta. • Change from pre-Oxbryta treatment period in haemoglobin. • Other outcomes include change in various pharmacokinetic markers, incidence of hospital events and adverse events of interest.	Recruiting, completion expected December 2028.

B.2.12. Interpretation of clinical effectiveness and safety evidence

The phase III HOPE trial was the primary clinical trial that evaluated the efficacy and safety of voxelotor in SCD.[3,91] Patients in the voxelotor 1500 mg group experienced a rapid and sustained improvement in Hb concentration, leading to improvements in a range of endpoints related to haemolytic anaemia. Hb improvements were similar with or without concurrent hydroxycarbamide and regardless of baseline anaemia severity and patient age.[3]

- 51% of the voxelotor 1500 mg group experienced a >1g/dL increase in Hb at 24 weeks, compared to 7% on placebo (primary endpoint, p<0.001). This increase occurred within 2 weeks and was sustained through 72 weeks.[3,91] A Hb increase of 1g/dL is equivalent to the intended effect of one unit of transfused blood.[105]

- Patients on voxelotor had an adjusted mean change from baseline of 1.1 g/dL (95% CI 0.9,1.4) at 24 weeks, whereas Hb in the placebo group fell slightly (-0.1 g/dL [-0.3, 0.2] P<0.001); improvement with voxelotor was sustained over 72 weeks.[3,91]

- 41% of voxelotor-treated patients had Hb ≥10 g/dL at 24 weeks, compared with only 9% on placebo.[91]

- Voxelotor reduced the incidence of worsening anemia.[3]

Significant reductions in haemolytic markers (indirect bilirubin and percentage of reticulocytes) were also observed in patients treated with voxelotor at week 24 and 72,[3] consistent with reduced levels of haemolysis in voxelotor-treated patients. Voxelotor was also associated with other benefits:

- Leg ulcers are an early sign of end-organ damage, resulting from vasculopathy and chronic inflammation.[121,122] All patients with leg ulcers treated with voxelotor 1500 mg in HOPE (N = 4) had their leg ulcers resolve (n = 3) or improve (n = 1). No patients treated with placebo had their leg ulcers improve.[93] Improvements in leg ulcers in patients treated with voxelotor was associated with improvements in Hb and haemolytic markers, suggesting voxelotor presents a clinical benefit for SCD patients with leg ulcers, by improving parameters of RBC health.[93]

- There was a numerical reduction in the annualised incidence rate (IR) of on-treatment VOCs with voxelotor 1500 mg: IR was 2.4 events/year in the voxelotor 1500 mg group and 2.8 events/year in the placebo group. The difference was not statistically significant; however, the study was not designed to detect a difference.[91]

- A significantly larger proportion of patients treated with voxelotor were rated as moderately or very much improved by their clinicians according to the Clinical Global Impression of Change (CGIC) at week 72.[91]

- Voxelotor was generally well tolerated throughout the treatment period (up to 72 weeks) and the incidence of AEs and serious AEs (SAE) was similar in groups receiving voxelotor and placebo.[91] The severity of events was comparable in both groups, and the majority of non-SCD related TEAEs were of grade 1-2 (placebo: 53%; voxelotor 1500 mg: 64%).[91]

Voxelotor has also shown important benefits in real-world use, evidenced by analysis of the Symphony database:

- In patients with ≥1 VOC in 3 months prior to initiating voxelotor, there was a 23% reduction (P<0.001) in the annualised incidence of VOCs, from 10.9 to 8.4.[96]

- Patients with recent transfusions (≥ 1 transfusion in 3 months before voxelotor initiation; N=190) had a 52% reduction (*P*<0.001) in the mean annualised rate of transfusion per patient-year (PPY) during the post-index follow-up period (7.0 before voxelotor vs 3.3 after voxelotor).[96]

- Patients had significantly fewer hospitalisations (all cause: -34%, P<0.001; VOC-related: -37%, P<0.001) in the post-index period after treatment with voxelotor.[96]

B.2.12.1. Strengths and limitations of clinical evidence

Strengths

A strength of the evidence base is the availability of data on voxelotor's efficacy for a follow-up period of up to 144 weeks,[92,106] confirming that patients experience a sustained improvement in Hb.

Another important strength of the evidence base is the availability of both trial data and data from real-world use. Data from the use of voxelotor in real-world practice is a valuable addition to the trial evidence, and confirms the results seen in the HOPE clinical trial and beyond. The real-world evidence is derived predominantly from the US, where voxelotor has been available in clinical practice since late 2019. Data from use of voxelotor in the UK (through the EAMS) are not yet available.

As well as raising Hb levels, voxelotor 1500 mg was associated with a significant improvement in markers of haemolysis (indirect bilirubin, change in % reticulocytes) at 24 and 72 weeks compared with placebo. These findings are consistent with reduced haemolysis,[3] and indicate that by inhibiting HbS polymerisation, voxelotor is a disease modifying therapy that addresses the underlying molecular basis of SCD and is likely to improve both short- and long-term outcomes.

Limitations

The evidence base has some limitations. The chronic complications resulting from the pathology of SCD evolve over time, and worsen as patients get older. The HOPE trial was not designed to show an effect on chronic complications, as these require a longer time scale for evaluation. The link to long-term outcomes in the modelling is therefore made using associations between Hb concentration and outcomes of interest derived from the Symphony database (see Section B.3.3.3). However, the relationship between Hb and these outcomes is robust, as discussed in Section B.3.3.3.1.

Voxelotor is indicated for the treatment of haemolytic anaemia and HOPE was not designed or powered to test its effect on VOCs.[91] However, patients receiving voxelotor 1500 mg had a numerically lower annualised incidence rate of vaso-occlusive crisis over 24 weeks (2.77, 95% CI 2.15-3.57) than placebo (3.19, 95% CI 2.50-4.07); the same was seen over 72 weeks (2.4, 95% CI 1.8-3.1 vs 2.8, 95% CI 2.2-3.6 for voxelotor and placebo, respectively)[91]. This trend is confirmed by real-world evidence from the Symphony database, showing that patients who had at least one VOC in the three months before starting voxelotor had a 23% reduction in the annualised rate of VOCs per person per year in the post index period ($p<0.001$).[96]

Like many clinical trials, HOPE did not detect an effect of voxelotor on HRQoL during the trial period as measured by EQ-5D-5L. Scores at baseline were high, making it difficult to detect an impact of the treatment effect. EQ-5D may also be insufficiently sensitive to capture all the HRQoL effects associated with SCD. It is noteworthy that people with SCD have never known full health, so they may value their default health state more highly than it would be valued by someone who had previously been healthy, making changes in their health state more difficult to capture.

B.2.12.2. Applicability to the decision problem

The study population of HOPE is broadly generalisable to SCD patients in England who require second line treatment for haemolytic anaemia, with the exception that patients receiving regular blood transfusions were not eligible (see below for a discussion of this issue).

The median age of the voxelotor 1500 mg group was 24 years, with a range from 12-59 years, and the majority (88%) had homozygous HbS (68%) or HbSβ0-thalassemia (20%) genotype. The placebo group was similar, with a median age of 28 years (range 12-64), although a slightly higher proportion of patients (80%) had homozygous HbS genotype and a slightly lower proportion (12%) had HbSβ0-thalassemia (n = 74/92 and 11/92, respectively). Median Hb at baseline was 8.7 g/dL (range 5.9-10.8) and 8.6 g/dL (6.1-10.5) in voxelotor 1500 mg and placebo groups, respectively. For the respective groups, 39% and 42% had had 1 VOC in the last 12 months and 61% and 58% had had 2-10.[3]

Patients were not required to have shown intolerance, ineligibility or insufficient efficacy with hydroxycarbamide in order to be enrolled in HOPE. However, in practice, patients who were already on hydroxycarbamide when they and their physicians decided they should enter the trial (64% and 63% in voxelotor 1500 mg and placebo groups, respectively) were likely to have made this decision because the management of their SCD was not optimal. As hydroxycarbamide is widely recommended as first line treatment for SCD (including by British Society of Haematology guidelines[4]), it is likely that patients who were not using hydroxycarbamide at baseline had taken it previously and stopped, or had been unwilling or ineligible to take it (see Section B.1.1 for additional discussion of applicability to the decision problem). Furthermore, a prespecified subgroup analysis showed that the effect of voxelotor on Hb was not significantly different between patients who were on hydroxycarbamide and those who were not. There is no reason to believe that patients in the submission population would experience a different treatment effect from voxelotor to that experienced by the overall trial population. In analysis of the individual patient-level data from HOPE performed for the economic modelling, Hb response was stratified by HC use to reflect the lower level of HC use in UK clinical practice (see Section B.3.3.1.1).

However, there are differences between the trial population and the patient population in clinical practice. A group of UK clinicians (Vora et al. 2022[123]) analysed two patient cohorts with trial-eligible genotypes aged 16+ or 18+ to assess eligibility for voxelotor and crizanlizumab based on trial eligibility criteria. Patients in the HOPE

trial were required to have had at least one documented VOC in the previous 12 months requiring prescribed analgesia, whereas 47.5% of one UK cohort and 73.9% of the second cohort had no documented VOC in the last 12 months. This affirms that for a significant proportion of patients, VOCs are not the primary manifestation of SCD. Secondly, patients receiving regular transfusions were not eligible for HOPE because of the confounding effect of transfusions on Hb-related endpoints. Vora et al. report that 18.4% of one cohort and 7.7% of the other cohort were on regular transfusions.[123] However, the EMA and anticipated MHRA marketing authorisation for voxelotor is broader than the trial criteria: voxelotor is licensed for treatment of haemolytic anaemia in all SCD patients aged 12+ (except where contraindicated).[2]

A limitation of the evidence base in terms of the submission is that the trial population differed from that specified in the decision problem, as patients treated with regular transfusions were excluded because of the confounding effect of transfusion on Hb endpoints. However, the treatment effect of voxelotor on Hb in such patients (if they were to be treated with voxelotor rather than transfusions; patients are not expected to be offered both treatments concurrently) is not expected to be different from that seen in the trial. Voxelotor offers an alternative to regular transfusions in some patients (patients requiring regular transfusions for the prevention of stroke are not expected to be offered voxelotor).

B.3 Cost effectiveness

B.3.1. Published cost-effectiveness studies

An SLR was conducted in line with NICE requirements to identify all relevant cost-effectiveness studies in children/adolescents (≥ 12 years) and adults (≥ 18 years) with SCD, irrespective of prior treatment. Database searches were initially conducted from database inception to 27 October 2021 and updated on 06 April 2022. In total ten economic evaluations from ten separate publications were identified for inclusion in this review. Full details of the review, including the PRISMA diagram and a description of all relevant studies informing the model, are given in Appendix G.

Table 23. Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Alashgar *et al.* [124]	2020	Decision-tree (payer perspective) Intervention: Crizanlizumab comparator: Hydroxycarbamide + Crizanlizumab	NR – Patients with SCD, 16 years or older	NR	Cost year: NR Currency: USD ($) Crizanlizumab + HC saves $78,444 per patient (61% less than total Crizanlizumab costs)	Crizanlizumab + HC is cost-effective compared to crizanlizumab alone
Cherry *et al.* [125]	2012	Markov (payer – UK NHS perspective) Intervention: TCD scans followed by blood transfusion where the scan revealed a blood velocity of > 200 cm/second Comparator (non-intervention): TCD scans only	NR – lifetime horizon run for patients aged 2 years at inception. Patients with SCD (HbSS/HbSβ0 genotypes) and no prior history of stroke.	<u>Discounted QALYs</u> Age 19-30: ○ Non-Intervention: 3216 ○ Intervention: 3367 ○ Incremental: 151 Age 31+: ○ Non-Intervention: 1263 ○ Intervention: 1344 ○ Incremental: 81 <u>Undiscounted QALYs</u> Age 19-30: ○ Non-Intervention: 6705 ○ Intervention: 7022 ○ Incremental: 317 Age 31+: ○ Non-Intervention: 4565	Cost year: 2010 Currency: GBP (£) <u>Discounted costs</u> Age 19-30: ○ Non-intervention: £ 12,195,631 ○ Intervention: £ 16,024,182 ○ Incremental: £ 3,828,551 Age 31+: ○ Non-Intervention: £ 3,586,150 ○ Intervention: £ 6,826,909 ○ Incremental: £ 3,240,758 <u>Undiscounted costs</u> Age 19-30:	<u>Discounted ICER</u> • Age 19-30: £ 25,326/QALY • Age 31+: £ 39,783/QALY <u>Undiscounted ICER</u> • Age 19-30: £ 24,743/QALY Age 31+: £ 40,394/QALY

				○ Intervention: 4863 Incremental: 298	○ Non-Intervention: £ 25,326,071 ○ Intervention: £ 33,169,658 ○ Incremental: £ 7,843,587 Age 31+: ○ Non-Intervention: £ 12,721,175 ○ Intervention: £ 24,767,537 Incremental: £ 12,046,362	
Karnon *et al.* [126]	2008	CUA (Payer – UK NHS perspective) Intervention: Deferasirox Comparator: Desferrioxamine	Mean age: 44 years; range: 3–81 years Patients with SCD requiring iron chelation.	NR	NR	NR
Rizvi *et al.* [127]	2013	Markov Intervention: Thromboprophylaxis Comparator: NR	NR - Pregnant women with SCD and no previous venous thromboembolism.	NR	Cost year: NR Currency: USD ($) NR	Prophylactic AC <$561 per month or VTE risk >4.97%: ICER $100,000/ QALY prophylactic AC with VTE risk ≥ 6.0% or prior SCD complication: ICER $76,811/ QALY

Spackman *et al.* [128]	2014	Decision-analytic model (payer – UK NHS perspective) Intervention: Preoperative transfusion Comparator: No preoperative transfusion	Mean age of 17.3 years. Patients with SCD (HbSS/HbSß0 genotypes) undergoing low- or medium-risk elective surgery.	Within-trial analysis Unadjusted QALYs • Preoperative transfusion Mean (SD): 0.849 (0.164) Range: 0.525- 1 • No preoperative transfusion Mean (SD): 0.857 (0.186) Range: 0.520- 1 Adjusted QALYs • Preoperative transfusion Mean (SD): 0.714 (0.040) • No preoperative transfusion Mean (SD): 0.696 (0.037) Incremental: 0.018 (0.048) Decision Model (long term extrapolation including transfusion complications) • Preoperative transfusion Mean (SD): 0.744 (0.092) • No preoperative transfusion	Cost year: 2011 Currency: GBP (£) Within-trial analysis Adjusted cost • Preoperative transfusion Mean (SD): 1706 (615) • No preoperative transfusion Mean (SD): 2442 (615) Incremental: -735 (869) Decision Model (long term extrapolation including transfusion complications) • Preoperative transfusion Mean (SD): 1481 (347) • No preoperative transfusion Mean (SD): 1897 (359) Incremental: -416 (514)	NR

				Mean (SD): 0.664 (0.081) Incremental: 0.080 (0.066)		
Adel *et al.*	2021	Decision- tree (payer perspective) Intervention: Crizanlizumab Comparator: L-glutamine	NR - Older adolescent and adult patients (≥16 years old) with SCD	NR	Cost year: 2020 Currency: USD ($) Average annual cost of treatment per patient: • Crizanlizumab (5mg/Kg): $189,014 • Crizanlizumab (2.5mg/Kg): $143,798 L-glutamine: $74,323	Crizanlizumab (2.5mg/Kg) vs L-Glutamine: $81,265 per SCD-related VOC averted Crizanlizumab (5mg/Kg) vs L-Glutamine:$459,620 per SCD-related VOC averted
DeMartino *et al.* [129]	2021	Budget impact assessment (payer perspective) Intervention: one-time gene therapy (theoretical) Comparator: SoC	13-45 years old patients with severe SCD	NR	NR	NR
NICE [TA743] [130]	2020	Markov (payer – UK NHS perspective) Intervention: Crizanlizumab Comparator: SoC (HC, blood transfusions)	Mean age (SD): 37.1 (15.4), 63% female. Patients with SCD aged ≥16 years.	NR	Cost year: 2018/2019 Currency: GBP (£) NR	Crizanlizumab with PAS vs SoC: £392,868.32/QALY

Pontinha *et al.*	2022	Markov (societal perspective) Intervention: Crizanlizumab Comparator: Hydroxycarbamide	NR – patients with SCD, 16 years or older	Incremental QALYs: 2.527	Cost year: 2020 Currency: USD ($) Incremental costs: $725,917	Crizanlizumab vs HC: $287,263/ QALY
Salcedo *et al.* [131]	2021	Markov (payer perspective) Intervention: hypothetical durable treatment (gene therapy cure) Comparator: SoC	NR – lifetime management of SCD in patients aged 1+	<u>Discounted:</u> Durable therapy: 26.4 QALYs SoC: 17.9 QALYS <u>Undiscounted:</u> Durable therapy: 66.2 QALYs SoC: 37.6 QALYs	Cost year: 2018 Currency: USD ($) <u>Discounted:</u> Durable therapy: $2,372,482 SoC: $1,175,566 <u>Undiscounted:</u> Durable therapy: $3,210,182 SoC: $2,770,348	<u>Discounted:</u> $140,877/ QALY <u>Undiscounted:</u> $15,332/ QALY
AC, anticoagulation; CUA, cost-utility analysis; HC, hydroxycarbamide; ICER, incremental cost-effectiveness ratio; LY, life years; NR, not reported; PAS, patient access scheme; QALY, quality-adjusted life years; SCD, sickle cell disease; SD, standard deviation; SoC, standard of care; TCD, transcranial Doppler; VTE, venous thromboembolism						

B.3.2. Economic analysis

Due to the limited number of cost-effectiveness studies identified in the SLR that were relevant to the population and intervention in the decision problem, a de novo economic model was constructed to support the current submission. The analysis presented is a cost-utility analysis, using a discrete event simulation (DES) model, comparing the use of voxelotor (with or without hydroxycarbamide [HC]), against current standard of care (SOC) in patients as a second line treatment for SCD (as defined below). The rationale for the choice of modelling approach is discussed in Section B.3.2.2.1.

B.3.2.1. Patient population

Voxelotor is indicated by the EMA for the treatment of haemolytic anaemia due to SCD in adults and paediatric patients 12 years of age and older as monotherapy or in combination with HC.[2] The same indication is expected to be granted by the MHRA. This economic evaluation considers the use of voxelotor as a second line treatment (L2+) for patients who are intolerant, ineligible or have an inadequate response to hydroxycarbamide, or are unwilling to receive hydroxycarbamide. The rationale for this choice of population is given in Section B.1.1.

It is anticipated that hydroxycarbamide (HC) will remain as the first-line option of choice for patients with SCD in the UK. However, HC monotherapy is not appropriate for all patients.

- Some patients are ineligible to receive HC due to contraindications (e.g. severe hepatic or renal impairment, toxic ranges of myelosuppression or hypersensitivity to active ingredients or excipients).[72]

- Some are intolerant and discontinue HC following treatment-related adverse events.

- Some have insufficient response to HC. While variation in clinical practice exists, clinical experts consulted using the modified Delphi Panel exercise (see Appendix U) indicated that following ≥6 months of treatment at maximum

allowed and/or tolerated dose, HC may be considered insufficiently effective if there is no reduction in the rate of VOCs or increased organ damage is observed.

- The experts also estimated that in UK clinical practice, [redacted] are unwilling to receive HC due to concerns relating to fertility, adverse events (AEs), or other concerns (see Appendix U).

Once treatment with HC is no longer an option or HC is no longer adequate as monotherapy, patients have limited options. Options include symptomatic management (i.e. no disease-modifying therapy) or initiate regular transfusion therapy (RTT; with or without HC, defined as regular transfusions provided as part of a treatment plan, rather than on an ad hoc or 'top-up' basis). However, some patients do not receive RTT due to the risks and complications associated with it (guidelines emphasise that transfusions should only be used when the benefits outweigh the risks[67]), or for religious or other reasons (see Appendix U for discussion of treatment options by clinical experts). Figure 20 shows the treatment options available to patients with SCD, by line of therapy.

The economic analysis focuses on L2+ SCD patients eligible for voxelotor. Voxelotor ineligible patients (i.e. those who are receiving RTT for stroke prevention, or are outside of the marketing authorisation or who are contraindicated on the basis of hypersensitivity to the active substance or to any of the excipients as per the SmPC[2]) are excluded from the analysis.

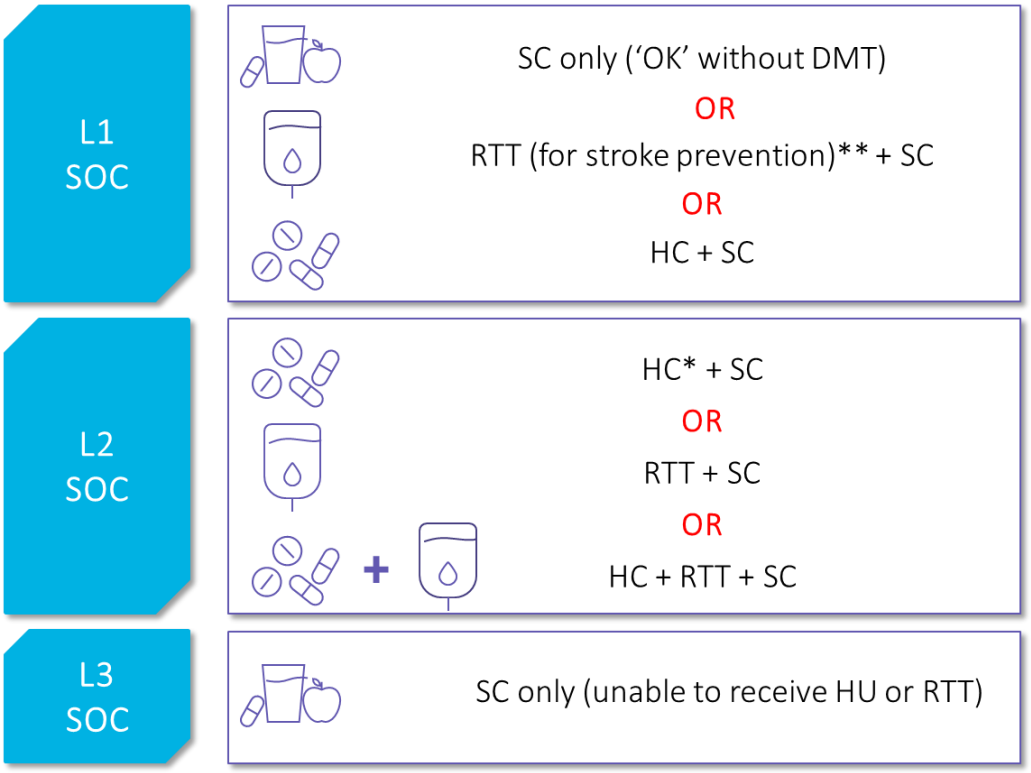


Figure 20. Treatment options available for patients with SCD

*HC can still be used as part of a regimen but is not sufficient as a monotherapy. If it is being used as a monotherapy, patients are not properly treated.

**Included here since voxelotor is not expected to replace RTT in this indication. Some of these patients are ineligible for HC and should therefore be in L2.

Abbreviations: RTT: regular transfusion therapy; DMT: disease modifying treatment; HC: hydroxycarbamide; SC: symptomatic care; SOC, standard of care.

B.3.2.2. Model structure

B.3.2.2.1. *Choice of modelling approach*

A de novo DES model was developed. Several potential modelling methodologies, including decision trees, Markov model cohorts, individual patient-level simulation and DES, were considered. While all models are accepted by NICE, additional considerations were made when selecting the most appropriate model structure. These include the ability to model disease outcomes long-term, the inclusion of competing risks, capturing heterogeneity, and the computational burden. Learnings from the modelling of SCD for the crizanlizumab submission were also taken into

account. The general limitations of the Markov model due to the requirement for mutually exclusive health states were critiqued within the context of SCD. It was noted that the model contained a limited number of health states that could not fully capture the complexities of SCD. The ERG suggested that a ‘time to event‘ analysis would be the optimal approach to model SCD.[132]

Decision tree models struggle to properly incorporate long-term costs and benefits, rendering them inappropriate for chronic diseases with ongoing treatment interventions. While Markov models handle long-term modelling well, it is complicated to include multiple non-mutually exclusive disease combinations within a Markov model. Further, tracking patient history is difficult and can lead to cumbersome models when included. Due to the limitations of the Markov approach and the requirement for mutually exclusive and exhaustive disease states within the model, it was decided that a discrete event simulation (DES) model would be the optimal approach to modelling SCD, an approach supported by the ERG’s critique of the crizanlizumab appraisal.[132] DES does not require a formal exposition of disease states since it is an event-driven model, and all possible events are modelled on a time to event (TTE) basis. DES is favoured over individual patient level simulation in cases where there is potential for multiple competing events. As there is a precedent in NICE SCD evaluations that time to event approaches should be considered,[130] a DES was determined to be the most appropriate model structure as it offers the most flexible way to incorporate the mixture of acute and chronic complications.

B.3.2.2.2. *Model structure*

The model was developed in Microsoft Excel® and Visual Basic for Applications, based on guidance from the NICE Decision Support Unit Technical Support Document 15.[133] The model was developed to simulate the TTE for all possible modelled events for each patient individually. Patients with SCD in the model may experience, or avoid, multiple comorbidities and complications over their lifetime. Furthermore, the incidences of acute and chronic complications are interconnected, with the increase in acute complications increasing the likelihood of chronic complications and vice versa. The DES model is well suited to accounting for both patient heterogeneity and risk of complications and death as a function of time,

clinical history and Hb level impacted by treatment. A simplified DES algorithm schematic is provided in Figure 21.

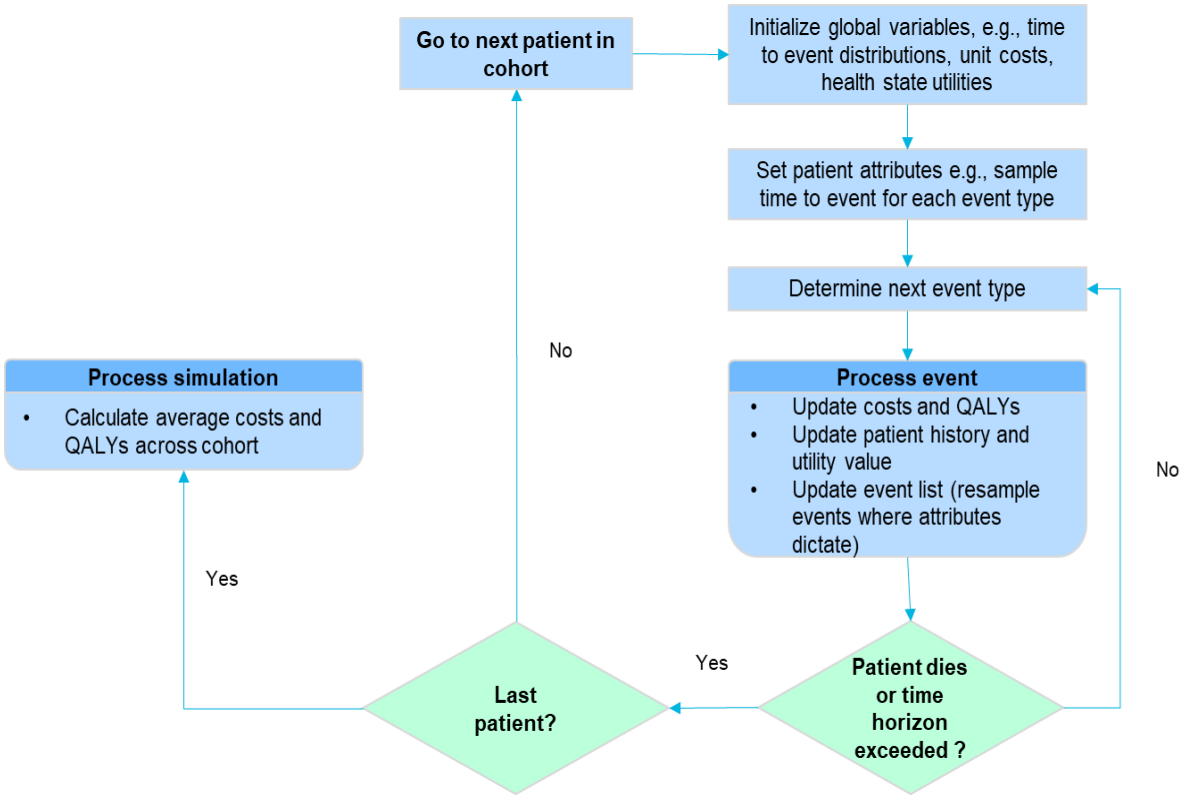


Figure 21. Simplified DES algorithm

DES, discrete event simulation; QALY, quality-adjusted life year.

B.3.2.2.3. *Event sampling*

The events in the model are comprised of SCD-related complications and death, in addition to discontinuation events for voxelotor, HC and regular transfusion. Events are first sampled from exponential TTE equations that are described in more detail in Section B.3.3.3. TTE is sampled using the following quantile function:

$$TTE = -\frac{\ln(X)}{re^{\sum c_i (a_i - \bar{a}_i)}}$$

Where X is a random draw between 0 and 1, r is the rate, c is the covariate estimate, a is the attribute value of the current agent in the model, and ā is the mean value of the covariate in the analysis data set.

An additional update event is used in the model to resample the events every year. In this way the extrapolations can be thought of as piece-wise exponential fits that are allowed to alter as the person in the model ages. An exponential survival distribution was used as there was no reason to believe there would be any temporal association between the hazard and time since the Hb assessment (other than age, the effect of which is captured as a covariate). Additionally, the frequent recurrences of certain events e.g., VOC, meant that other survival functions might not be appropriate, since they would contain an assumption that the shape of the hazard function remains the same for subsequent events.

B.3.2.3. Features of the economic analysis

Table 24 summarises the features of the economic analysis and provides a comparison with the only previous NICE Technology Appraisal in SCD, that of crizanlizumab for preventing sickle cell crises in SCD (TA743).[130] It should be noted that voxelotor and crizanlizumab have different indications within SCD, voxelotor being indicated for the treatment of haemolytic anaemia and crizanlizumab for the prevention of recurrent VOCs.[68] The two treatments are not therefore directly comparable, and crizanlizumab is not listed as a comparator in the final NICE scope.

B.3.2.4. Comparison with the NICE reference case

The values chosen for the economic analysis (see Table 24) are in line with the NICE reference case.

Table 24. Features of the economic analysis

	Previous evaluations	**Current evaluation**	
Factor	**TA743**[130] (crizanlizumab)	**Chosen values**	**Justification**
Time horizon	55 Years	Lifetime	To reflect the chronic nature of SCD and related complications and the lifetime use of treatments used to manage SCD, as per NICE reference case.
Perspective	NHS and Personal Social Service (PSS)	NHS and Personal Social Service (PSS)	As per NICE reference case

Discounting	3.5%	3.5%	As per NICE reference case
Treatment waning effect?	Not applied (discontinuation act as proxy)	Not applied	Data from HOPE trial showed mean change in Hb remains stable up to 72 weeks up to 72 weeks in HOPE, and up to 144 weeks in the open-label extension study. Treatment effect returns to baseline after discontinuation.
Source of utilities	SF-36 assessments from the LEGACY registry study were grouped based on annualised VOC incidence (<1 VOC, ≥1–<3 VOC, or ≥3 VOC) and mapped to EQ-5D-3L using the algorithm published by Rowen *et al.* (2009). EQ-5D-3L utilities were applied to VOC health states in the base case analysis.	Overall population: UK population norms (adjusted to match HOPE population) Decrement due to SCD: calculated from HOPE Utility decrements for SCD complications were taken from suitable sources in the literature	The modelling approach was different to that used for crizanlizumab (DES rather than Markov, and based around Hb rather than VOCs), necessitating a different approach to utilities. The rationale for the choice of utilities for each element is given in Section B.3.4.4.
Source of costs	Costs were sourced from NHS reference costs and auxiliary price lists, eMIT, BNF, PSSRU, NICE guidelines, and supplemented by the literature (Guest 2017).	Costs were drawn from a range of sources, including NHS costs, costs from previous TAs and, where necessary, costs from the literature.	The rationale for the choice of costs for each element is given in the sections below.

B.3.2.5. Intervention technology and comparators

B.3.2.5.1. *Intervention*

The intervention in the economic evaluation is voxelotor at the recommended dose of 1500 mg once daily, as monotherapy or in combination with HC as per the SmPC.[2] Voxelotor acts by inhibiting the polymerisation of HbS,[2] which is the underlying molecular event in the pathology of SCD. HbS polymerisation leads to the sickling and breakdown (haemolysis) of red blood cells, resulting in haemolytic anaemia and a cascade of pathology that results in the complications seen in patients with SCD (see Section B.1.3.1.1 and Figure 1).

Voxelotor is associated with a rapid and sustained increase in Hb. In the pivotal trial (HOPE, NCT 03036813) patients in the voxelotor 1500 mg group had an adjusted (least square [LS]) mean change in Hb from baseline to 24 weeks of 1.1 g/dL (95% CI, [redacted]), compared with -0.1 g/dL (95% CI, [redacted]) in the placebo group (P< 0.001).[3] At 72 weeks the change was 1.02 g/dL (95% CI, [redacted]) and 0.02 g/dL(95% CI, [redacted]) . Full details of trial design and results are given in Section B.2.6. Patients eligible for the trial were those aged 12–65 years with confirmed SCD, a Hb level between 5.5–10.5 g/dL, and 1–10 VOCs in the previous 12 months. Patients using HC at a stable dose for at least 3 months before the trial were eligible and could continue with HC. Patients were randomized to up to 72 weeks of once-daily oral administration of either 1500 mg voxelotor, 900 mg voxelotor, or placebo. Only data relating to the 1500 mg arm are used in the modelling, as this is the licensed dose.

B.3.2.5.2. *Comparator*

The relevant comparator for the economic model is SOC for L2+ patients (referred to as L2+ SOC). In the modelled L2+ population SOC is composed of either HC only, RTT (defined as ≥6 transfusions per year) only, RTT + HC, or symptomatic care only (Figure 20). Both the intervention and the comparator are given in addition to symptomatic care, which is received by all patients.

The treatment mix in the economic model was informed by the modified Delphi panel of UK clinical experts (see Appendix U). Of patients eligible for HC, the experts

considered that the proportion of patients who were willing to take HC was [redacted]% (with the remaining being unwilling to take HC). They then were able to provide estimates on the proportion of L2+ patients who would receive HC and/or RTT in the SOC arm or in addition to voxelotor. The experts stated that in very few cases a patient would be treated with both a combination of RTT and voxelotor, but the great majority of patients receiving voxelotor would not receive RTT in addition. Patients not receiving voxelotor, HC or RTT are assumed to only receive symptomatic management. A weighted average was then calculated to determine the proportion of patients in the intervention (voxelotor) and standard of care arms who receive HC and RTT (Table 25).

Table 25. Weighted* treatment mix for the intervention and the comparator

	SOC	Voxelotor
HC	[redacted]	[redacted]
RTT	[redacted]	[redacted]
RTT & HC	[redacted]	[redacted]
Neither RTT nor HC	[redacted]	[redacted]

HC, hydroxycarbamide; RTT, regular transfusion therapy; SOC, standard of care

*Weighted for willingness to take hydroxycarbamide, with the assumption that [redacted] are willing to take hydroxycarbamide

Patients receiving RTT, the majority (95%) are assumed to receive automated red cell exchange transfusion (ARCET), supported by BSH guidelines which state that "Automated exchange should be available to all patients and not be limited by resources" and aligning with the approach in NICE TA743.[66] Based on feedback from clinical experts, it was nonetheless assumed that [redacted]% of patients on RTT would receive top-up transfusions and not ARCET due to inaccessibility, ineligibility or refusal of ARCET(see Appendix U).

B.3.2.6. Treatment continuation rule

Not applicable.

B.3.3. Clinical parameters and variables

B.3.3.1. Incorporation of clinical efficacy into the model

B.3.3.1.1. *Efficacy of voxelotor*

Treatment effect data for the voxelotor arm (i.e. the effect of voxelotor 1500 mg/day on Hb level) was obtained from the HOPE trial (See Section B.2.3). At baseline, the median age of patients in the voxelotor arm was 24 years and in the placebo arm 28 years; patients were primarily Black or Arab/Middle Eastern. Most patients were homozygous HbS or Sβ0-thalassemia and the median baseline Hb was 8.7 g/dL in the voxelotor group and 8.6 g/dL in the placebo group. Of note, patients on RTT were excluded from the trial as it would have confounded the effect of voxelotor on Hb. In the HOPE trial, 65.3% of patients were on HC at baseline (Section B.2.3.2 Table 6). According to information gathered by the modified Delphi panel of nine English clinical experts with experience in treating SCD, the proportion of patients on HC therapy in the UK is significantly lower (see Appendix U). To ensure the analysis reflects clinical practice in the UK and following prior guidance from NICE,[130] the economic analysis was stratified by HC use at baseline.

The primary end point was the percentage of participants who had a Hb response, which was defined as an increase of more than 1.0 g/dL from baseline to week 24 in the ITT analysis (see Appendix N for additional detail).[3] The proportion of responders in the voxelotor and placebo groups at 24 weeks, according to baseline HC use, is presented in Table 26.

Table 26. Responders (≥1 g/dL in Hb) at 24 weeks, by HC use at baseline (intent-to-treat population)

	Baseline HC n (%)	**No baseline HC n (%)**
At 24 weeks (base case)		
Voxelotor, 1500mg	[redacted] (55.2%)	[redacted] (43.8%)
Placebo	[redacted] (5.2%)	[redacted] (8.8%)
Source: CSR[134], EMA EPAR[1]:		

In addition to the proportion of responders, change from baseline in Hb was used in the economic model to determine the impact of treatment on response, using

analysis of individual patient-level data. As previously mentioned, to ensure comparability with UK clinical practice in terms of the proportion of patients with and without HC use, treatment effect data on change in Hb in the model was stratified by use of HC. Based on the proportion of responders and non-responders, and the resulting mean increase in Hb levels, the change from baseline in Hb for the voxelotor and placebo arm was calculated (Table 27). Different time points (at 72 weeks) and metrics (over 72 weeks) were explored in scenario analyses.

Table 27. Change in Hb from baseline (g/dL) at different time points, by HC use at baseline (intent-to-treat population).

	Baseline HC Change in Hb (SE)	**No baseline HC Change in Hb (SE)**
At 24 weeks (base case)		
All patients	[redacted]	[redacted]
24-week responders	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Non-responders*	[redacted]	[redacted]
At 72 weeks (scenario analysis)		
All patients	[redacted]	[redacted]
24-week responders	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Non-responders*	[redacted]	[redacted]
Over 72 weeks (scenario analysis)		
All patients	[redacted]	[redacted]
24-week responders	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Non-responders*	[redacted]	[redacted]

*Those missing the 20 and 24 week assessment are considered non-responders
CI, confidence interval; Hb, haemoglobin; HC, hydroxycarbamide; SE, standard error.
Source: GBT data on file

Applicability of HOPE trial to L2+ patients

The HOPE trial inclusion/exclusion criteria allowed for patients who did not report ineligibility for or a history of HC treatment at enrolment; these patients, if included, would be considered as receiving first line treatment with voxelotor. While this calls

into question the extent to which the aggregate efficacy results are applicable to the specific group of L2+ patients, several reasons suggest it is reasonable to assume that they are applicable.

Due to the inherent risks associated with enrolling patients in a clinical trial it is reasonable to conclude that clinicians who enrolled patients currently receiving HC did so because HC was delivering inadequate efficacy and their patient would benefit from an investigational product. In the HOPE trial, 64% of patients were receiving HC at baseline. British guidelines[4] recommend that all SCD patients should be offered HC, as do many others around the world. It is reasonable to assume that the 36% in the HOPE trial not receiving HC had been offered treatment with HC and had either used and stopped it, declined to use it, or had been evaluated for use of HC but were considered by their physician to be ineligible. Thus it is reasonable to assume that the HOPE study population is comparable to the proposed population for reimbursement (intolerant, ineligible, unwilling to take or have an inadequate response to HC), and the efficacy results from the trial can therefore be applied to the L2+ patient population that is modelled in the cost-utility model.

To assess the general applicability of the overall trial results to different subgroups, a heterogeneity of treatment effects analysis on the effects of voxelotor on change in Hb was implemented using subgroup analysis. Since there is limited information available on how L2+ patients differ from first line patients apart from the obvious prior HC use, subgroups were defined regarding various aspects in order to cover as broad a spectrum as possible.

Subgroup analyses were performed using two different datasets: the HOPE clinical trial[91] and the Symphony Health Solutions Integrated Dataverse Database (hereafter referred to as the Symphony database), a large, nationally representative provider-centric repository of US healthcare data that includes demographic information (e.g., age, sex) from medical claims (e.g., diagnoses and procedures), pharmacy claims (e.g., dosing and filling of drugs), and laboratory data for selected persons. Medical and pharmacy claims are sourced from adjudication networks, service bureaus, and pharmacy organisations serving patients participating in commercial health plans as well as public insurance programs (e.g., Medicaid and Medicare). These data are de-

identified prior to their release to study investigators, and their use for the research described herein is fully compliant with the Health Insurance Portability and Accountability Act Privacy Rule and federal guidance on Public Welfare and the Protection of Human Subjects. Data used from the Symphony database spanned from January 1, 2012, through to July 31, 2020. Voxelotor has been approved for use in the US since November 2019, and evidence from real-world clinical practice there provides additional evidence for the clinical effectiveness of voxelotor.

In both studies, subgroups were defined regarding prior or concomitant exposure to HC treatment, pathophysiologic variables (Hb level at baseline, prior number of VOCs in the past 12 months), and history of comorbidities, though exact definitions of the subgroups differed slightly between the two studies. A detailed description of the subgroups can be found in Appendix M.

Table 28 presents the results of the subgroup analyses, both from the HOPE and the Symphony data analyses. Overall, mean changes in Hb with voxelotor were similar across different subgroups. Across most subgroups, differences in treatment effects were not statistically significant, except in subgroups relating to baseline Hb levels and VOC history. The mean increase in Hb was significantly greater in individuals with lower baseline Hb values (≤7.5 g/dL vs >7.5g/dL in the analysis of the Symphony data). Additionally, the mean increase in Hb was significantly greater in patients with 1 VOC in the last 12 months as compared to 2-3 VOCs (HOPE data analysis), but the trend was not observed in patients with ≥4 VOCs: the effect on patients with ≥4 VOCs was similar to those with only one VOC. The analysis of the Symphony data did not indicate any differences in treatment effect by VOC history

Table 28. Analysis of voxelotor effect on change in Hb by subgroup

Subgroup	N	Mean change in Hb vs placebo / from baseline (95% CI)	p-value (difference)	Dataset used
Baseline HC use				
Yes	[redacted]	[redacted]		HOPE
No	[redacted]	[redacted]	[redacted]	
History of HC use				
Yes	[redacted]	[redacted]		HOPE
No	[redacted]	[redacted]	[redacted]	

HC use during the 90 days prior to voxelotor initiation				
Yes	[redacted]	[redacted]		Symphony
No	[redacted]	[redacted]	[redacted]	
Baseline Hb level				
<8 g/dL	[redacted]	[redacted]		HOPE
8 to <9 g/dL	[redacted]	[redacted]	[redacted]	
≥9 g/dL	[redacted]	[redacted]	[redacted]	
			[redacted]	
Baseline Hb level				
≤7.5 g/dL	[redacted]	[redacted]		Symphony
>7.5 g/dL	[redacted]	[redacted]	[redacted]	
VOC history during 12 months prior to voxelotor initiation				
1	[redacted]	[redacted]		HOPE
2-3	[redacted]	[redacted]	[redacted]	
≥4	[redacted]	[redacted]	[redacted]	
			[redacted]	
VOC history during 12 months prior to voxelotor initiation				
<2	[redacted]	[redacted]		Symphony
≥2	[redacted]	[redacted]	[redacted]	
[redacted]				
Yes	[redacted]	[redacted]		HOPE
No	[redacted]	[redacted]	[redacted]	
Presence of ≥1 comorbidity during 12 months prior to voxelotor initiation				
Yes	[redacted]	[redacted]		Symphony
No	[redacted]	[redacted]	[redacted]	
Note: The full results of both analyses (using the HOPE clinical trial and Symphony database) can be found in Appendix M.				

A limitation of this subgroup analysis is that the sample sizes of the subgroups may be too small to reliably detect differences in effect sizes, which accordingly can lead to false negatives. With sample sizes in clinical trials often determined based on power needed to detect treatment effects in the overall sample, this is a common challenge in subgroup analyses.[135] For most subgroups, however, the differences in treatment effects are minimal and likely to be insignificant. It can therefore be assumed that these are not merely false negatives due to small sample sizes. Particularly regarding HC use, which is the most important distinguishing feature of patients considered as first and second line, treatment effects hardly differ between

subgroups, and p-values for the statistical significance of the differences are close to one, thus clearly indicating insignificance.

A further consideration is that the real-world effect of voxelotor[96,136,137] is consistent with results observed in the clinical trial, measured as estimated Hb changes of around 1g/dL as seen in HOPE (at 72 weeks in HOPE, 89% of patients had achieved an Hb increase from baseline of >1g/dL). While one cannot guarantee that the results observed in the real-world are all in L2+ patients, according to clinical practice in the US, it is reasonable to assume that patients would have been offered HC as a first option.[138] As such, real-world effectiveness results from Symphony are likely to reflect second-line effectiveness. **Based on the results of the analyses which show a consistent treatment benefit across different subgroups, as well as in view of the above considerations, it is reasonable to apply the efficacy results from the HOPE clinical trial to the patient population in the cost-utility model.**

B.3.3.1.2. *Efficacy in the comparator arm*

As noted above, the most appropriate comparator is current SOC for L2+ patients. As the efficacy data from HOPE used in the model is stratified by HC, the differences in the proportion of patients on HC is corrected for in the model. However, as patients on RTT were excluded from the HOPE trial, any potential treatment effect of RTT is not captured in the HOPE trial. The relationship between Hb levels and RTT therapy was therefore explored in a literature review.

One SLR conducted in 2016, and updated in 2020, was identified that evaluated the efficacy of conservative or aggressive preoperative transfusion for the prevention of SCD or surgery-related complications in patients with SCD undergoing elective or emergency surgery.[139,140] Two further RCTs and one quasi-RCT were also identified, but no trials specifically evaluating RTT were identified. A second SLR conducted in 2016, and update in 2019, attempted to determine the impact of RTT versus SOC or other pharmacological treatment, on outcomes associated with chronic chest complications in patients of any age with SCD[141,142]; no RCTs were identified. In 2017, an SLR was conducted to identify RCTs evaluating the effectiveness of RTT versus standard of care or HC to reduce or prevent silent cerebral infarcts in patients

of any age with SCD.[143] No RCTs conducted in adults were identified. Two trials that included adolescents as well as children were identified in the SLR, but did not report results separately for adolescents.[144,145] Estcourt et al.[146] conducted another SLR in 2017 to identify RCTs evaluating the effectiveness of RTT versus standard of care or HC to prevent primary or secondary stroke in patients of any age with SCD. Two trials that included adolescents as well as children were identified in the SLR; however, these were the same two trials identified in the 2017 SLR for prevention of silent cerebral infarcts that did not report results separately for adolescents.[144,145]

Given the absence of applicable published data despite the extensive search, in the base case no change in Hb levels among patients on RTT is explicitly modelled. However, RTT is included as a covariate in the TTE analysis and RTT therefore influences the incidence of complications within the model (see Section B.3.3.3). Given the lack of data on the impact of RTT on Hb levels, an analysis was done using data from the Symphony database among patients receiving six or more transfusions per year. Results from that analysis are used in a scenario analysis which assumes a change of 0.8 g/dL in Hb following treatment with RTT. Unlike the Hb increase with voxelotor, which remains essentially constant whilst on treatment, the effect of transfusions on Hb decays over time, so that patients experience an initial boost to Hb but levels then gradually fall back until the next transfusion. This can lead to patients experiencing fatigue and other anaemia symptoms in the run-up to their next transfusion.[147] The waning of Hb levels between transfusions is not captured in the model. The scenario with the assumption of a 0.8 g/dL increase may overestimate the effect of transfusion on Hb over the treatment period. The scenario effectively assumes a constant relative difference of 0.8 g/dl for those on transfusion vs those not on transfusion. This is clearly a conservative assumption biasing against voxelotor for the reasons given above.

B.3.3.1.3. *Linking change in Hb to other SCD-related outcomes and events*

The chronic complications resulting from organ damage caused by the pathology of SCD evolve over time, and worsen as patients get older. The HOPE trial was not designed to show an effect on chronic complications, as these require a longer time scale for evaluation. The link to long-term outcomes in the modelling is therefore

made using associations between Hb concentration and outcomes derived from the Symphony database. To maximise applicability to the UK, patients in Symphony were weighted to patient characteristics derived from the HES/CPRD database using matching-adjusted indirect comparison methods. The process by which Hb is linked to other outcomes in the model is described fully in Section B.3.3.3. The strength of the surrogacy relationship is also discussed in that section.

B.3.3.1.4. *Treatment efficacy over time*

The base case assumes no treatment waning effect, that is, the change in Hb observed at 24 weeks is assumed to be the same over the time horizon of the model. Once treatment is discontinued, Hb returns to its baseline value for each simulated individual.

This assumption is supported by results after 72 weeks of treatment with voxelotor, which showed that after an initial peak in Hb, the mean change in Hb remains stable over time (up to 72 weeks in HOPE[91] and 144 weeks in the open-label extension[92,106]). A treatment waning effect was explored in a scenario analysis.

B.3.3.2. Treatment discontinuation

B.3.3.2.1. *Voxelotor*

Time to discontinuation (TTD) was based on data from the HOPE trial and was stratified in the model by responder status. TTD was defined as time from treatment initiation to discontinuation (please see Appendix O for additional detail). TTD was determined using Kaplan-Meier methods. A total of 90 patients were included in the analysis of whom 25 discontinued treatment during the study (the remaining 65 completed the trial on therapy).

[redacted]. Among Hb responders, [redacted] discontinued treatment during the study compared with [redacted] among non-responders. The Kaplan-Meier estimated probabilities of TTD at 72 weeks for Hb responders and non-responders were [redacted], respectively. Median TTD was not reached for either group. The Kaplan-Meier estimated TTD for patients receiving voxelotor 1500 mg daily, by responder status, is shown in Figure 22. Of note,

patients who discontinue voxelotor do not switch to another treatment. In the model base case, the Kaplan-Meier probabilities are converted to annualised rates and are used to populate exponential models with no covariates to estimate the time to discontinuation for each person treated with voxelotor.

Figure 22. Kaplan Meier estimated TTD for patients receiving voxelotor 1500 mg daily, by baseline hydroxycarbamide use

Time – weeks

B.3.3.2.2. *Regular transfusion therapy*

While alloimmunisation, among other AEs, may ultimately result in the discontinuation of CTT, rates of alloimmunisation among patients on RTT reported in the literature vary significantly (Table 29). Moreover, it is unclear how SCD patients are treated once RTT is discontinued. Given that SCD patients are recommended to receiving matched blood donation[66] which reduces the risk of alloimmunisation, it was assumed that 5.0% of patients who receive RTT discontinue annually. As this assumption is highly uncertain, it was tested in scenario analyses.

Table 29. Rates of alloimmunisation identified in the literature

Study design	%	Time period	Population	Source
RCT	6.78%	19.6 months	Children	Miller 2001[148]
RCT	4.0%	3 years	Children	DeBaun 2014[149]
Interventional	7.14%	12 years	Children	Mirre 2010[150]
Retrospective study	7.0%	11.28 months	Children	Franco 2020[151]
Literature review	4.4% - 76%	N/A	N/A	da Cunha Gomes 2019[152]
Literature review	0% - 7%	N/A	N/A	National Heart, Lung, and Blood Institute [153]

N/A: not applicable; RCT: randomised controlled trial

B.3.3.2.3. *Hydroxycarbamide*

Due to a lack of evidence identified in the literature, the yearly discontinuation rate for HC was assumed to be 5%. As this assumption is highly uncertain, it was tested in scenario analyses.

B.3.3.3. Linking clinical events to Hb level in the model

Extensive evidence has linked chronic haemolytic anaemia in SCD with adverse short-term and long-term outcomes, and even modest reductions in Hb are of clinical importance, correlating with SCD-related morbidity and mortality.[16,154] The evidence for the link between Hb levels and SCD-related outcomes is described in Section B.1.3.1.2, and the strong surrogacy relationship is evaluated in Section B.3.3.3.1 below.

To the best of our knowledge, the extent and strength of the underlying relationships between Hb and various potential complications of SCD have not been evaluated within a single, large, contemporaneous cohort of patients with SCD. This was therefore undertaken to inform the economic model, as described below and in Appendices P, Q and R.

The list of relevant SCD-related complications shown in Table 30 was developed in consultation with UK clinical experts at an advisory board held by video call in January 2022. As the exploration of some complications was not feasible, not all were included. For example, fatigue, strongly associated with anaemia/low Hb levels[155] and a major problem among SCD patients,[156] is an important complication but hard to correctly quantify in a database. Silent cerebral infarction, also a highly prevalent comorbidity in SCD patients,[157] with a positive association with stroke,[157] is another example of complications not explicitly modelled. It should be noted that, in the case of silent cerebral infarction, while not explicitly modelled, its impact on stroke is inherently embedded in the incidence of stroke estimated from a database.

Table 30. Complications evaluated in Symphony database and included in economic model.

Event	Included in the model
Acute renal failure	Yes
Arrythmias	Yes
Cardiomegaly	Yes
Cellulitis	No - uncredible direction of effect
Chronic kidney disease	Yes
Depression	No - uncredible direction of effect

End-stage renal disease	Yes - patients must be diagnosed with chronic kidney disease prior to having end-stage renal disease
Fatigue	Dropped due to identification issues
Gallstones	Yes
Heart failure	Yes
Hyposplenism	No- mostly in children
Leg ulcer	Yes
Myocardial infarction	No - uncredible direction of effect
Myocardial injury	No - uncredible direction of effect
Neurocognitive impairment	Dropped due to identification issues
Opioid dependence	No- small effect
Osteomyelitis	Yes
Osteonecrosis	Yes
Pulmonary hypertension	Yes
Pneumonia	See vaso-occlusive crisis
Priapism	Yes
Retinopathy	No - uncredible direction of effect
Silent cerebral infarct	No - due to identification issues
Sepsis	Yes
Splenic, hepatic sequestration	Dropped due to identification issues
Stroke	Yes
Vaso-occlusive crisis	Yes - joint endpoint which includes vaso-occlusive crises complicating to acute chest syndrome (ACS) or not. In HOPE, ACS and pneumonia are deemed indistinguishable and therefore considered the same. When looking in databases, there is no code for ACS and pneumonia is therefore used as proxy for ACS.
ACS, acute chest syndrome	

Two data sources were identified to determine the impact of Hb levels on clinical events: one in the US (Symphony, described previously) and one in the UK (Hospital Episode Statistics [HES] in the Clinical Practice Research Database [CPRD]). HES provides secondary care data, including admitted patient care, outpatient and datasets from accident and emergency department, while CPRD is primary care data. While it would have potentially been more relevant to use the UK dataset, in the relevant L2+ population there was a sample size of only 2,106 patients who had Hb levels in the HES/CPRD database (Hb values were missing for 1847 patients). Thus, given the large data available in Symphony, it was decided this database would be a more suitable source. The Symphony dataset was matched to the target

HES/CPRD population, thus retaining a large sample size aligned with a relevant UK population. Details on the selection of the relevant patient population are described in Appendix P.

Patients in the Symphony database were weighted using matching-adjusted indirect comparison methods. A comparison of the Symphony and HES/CPRD dataset, alongside the HOPE trial is presented in Table 31.

Table 31. Comparison of baseline characteristics in Symphony and HES/CPRD

Characteristic	Symphony	HES/CPRD		HOPE
	All Patients (N = 14,971)	All Patients (N = 3,953)	L2+ patients (N = 2,106)	N = 274
Age, mean (SD), y	[redacted]	[redacted]	[redacted]	28 (11.6)
Age 12 - <18 – no. (%)	[redacted]	[redacted]	[redacted]	46 (16.8)
Female – n (%)	[redacted]	[redacted]	[redacted]	159 (58.0)
Number with Hb reading	[redacted]	[redacted]	[redacted]	274 (100)
Index Hb value, mean (SD), mg/dL	[redacted]	[redacted]	[redacted]	[redacted]
VOCs in the last 12 months - no. (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1-2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5 or more	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxycarbamide treatment - n (%)				
Current	[redacted]	[redacted]	[redacted]	179 (65.3)
Prior	[redacted]	[redacted]	[redacted]	NA
Regular transfusion therapy - n (%)				
Current	[redacted]	[redacted]	[redacted]	0
Prior	[redacted]	[redacted]	[redacted]	NA
History of complications - n (%)				
ARF	[redacted]	[redacted]	[redacted]	
Arrythmias	[redacted]	[redacted]	[redacted]	
Cardiomegaly	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]			[redacted]
CKD	[redacted]	[redacted]	[redacted]	[redacted]
ESRD	[redacted]	[redacted]	[redacted]	

Any kidney failure	[redacted]	[redacted]	[redacted]	
Gallstones	[redacted]	[redacted]	[redacted]	
Heart failure	[redacted]	[redacted]	[redacted]	
Hyposplenism	[redacted]			[redacted]
Leg ulcer	[redacted]	[redacted]	[redacted]	[redacted]
Osteomyelitis	[redacted]	[redacted]	[redacted]	[redacted]
Osteonecrosis	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]			[redacted]
Priapism - male gender only	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]

ARF, acute renal failure; CKD, chronic kidney disease; ESRD, end stage renal disease; Hb, haemoglobin; NA, not applicable; SCD, sickle cell disease; SD, standard deviation; TTE, time to event; VOC, vaso-occlusive crises; y, year

Following the identification of the relevant population, a study was conducted using real-world data from Symphony, in order to characterise the patient population at baseline inclusive of comorbidities history from which individual characteristics of simulated patients could be drawn correctly accounting for the correlation within comorbidities and their link to Hb levels.[158] Further, the larger sample size available in Symphony allowed for the use of all important covariates (notably Hb). Study outcomes (i.e., events) were selected based on review of the literature and clinical expert opinion and included acute renal failure (ARF), arrythmias, cardiomegaly, CKD, end stage renal disease (ESRD), gallstones, heart failure, leg ulcer, osteomyelitis, osteonecrosis, pulmonary hypertension, pneumonia or VOC (composite outcome), priapism, sepsis, and stroke. CKD was defined to include only Stages 3+ disease (i.e., stage 1 and 2 CKD were not considered as events). The first occurrences of each event were assessed during the “follow-up period”, which was defined as the period beginning with the index date and ending with the last activity date (information on health plan enrolment is not available in the Symphony Database). Analyses of “chronic” conditions—CKD, heart failure, and pulmonary hypertension (PH)—were limited to patients without history of the condition at the index date. Analyses of ESRD were limited to patients with history of CKD and analyses of priapism were limited to males only. With the exception of stroke, the occurrence of the event during the follow-up period was identified based either (a) ≥1

acute-care hospitalisation with a corresponding principal or secondary diagnosis code or (b) ≥2 ambulatory encounters, excluding laboratory visits, with a diagnosis code in any position separated by at least 30 days. For stroke, occurrence of the event was identified based on ≥1 acute-care hospitalisation with a corresponding principal or secondary diagnosis code (i.e., and hospitalisation for stroke was required). Stroke included ischemic and haemorrhagic events. Further, by including RTT as a covariate in the TTE analysis, RTT influences the incidence of complications.

Following this, for each event, estimated regression equations were used with index Hb value, age, number of VOCs during the 12-months pre-index, and the interaction between Hb and number of VOCs during the 12-months pre-index entered as continuous variables. The regression equations generated predicted survival distributions which were compared against Kaplan Meier distributions. An exponential survival distribution was used as there was no reason to believe there would be any temporal association between the hazard and time since the Hb assessment. This assumption was confirmed by visual inspection of the hazard functions which were generally constant. The TTE analysis was assessed using accelerated failure time (AFT) regression (Table 32 and Table 33). For patients who experienced the complication during the follow-up period, the TTE for each outcome was defined as the time (in months) from index Hb assessment to the date of the first occurrence of the complication during the follow-up period. For remaining patients, the TTE for the complication was set to the last activity date. Patients who did not experience the complication during the follow-up period were censored. For further details on the TTE analysis please see Appendix Q.

Table 32. AFT regressions patients weighted to match patients in HES/CPRD

	ARF	Arrythmias	Cardio-megaly	CKD	ESRD	Gall-stones	Heart Failure	Leg ulcer	Osteo-myelitis
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Effective Sample Size	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median Follow-up, Years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate (Months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Covariates									
Age, Years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female (vs male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Index Hb Value (mg/dL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC Count	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb x VOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxycarbamide treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regular transfusion therapy**									
Ever	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of complications (vs. no)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arrythmias	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiomegaly	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESRD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gallstones	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leg ulcer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteomyelitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteonecrosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pulmonary hypertension	[redacted]								
Pneumonia or VOC	[redacted]								
Priapism									
Sepsis	[redacted]								
Stroke	[redacted]								
Probability of event at 12 months	[redacted]								
Kaplan-Meier	[redacted]								
Regression-predicted	[redacted]								

*P-value<.05; †P-value<.01 ‡ P-value<.001; § P-value<.0001

**Defined as ≥6 transfusions per year

ARF, acute renal failure; CKD, chronic kidney disease; ESRD, end stage renal disease; VOC, vaso-occlusive crises.

Table 33. AFT regressions patients weighted to match patients in HES/CPRD continued

	Osteo-necrosis	Pulmonary Hypertension	Pneumonia or VOC	Priapism	Sepsis	Stroke
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Effective Sample Size	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median Follow-up, Years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate (Months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Covariates						
Age, Years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female (vs male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Index Hb Value (mg/dL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC Count	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb x VOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxycarbamide treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regular transfusion therapy**						
Ever	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of complications (vs. no)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arrythmias	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiomegaly	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESRD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gallstones	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leg ulcer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteomyelitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteonecrosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia or VOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Priapism						
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probability of event at 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regression-predicted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*P-value<.05; †P-value<.01 ‡ P-value<.001; § P-value<.0001

ARF, acute renal failure; CKD, chronic kidney disease; ESRD, end stage renal disease; VOC, vaso-occlusive crises.

The incidence of almost all complications (with the exception of ESRD) are statistically significantly linked to Hb level. The impact of Hb level on complication incidence varies between [redacted] for stroke and [redacted] for PH. Baseline Hb level was estimated to have the largest impact on the reduction in incidence of PH, leg ulcer, CKD and Cardiomegaly.

The average relative difference between the probability of event at 12 months based on the regression-predicted estimate when compared to the Kaplan-Meier based estimate is [redacted]% thereby suggesting that, if anything the model is conservative in that the lower the complications incidence the less the room for voxelotor through Hb to reduce it. As such, if on average the regression-predicted estimate is lower than the Kaplan-Meier based estimate, the model could potentially be assuming an underestimation of event incidence. However, this is not the case. As shown in the validation section (Section B.3.13), the model predicted incidence is closely in line with available UK data.

B.3.3.3.1. *Strength of the surrogacy relationship between Hb and outcomes in SCD*

The link to long-term outcomes in the modelling is made using associations between Hb concentration and a range of SCD-related outcomes (SCD-related events and complications), taken from the Symphony database and validated using HES/CPRD data. The use of surrogate endpoints in decision making is outlined in Section 4.6 (modelling methods) of the NICE manual on health technology evaluations.[159] This refers to the three levels of evidence for surrogate relationships proposed by Ciani et al. 2017.[160] An evaluation of the surrogacy relationship using this framework is set out in Table 34 below, showing strong evidence to support the relationship.

Table 34 Evidence for surrogate relationship between Hb and SCD outcomes (association between higher Hb and reduced risk of events and complications)

Level 3: biological plausibility of relation between surrogate end point and final outcomes
In SCD there is a biologically plausible link between Hb levels and risk of SCD-related events and complications. Anaemia (low Hb level) in SCD is the result of haemolysis (red

cell breakdown) and is termed haemolytic anaemia. As explained in Section B.1.3.1.1, the fundamental molecular event in SCD is Hb polymerisation: polymerisation leads to RBC sickling, and sickling is the cause of haemolysis. Lower Hb concentration is a direct indicator of increased haemolysis, which in turn indicates increased disease activity at the pathophysiological level and thus poorer red blood cell health. Over the long term, higher disease activity can plausibly be expected to result in an increased risk of SCD-related events and complications.

Level 2: consistent association between surrogate end point and final outcomes (usually derived from epidemiological or observational studies).

There is a large amount of observational evidence linking Hb levels to outcomes in SCD.
1: A meta-analysis by Ataga et al. of 41 studies (mainly retrospective and prospective cohort studies) showed lower haemoglobin concentration was consistently associated with higher incidence or history of stroke, silent cerebral infarct, increased transcranial doppler (TCD) velocity, albuminuria, pulmonary hypertension and mortality, in SCD patients of all ages (see Section B.1.3.1.2 for detail; the study was funded by GBT).[16]

2: An association between Hb levels and time to event for a range of outcomes was found in both the Symphony health claims database and the HES/CPRD database – see Appendices P and Q for details.

3: An additional analysis of HES/CPRD by Telfer et al.[17] found that an increase in Hb of 1 g/dL was associated with a statistically significant reduction in risk for 6 common end organ damage outcomes and clinical complications (leg ulcer, pulmonary hypertension, chronic kidney disease, end-stage renal disease, acute chest syndrome and stroke; see Section B.1.3.1.2 for details) over a 12-year period.

Evidence is also available from a number of studies published after the inclusion date for the Ataga meta-analysis, as described in Section B.1.3.1.2.

Level 1: the technology's effect on the surrogate end point corresponds to commensurate effect on the final outcome as shown in randomised controlled trials

Level 1 requires RCTs that report both the surrogate and the final outcomes.[161] SCD is a rare condition and the systematic review and meta-analysis by Ataga et al. of studies relating Hb concentrations to outcomes identified only 1 RCT (literature search dated February 2019).[16] However, 40 observational studies were available, and a meta-analysis was performed, meaning that this study provides a higher level of evidence than individual studies alone. The authors concluded that “chronic anemia is associated with worse clinical outcomes in individuals with SCD and even modest increases in hemoglobin concentration may be beneficial in this patient population”.

The only RCT available of voxelotor in SCD is the HOPE study, which showed a mean change from baseline in Hb of 1.3 g/dL (SD 0.9) over the 72-week treatment period.[91] As many SCD-related complications develop progressively over a long period, the effect of the Hb improvement with voxelotor on many of these outcomes could not be captured, and the trial was not powered to do so. Patients treated with voxelotor had numerically lower incidences of VOCs than the placebo group[91] and there was a potential clinical

benefit for patients with leg ulcers;[93] however, these differences did not reach statistical significance.
Summary In summary, the relationship between higher Hb levels and reduced risk of SCD-related events and complications is biologically plausible and supported by extensive observational evidence, including a meta-analysis of mainly observational data. In addition, there is some evidence from the HOPE RCT to support the association. Taken together, this constitutes strong evidence for the surrogacy relationship.

B.3.3.4. Mortality

Organ damage and vaso-occlusion in SCD can cause premature mortality from conditions such as liver failure, lung injury, kidney failure, infection, stroke, pulmonary hypertension, and acute chest syndrome.[162-164]

To determine mortality in the model excess mortality was incorporated for acute renal failure (ARF), sepsis, stroke, pulmonary hypertension, chronic kidney disease (CKD), end-stage renal disease (ESRD), and VOC. Excess mortality rates associated with specific comorbidities were derived from the HES CPRD database.[165] Briefly, 12,331 patients with SCD were identified from both the CPRD and HES datasets using diagnostic codes (SNOMED and ICD-10 codes respectively). Cases and controls were matched using simple matching on age at index, gender and general practitioner practice. Simple mortality estimates show that the most common causes of death due to complications are:

- Stroke
- Pulmonary hypertension
- VOC
- Sepsis
- Renal insufficiency including CKD, ESRD, and ARF.

We defined the most common complications that cause of death for patients with SCD as those that affected >0.1% of the total cohort (including those who did not die). Excess mortality is measured as the difference between the reported number of deaths

for patients with SCD in a given period of time and the estimate of the expected deaths for that period had the condition (SCD in this case) not occurred. To produce an estimate of expected deaths, firstly a regression model is fitted using historical death data on controls, meaning no SCD patients. The regression coefficients derived from this model are then used to project the number of deaths normally expected if no further conditions were present on cases, meaning SCD patients. This procedure was conducted for the period of 1 April 2007 to 31 March 2019, and recorded and projected death counts were retrieved for every six months interval. For each complication a standardised mortality ratio (SMR) was calculated using the following formula:

$$SMR = \frac{reported\ deaths\ for\ those\ having\ complications}{expected\ deaths\ for\ those\ having\ complications\ in\ the\ absence\ of\ complication}$$

The mortality in the model was estimated by first calculating an age/sex adjusted general population mortality rate which were taken from the UK Office for National Statistics.[166] This rate was then adjusted by applying the maximum of the SMR for any condition the person in the model might have. It was thought that by accounting for the major cause of death in SCD, that any Hb link to death would be indirectly accounted for, and therefore no further adjustment was made. The only exception to this was that for stroke the case fatality rate was applied to the acute event to account for the fact that persons surviving to be followed up in the database were already likely to have survived the acute stroke episode.[167]

Table 35. Excess mortality due to complications from SCD

Parameter	Excess mortality input	Source
Case fatality (% of acute event)		
Stroke	13%	Strouse [167]
Standardised mortality ratio		
ARF	[redacted]	HES CPRD[165]
CKD	[redacted]	
ESRD	[redacted]	

Pulmonary hypertension	[redacted]	
Sepsis	[redacted]	
Stroke	[redacted]	
VOC	[redacted]	
ARF, acute renal failure; CKD, chronic kidney disease, ESRD, end-stage renal disease, SCD, sickle cell disease; SMR, standardised mortality ratio; VOC, vaso-occlusive crisis.		

B.3.3.5. Role of clinical experts

UK clinical experts were consulted extensively. The main consultation process was a modified Delphi panel exercise, which is reported in Appendix U. In addition, an advisory board with clinicians and payers was held by video conference in January 2022; incidences where information came from this advisory board have been noted in the text. Additional follow-up consultations were held with clinical experts by email and teleconference.

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

HRQoL outcomes were collected in the HOPE trial, using EQ-5D-5L, a standardised instrument for measuring health outcomes. Patients were assessed at baseline and every 4 weeks up to week 24, then every 12 weeks up to week 72. Data from the EQ-5D-5L, including the index score and visual analogue scale (VAS) score were summarised descriptively by treatment group. Results are shown in Section B.2.6.6, Table 13.

B.3.4.2. Health-related quality-of-life studies

An SLR was conducted in line with NICE requirements to identify health state utility and disutility values for adolescents (≥ 12 years) and adults (≥ 18 years) with SCD, irrespective of prior treatment. Database searches were conducted from database inception to 06 April 2022, incorporating several SLR updates. In total 15 studies from 17 publications met the eligibility criteria and were included in this review. Due to the wide range of complications experienced by patients with SCD, two targeted literature

reviews (TLRs) were conducted to supplement the SLR and capture the utilities and disutilities of complications commonly associated with SCD. Database searches for complications TLR 1 were conducted from database inception to 06 April 2022 and identified 76 studies from 85 publications which were included in this review. Database searches for complications TLR 2 captured studies published from January 2011 to 07 April 2022 and identified 82 unique studies from 86 publications which were included in this review. Full details of the reviews, including the PRISMA diagrams and a description of all relevant studies informing the model, are given in Appendix H.

B.3.4.3. Adverse reactions

The effects of adverse reactions on HRQoL are described under 'utility decrements due to treatments' in Section B.3.4.4.2 below.

B.3.4.4. Health-related quality-of-life data used in the cost-effectiveness analysis

B.3.4.4.1. *Baseline utilities*

To derive the baseline utility for the model, the overall population utility was taken from UK general population utility values, adjusted for sex and age to match the HOPE trial population.[168] The overall population utility at base was calculated to be [redacted] (standard error: [redacted]).[169] A range of utility decrements were then applied as explained in the next section.

B.3.4.4.2. *Utility decrements*

Utility decrement due to SCD

In order to determine the utility decrement due to SCD, EQ-5D-5L data from the HOPE trial was mapped to EQ-5D-3L using UK tariffs based on the method recommended by NICE[161] and developed by the Decision Support Unit.[170] The estimated mean utility among SCD patients was 0.831. Applying the mean utility from the general population of the same age and sex (mean age 29 years, 42% male), based on Ara et al.[168] results in a utility decrement due to SCD of [redacted] (standard error: [redacted]).

Utility decrement due to treatments

Utility decrements associated with HC were not included. An analysis conducted at the University of Connecticut on the MeSH RCT found that there was no difference in HRQoL in SCD patients on HC versus not on HC (see Appendix M).[169] In light of this, it was assumed that any AEs occurring while on treatment with HC would either not have a major impact on HRQoL or that the positive impact from the efficacy of the drug would compensate for any negative AE effects.

Utility decrements associated with RTT were included. The disutility of being on regular transfusions was taken from a study by Osborne et al. of adult thalassemia patients on transfusion;[171] this source was used by Cherry et al. in a cost-effectiveness evaluation carried out under the NIHR Health Technology Assessment programme, and it was assumed that the utility values in thalassemia patients are identical to those of SCD patients. Using the values reported in Osborne et al.[171], Cherry et al. estimated the disutility of being on RTT by calculating the difference between "pre-stroke off transfusion" and "pre-stroke on transfusion", which was calculated to be 0.03.[172] This decrement was applied to patients on RTT in the model.

No utility decrement was applied for AEs on voxelotor. This is because the EQ-5D data from the trial found no significant difference between the voxelotor and placebo arms. It was therefore assumed that treatment with voxelotor does not adversely affect HRQoL.

Utility decrement due to complications

Utility decrements for both acute and chronic complications were incorporated into the model. For acute complications, disutilities were applied once on event occurrence and were derived by multiplying the utility decrement by the duration of each complication (Table 36). Where data on duration were not available, durations were estimated by doctors from GBT's medical department. For chronic complications, disutilities were applied following diagnosis on an annual basis. As VOCs can be treated at home or in hospital, the proportion of VOCs treated at home was determined from the International

Sickle Cell World Assessment Survey (SWAY) that found that among UK patients (n=299), 42% of VOCs were managed at home in the last 12 months.[173].

Table 36. Utility decrements associated with SCD complications

Complication	Disutility	Duration (days)[a]	Source
Acute complications			
Acute renal failure	0.27	182.63	Weighted average of utility decrements: in ICU (assumed duration of eight days), in hospital ward (assumed duration: 19 days), and post-discharge (remaining days up to six months after event), based on utility values reported in Hall et al.[174] As Hernandez et al.[175] reports that at 12 months, utility values had returned to baseline, a duration of only 6 months was considered. In Hall et al.,[174] values on patient disutility while in ICU are assumed to be equivalent to the utility of an unconscious patient reported in the EQ-5D scoring manual (–0.402 for eight days)[Kind et al.[176]]. The utility values of patients in the hospital ward and post-hospital discharge states was derived from a clinical trial (Hernández et al.[175]): 0.44 for in hospital ward (post-ICU), 0.62 for discharged (post-ICU). Applying a mean utility for the general population of the same age and sex based on Ara et al. [168] results in a disutility of 1.231 for the first 8 days in ICU, a disutility of 0.389 for the first 19 in ward, and a disutility of 0.209 for the remaining days (up to six months)
Arrythmia	0.07	30.44	Based on the value from Evans et al. [177] as reported in NICE TA743 - Table 33[130] Disutility is the difference in utility of patients with cardiac arrhythmia undergoing ablation therapy 1-year after procedure (0.84) and before procedure (0.77).
Cardiomegaly	0.07	365.25	Same as arrythmia
Gallstones	0.12	42.15	Based on the disutility value for gallstones used in Appendix J of NICE CG188[178], as reported in NICE TA743 - Table 33.[130]

			Disutility is calculated as the difference between the utility of patients at 6-weeks post recovery from surgery for gallstones (0.849) and patients hospitalised with gallstones (0.729).
Leg ulcer	0.15	135.89	Weighted average of four studies, both in disutility and duration. Michaels et al.[179] reports the utilities of 213 UK patients, with a disutility of 0.128 and a time to healing of 62.5 days. This value as also used in NICE TA743 - Table 33.[130] Guest et al.[180] reports the utilities based on 90 patients in the UK, and found a disutility of 0.087 with a time to healing of 92.8 days. Epstein et al.[181] reports utilities of 450 patients recruited from 20 vascular centres in the UK and found a disutility of 0.091; the time to healing was not reported. Chuang et al.[182] reports utilities in 337 patients collected alongside the VenUS III trial and found a disutility of 0.263 with a time to healing of 252.3 days.
Osteomyelitis	0.466	651.36	Weighted average of two studies. Hotchen et al. [183], as reported in NICE TA 743 - Table 33.[184], reports the disutility among 71 patients as the difference in utility value of patients with long bone osteomyelitis undergoing surgery at baseline 1-year after procedure (0.740) and before surgery (0.284). Arshad et al. [185]reports the disutility among 14 patients as the difference in utility value for patients after a 21.4 month follow-up with osteomyelitis of the femur (0.360) versus age and gender-matched general UK population (0.879).
Osteonecrosis	0.13	121.75	Weighted average of utility decrements in different osteonecrosis stages as reported in Marks et al.[186] Reported utilities by Bucholz-Ogden grades were 0.8 (Stage I, n-7), 0.81 (Stage II, n = 77), 0.82 (Stage III, n = 18) and 0.78 (Stage IV, N = 15). Applying a mean utility for the general population of the same age based on Kind et al.[176] results in an average disutility of 0.13.
Pneumonia	0.688	60.88	Weighted average of two studies. It was assumed that the disutility of pneumonia is the same as the disutility associated with acute chest syndrome (ACS), which, according to the HOPE clinical trial definition, is undistinguishable from pneumonia. Lloyd et al.[187], as reported in NICE TA 743 - Table 33[184], reports the disutility among 112 patients with asthma, as the difference in utility between patients with chronic

			asthma (0.89) and patients with exacerbations requiring hospitalization (0.33), resulting in a disutility of 0.560. Galante et al.[188] reports the utility among 73 hospitalized pneumonia patients (0.035) versus the general population (0.921), resulting in a disutility of 0.886.
Priapism	0	---	An appropriate disutility value could not be identified for priapism, thus, no disutility value was applied in the model. As priapism is only expected to last a few hours, the per cycle disutility value would be expected to be close to zero; the assumption of zero disutility is not expected to have a major impact on the results. This assumption aligns with NICE TA743 - Table 33.[130]
Sepsis	0.223	365.25	Weighted average of four studies providing disutility at different time points. Drabinski et al.[189] reports the disutility as the difference between the utility of sepsis survivors at day 30 (0.53) and general population (0.827). Of note, the calculations in NICE TA 743 - Table 33 [184], assume the disutility to be the difference between the utility of sepsis survivors at day 180 (0.69) and sepsis survivors at day 30 (0.53), reported in Drabinski et al.[189]. Contrin et al.[190] reports the utility of Brazilian patients with one-year minimum follow-up. Disutility was calculated as the difference between the utility for sepsis (-0.295) versus the general population (0.827). Galante et al.[188] reports the disutility of sepsis in the ICU as the difference between sepsis (-0.295) and general population (0.921). Gardner et al.[191] reports the utility among US patients. Disutility calculated as the difference between the utility at 12 months (0.579) and the generation population (0.832); this difference is the same at 12 months. Duration of the disutility is assumed to be 8 days in ICU (Contrin et al.[190]), 12 days in ward (Contrin et al.[190]) and the remaining period up to one ward post-discharge (Gardner et al.[191]). For each period, the disutility was taken from Galante et al.[188] for the ICU[188], Drabinski et al. for ward [189]and for post-discharge, a weighted average of Gardner et al.[191], Contrin et al. [190] and Galante et al.{Galante, 2011 #196.
Vaso-occlusive crisis	0.033	365.25	The total utility decrement used for vaso-occlusive crises (VOCs) is composed of the disutility of a VOC plus the disutility of ACS/pneumonia for patients who experience this complication. Based on utility values from Anie et al. [192], as used in NICE TA743 - Table 34 [130], the disutility of a VOC is 0.007. The disutility of ACS/pneumonia is 0.56 per two-month episode [187], which equals 0.093 when transformed to a per cycle disutility.

			The probability of an ACS/pneumonia complication was derived from VOC and pneumonia events reported in the HOPE clinical trial (Tables 30 and 32 of the CSR)[100] for all treatment arms (58 pneumonia events per 763 VOCs, 7.6%).
Chronic complications			
Chronic kidney disease	0.053	Chronic	Weighted average of utility decrements derived from Jesky et al.[193], Blakeman et al.[194] and Eriksson et al.[195] and Nguyen et al.[196]. Jesky et al.[193] reports the utility among CKD Stage 3 patients (average age 60 years, 68% male) of 0.8. Applying a mean utility for the general population of the same age and sex based on Ara et al. [168] results in a disutility of 0.030. Blakeman et al.[194] reports the utility among 221 CKD Stage 3 patients (average age 72 years, 41% male) of 0.67. Applying a mean utility for the general population of the same age and sex based on Ara et al. [168] results in a disutility of 0.099. Eriksson et al.[195] reports the utility among 864 CKD Stage 3 patients (average 63 years old, 60% male) with anaemia of 0.78. Applying a mean utility for the general population of the same age and sex based on Ara et al. [168] results in a disutility of 0.049 Nguyen et al.[196] reports the utility among 190 CKD Stage 3 patients. The mean disutility among stage CKD 3A patients without albuminuria is 0.04 and the mean utility among stage CKD 3B patients with albuminuria is 0.18
End stage renal disease	0.083	Chronic	Weighted average of utility decrements derived from Jesky et al.[193] and Eriksson et al.[195] Jesky et al.[193] reports the utility among 498 CKD Stage 4/5 patients (average age 68 years, 58% male) of 0.735. Applying a mean utility for the general population of the same age and sex based on Ara et al. [168] results in a disutility of 0.057. Eriksson et al.[195] reports the utility among 343 CKD Stage 4 and 509 dialysis patients (average age 66 years, 60% male) of 0.705. Applying a mean utility for the general population of the same age and sex based on Ara et al. [168] results in a disutility of 0.097. Nguyen et al.[196] reports the utility among 5 CKD Stage 4/5 patients (average age 72 years). The mean disutility among stage CKD 4/5 patients is 0.28.

Heart failure	0.306	Chronic	Based on Matza et al.[197] who estimated health state utilities through interviews with UK general population respondents (n = 200; average age 46.6 years, 45% male) using the time trade-off technique. The reported mean utility for acute heart failure was 0.57. Applying a mean utility for the general population of the same age and sex based on Ara et al.[168] results in a disutility of 0.306.
Pulmonary hypertension	0.21	Chronic	Keough et al.[198], estimated QoL data from 177 patients participating in the VITAL study (effect of bosentan on QoL in patients with WHO Functional Class III or IV pulmonary hypertension). Disutility is estimated as the difference in utility of patients in functional class I (0.73) and functional class IV (0.52); assuming patients would have more severe pulmonary hypertension if admitted to hospital for acute event, as used in NICE ID12 (discontinued [GID-TAG382]). The same values are reported in NICE TA743 - Table 33[130].
Stroke, months 1-6	0.546	Chronic	Matza et al.[197] estimated the health state utilities representing different cardiovascular conditions through interviews with 200 UK general population respondents (n = 200, mean age 46.6 years, 45% male). Participants valued the health states in time trade-off tasks with time horizons of one year for acute states and ten years for chronic states. A mean utility of 0.33 was reported for acute stroke and 0.52 for chronic stroke, resulting in a disutility of 0.546 for acute stroke and 0.356 for chronic stroke when considering the same age and sex based utility of Ara et al.[168].
Stroke, months 7-12	0.546	Chronic	
Stroke, months 13+	0.36	Chronic	

ACS, acute chest syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; CSR, clinical study report; ESRD, end-stage renal disease; ICU, intensive care unit; RCT, randomised controlled trial; QoL, quality of life; UK, United Kingdom; VOC, vaso-occlusive crises.

[a]All estimates of duration provided by clinical opinion unless otherwise stated.[169]

B.3.4.4.3. *SCD and treatment response*

In the HOPE trial, no difference in utility was noted between treatments arms nor over time compared to baseline. However, the mean utilities recorded in both groups were very close to population norms for the UK. Additionally, they were higher than utilities reported in the literature for general SCD patients.[192,199] Both of these observations mean it is questionable how well these values reflect utilities in patients with SCD beyond the trial. Furthermore, utility values stratified by Hb level were required to inform the model. The literature review of utility, described in Appendix H, did not identify any studies reporting utility by Hb level in SCD. Studies of utility by Hb level in other health conditions were not considered relevant: other subtypes of anaemia (e.g. iron deficiency anaemia, or anaemia caused by reduced erythropoietin production such as found in CKD) are caused by different physiological processes and are not generalisable to haemolytic anaemia in SCD, as haemolytic anaemia is just one manifestation of the cascade of pathology that results from haemolysis (see Section B.1.3.1.1), pathology which is not equivalent to that seen in other types of anaemia.

In the absence of published data, an analysis was performed on data from the Patient Journey survey, a study sponsored by GBT enrolling patients (n = [redacted]) with SCD from the UK ([redacted]%), France ([redacted]%), Brazil ([redacted]%), Germany ([redacted]%), Spain ([redacted]%), Italy ([redacted]%), and Canada ([redacted]%), described in Appendix T.[169] Survey data collected included demography, symptoms, current and previous treatments, Hb levels, and HRQoL, among others. To assess the relationship between Hb levels and HRQoL, linear models of utilities as a function of Hb were adopted including patient age as a covariate. Details of survey methodology and statistical models are given in Appendix T. The resulting estimated utility increment per 1g/dL increase in Hb was calculated to be [redacted] (Table 37). This relationship was applied in the model to all patients, irrespective of treatment arm.

Table 37. Results from the linear model of utilities on Hb levels and age.

Parameter	Estimate	SE	p-value
Intercept	[redacted]	[redacted]	[redacted]
Hb	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]
Hb, haemoglobin; SE, standard error. Residual standard error: 0.2347			

B.3.4.4.4. *Caregiver disutilities*

SCD affects caregivers as well as patients themselves, as detailed in Section B.1.3.1.7. Thus, the model accounted for caregiver disutilities in the base case for multiple acute and chronic conditions associated with SCD (Table 38). Caregiver disutilities were included as a one-off utility upon event.

B.3.4.4.5. *Summary of utility values for cost-effectiveness analysis*

As a large number of event-related disutilities are used in the model, a single summary table has not been created. Values can be found in the individual tables in this section.

Table 38. Annual caregiver disutilities associated with complications

Complication	Disutility	Source
Acute renal failure	0.03	Thomas et al.[200] assessed informal carers' HRQoL depending on the number of hours of care provided, based on a sample of 195,364 carers in England. From informal feedback from three UK SCD patients, it was assumed that any week with an event implies 50+ hours of support (with an associated utility of 0.77 (95% CI, 0.76–0.77), compared to the standard 10-19 hours of support (with an associated utility of 0.80 (95%CI 0.80–0.81). The difference (0.03) was assumed to be the disutility for one year of support; the duration of acute renal failure is assumed to be 182.63 days.
Arrythmias	0.03	Squire et al.[201] assessed the HRQoL of heart failure patients and their caregivers in England. The EQ-5D-5L weighted index for caregivers was 0.75 for a mean age of 69 years. Compared to the UK norm for EQ-5D at a mean age of 70 years (0.78), the disutility was assumed to be 0.03; the duration of arrythmias is assumed to be 30.44 days
Cardiomegaly	0.03	Squire et al.[201] assessed the HRQoL of heart failure patients and their caregivers in England. The EQ-5D-5L weighted index for caregivers was 0.75 for a mean age of 69 years. Compared to the UK norm for EQ-5D at a mean age of 70 years (0.78), the disutility was assumed to be 0.03; the duration of cardiomegaly is assumed to be 365.25 days.
Chronic kidney disease	0.06	Davidson et al.[202] reported weighted QALYs based on interviews with caregivers of older people in a Swedish population. Davidson reports the R-QALY weight, defined as the effect on a relative's QALY weight due to being a relative of a disabled or sick individual. The R-QALY is calculated as family caregiver utility minus hypothetical scenario of a family member in good health minus the age/sex-adjusted population mean caregivers disutility. The disutility is applied on a chronic basis.
End stage renal disease	0.05	Paschou et al.[203] reported the mean EQ-5D utility from spouses of dialysis independent patients as 0.769 and from spouses of dialysis dependent patients as 0.716. The disutility for caregivers of end-stage renal disease was calculated as the difference of the two. The disutility is applied on a chronic basis.

Gallstones	0.03	Thomas et al.[200] assessed informal carers' HRQoL depending on the number of hours of care provided, based on a sample of 195,364 carers in England. From informal feedback from three UK SCD patients, it was assumed that any week with an event implies 50+ hours of support (with an associated utility of 0.77 (95% CI, 0.76–0.77), compared to the standard 10-19 hours of support (with an associated utility of 0.80 (95%CI 0.80–0.81). The difference (0.03) was assumed to be the disutility for the duration of the event (six weeks or 42.15 days)
Heart failure	0.03	Squire et al. [201] assessed the HRQoL of heart failure patients and their caregivers in England. The EQ-5D-5L weighted index for caregivers was 0.75 for a mean age of 69 years. Compared to the UK norm for EQ-5D at a mean age of 70 years (0.78), the disutility was assumed to be 0.03. The disutility is applied on a chronic basis.
Leg ulcer	0.03	Thomas et al.[200] assessed informal carers' HRQoL depending on the number of hours of care provided, based on a sample of 195,364 carers in England. From informal feedback from three UK SCD patients, it was assumed that any week with an event implies 50+ hours of support (with an associated utility of 0.77 (95% CI, 0.76–0.77), compared to the standard 10-19 hours of support (with an associated utility of 0.80 (95%CI 0.80–0.81). The difference (0.03) was assumed to be the disutility for one year of support; at an estimated duration of 304 days for a leg ulcer, the disutility was assumed to be 0.025.
Osteomyelitis	0.03	Thomas et al.[200] assessed informal carers' HRQoL depending on the number of hours of care provided, based on a sample of 195,364 carers in England. From informal feedback from three UK SCD patients, it was assumed that any week with an event implies 50+ hours of support (with an associated utility of 0.77 (95% CI, 0.76–0.77), compared to the standard 10-19 hours of support (with an associated utility of 0.80 (95%CI 0.80–0.81). The difference (0.03) was assumed to be the disutility the duration of the event (21 months or 651.36 days).
Osteonecrosis	0.03	Thomas et al.[200] assessed informal carers' HRQoL depending on the number of hours of care provided, based on a sample of 195,364 carers in England. From informal feedback from three UK SCD patients, it was assumed that any week with an event implies 50+ hours of support (with an associated utility of 0.77 (95% CI, 0.76–0.77), compared to the standard 10-19 hours of support (with an associated utility of 0.80 (95%CI 0.80–0.81). The difference (0.03) was assumed to be the disutility for the duration of the event (4 months or 121.75 days).
Priapism	0.00	Assumed to be zero.

Pulmonary hypertension	0.03	Squire et al.[201] assessed the HRQoL of heart failure patients and their caregivers in England. The EQ-5D-5L weighted index for caregivers was 0.75 for a mean age of 69 years. Compared to the UK norm for EQ-5D at a mean age of 70 years (0.78), the disutility was assumed to be 0.03. The disutility is applied on a chronic basis.
Sepsis	0.03	Thomas et al.[200] assessed informal carers' HRQoL depending on the number of hours of care provided, based on a sample of 195,364 carers in England. From informal feedback from three UK SCD patients, it was assumed that any week with an event implies 50+ hours of support (with an associated utility of 0.77 (95% CI, 0.76–0.77), compared to the standard 10-19 hours of support (with an associated utility of 0.80 (95%CI 0.80–0.81). The difference (0.03) was assumed to be the disutility for the duration of the event (one year).
Stroke, months 1-6	0.14	Based on the utilities reported in Van Exel et al.[204], Wittenberg et al.[205] calculated a utility decrement of 0.14 for substantially burdened caregivers of stroke survivors (difference between reported utility of 0.67 and population norm of 0.81)
Stroke, months 7-12	0.14	As no value was identified for disutility for caregivers between 7 and 12 months post-stroke, and as the utility for stroke patients is assumed to be constant throughout the first year, the same disutility as stroke months 1-6 is applied.
Stroke, months 13+	0.08	Persson et al.[206] estimated QALYs among stroke survivors, controls and spouses. The reported mean QALY weight among spouses of dependent stroke survivors (n = 50) was 0.69 while the mean QALY weight among controls (n = 245) was 0.77. The disutility for caring for someone with a stroke was calculated as the difference between the two. The disutility is applied on a chronic basis.
VOC	0.001	Thomas et al.[200] assessed informal carers' HRQoL depending on the number of hours of care provided, based on a sample of 195,364 carers in England. From informal feedback from three UK SCD patients, it was assumed that any week with an event implies 50+ hours of support (with an associated utility of 0.77 (95% CI, 0.76–0.77), compared to the standard 10-19 hours of support (with an associated utility of 0.80 (95%CI 0.80–0.81). The difference (0.03) was assumed to be the disutility for the duration of the event. The duration of a VOC is assumed to be 12 days (NICE TA 743)[130], while the duration of a complication (pneumonia/ACS) is assumed to be 6 months and occurs in 7.6% of VOC cases. Thus the duration of the event is 24.88 days., yielding a disutility of 0.001

CI, confidence interval; HRQoL, health-related quality of life; QALY, quality-adjusted life year; SCD, sickle cell disease; UK, United Kingdom; VOC, vaso-occlusive crisis

B.3.5. Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted in line with NICE requirements to identify direct and indirect costs and healthcare resource utilisation related to the management of adolescents (≥ 12 years) and adults (≥ 18 years) with SCD, irrespective of prior treatment. Database searches were conducted from database inception to 06 April 2022, incorporating several SLR updates. In total, 27 unique studies from 31 publications met the eligibility criteria and were included in this review. Full details of the review, including the PRISMA diagram and a description of all relevant studies informing the model, are given in Appendix I.

This model considers the perspective of the NHS and PSS, and therefore only costs that would be incurred by the NHS and PSS are included. PSS costs are often not available and have therefore not been included in some cases; where available, they were included. All costs are reported in 2020 British pounds (£) and, where needed, were inflated using the Office of National Statistics consumer price inflation time series.[207]

The following cost components were considered in the model:

- Disease modifying treatment acquisition costs;
- Symptomatic management costs;
- Costs associated with acute and chronic complications;
- Monitoring costs; and
- Adverse events costs.

SCD is a complex condition, and the economic model incorporates costs for a large number of elements. These are costed in various ways within the NHS. Costs have been drawn from a range of sources, including NHS costs, costs from previous TAs and costs from the literature. Where NHS costs have been used, relevant descriptive information is given in the tables.

B.3.5.1. Intervention and comparators' costs and resource use

A summary table of treatment costs is provided in Section B.3.5.1.4, Table 40.

B.3.5.1.1. *Voxelotor cost*

Based on internal forecasts from GBT, the annual cost of voxelotor per patient is £[redacted]; this cost reflects a [redacted], and assumes a recommended daily dose of 1500 mg. Each bottle of voxelotor contains 90 pills (500 mg each) and thus provides a 30-day supply. Based on the adherence of [redacted]% observed in the HOPE trial,[100] the annual cost of the drug, adjusted for adherence is £[redacted]. Thus, the adherence adjusted daily cost of voxelotor is £[redacted]. For patients with ESRD, the adherence adjusted cost per day based on a total daily dose of 1000 mg is £[redacted]. In addition to the acquisition cost of voxelotor, an annual dispensary cost of £15.36 is applied (6 prescriptions per year).[208]

B.3.5.1.2. *Regular transfusion therapy costs*

Based on the expert opinion solicited through the modified Delphi panel (Appendix T), [redacted]% of patients treated with RTT are assumed to be treated with ARCET and the remaining [redacted]% receiving simple top-up transfusions. This assumption is in line with the BHS guidelines which state that "The choice of transfusion method, simple or exchange, should be based on clinical judgement of individual cases […]. Automated exchange should be available to all patients and not be limited by resources."[66] RTT costs were estimated as a weighted average of top-up and ARCET. The calculation assumes a proportion of patients on simple top-up transfusions are receiving chelation therapy. This proportion is lower in the voxelotor arm as demonstrated in RWE.[209]

Automated exchange transfusion costs

The cost of was based on the NICE evaluation of crizanlizumab[130] and was assumed to include staff time, disposables for first and subsequent units of blood, and the unit cost for blood. Based on the NICE evaluation of crizanlizumab, and validated by the expert panel (see Appendix U), the cost of RTT includes staff time, disposables for the first and subsequent units of blood, and 10 units of blood per transfusion, for a total of £[redacted]

per transfusion (Table 40). According to the BHS guidelines, ARCET allows for an extended interval between transfusions of six weeks.[210] As such, based on both the expert opinion of the panel (see Appendix U) and in alignment with the NICE evaluation TA743,[130] the model assumes one transfusion would be given every [redacted] ([redacted]/year) for patients in both the voxelotor arm and the SOC treatment arm (patients on voxelotor are not expected to receive RTT, as explained in Section B.3.2.5). It is worth noting that an analysis of SCD patients in the HES database found a similar number of transfusions at (mode) [redacted] transfusions per year.[169]

Acute RBC transfusion costs

The cost of a simple acute top-up transfusion was calculated to be £608.38 per transfusion, based on a weighted calculation of transfusion costs for those aged 12–18 and those aged 19 years and older, based on the NHS reference costs.[211] Use of acute top-up RBC transfusions, separate from RTT, was stratified by treatment arm. Incidence of acute transfusions were based on the annualised transfusion event rates post initiation of treatment as observed in the real-world Symphony study[96]. Patients treated with voxelotor were assumed to receive 3.42 and 3.29 acute transfusion per year, on HC and not on HC, respectively. Patients on SOC but not receiving RTT were assumed to receive 7.01 and 6.93 acute transfusions per year, on and not on HC, respectively.

Patients receiving acute transfusions may require iron chelation therapy to prevent transfusional iron overload. According to the expert panel (see Appendix U), [redacted]% of adults and [redacted]% of adolescents with SCD on SOC also receive chelation therapy. Patients who use voxelotor would be expected to reduce their need of chelation therapy by [redacted]% and [redacted]%, resulting in [redacted]% of adults and [redacted]% of adolescents receiving chelation therapy. Based on a weighted average of type of chelation therapy agents used, as determined by the expert panel, and when costed as per the British National Formulary (BNF),[212] the annual cost of chelation therapy is £12,864.95 and £9,880.09 for adults and adolescents (Table 39). The cost of chelation therapy weighted by the proportion of patients receiving is reported in Table 40.

Table 39.Cost of chelation therapy, by age group

	% Using	Cost per day	Source
Adults			
Deferasirox (14 mg/kg/day @ 61 kg)	[redacted]	£42.00	https://www.medicines.org.uk/emc/medicine/32428#gref
Deferiprone (25 mg/kg @ 61 kg)	[redacted]	£3.90	https://www.medicines.org.uk/emc/product/10908/smpc#gref
Deferoxamine mesylate (40 mg/kg/day @61 kg)	[redacted]	£23.32	https://www.medicines.org.uk/emc/product/5/smpc#gref
Annual cost - adults			[redacted]
Adolescents 12-17 years old			
Deferasirox (14 mg/kg/day @ 42 kg)	[redacted]	£29.40	https://www.medicines.org.uk/emc/medicine/32428#gref
Deferiprone (25 mg/kg @ 42 kg)	[redacted]	£3.90	https://www.medicines.org.uk/emc/product/10908/smpc#gref
Deferoxamine mesylate (40 mg/kg/day @ 42 kg)	[redacted]	£18.65	https://www.medicines.org.uk/emc/product/5/smpc#gref
Annual cost - 12-17 years old			[redacted]

B.3.5.1.3. *Hydroxycarbamide costs*

As per the electronic market information tool (eMIT), the cost per packet of 100 capsules of 500 mg HC is £9.54, resulting in a daily drug cost of £0.39 based on a dose of 35 mg / kg and an average weighted mean weight of 63.1 kg for adolescents and adults (Table 40). While no studies were identified reporting adherence to HC in the UK, one study based on self-reported adherence using a visual analogue scale in Ireland[213] and one study (with two publications) based on the medication possession ratio in the US Medicaid setting[214,215] were identified. Adherence to HC in the model was thus calculated as a weighted average of the two identified studies resulting in an adherence of 49.7% for HC use. Based on the daily dose, the adherence-adjusted annual treatment cost of HC was calculated as £70.80. In addition to the acquisition cost of HC, a dispensary cost of £2.56 per prescription is applied, assuming six prescriptions per year given the adherence (Table 40).[208]

B.3.5.1.4. *Summary of treatment costs*

Table 40. Treatment costs

Treatment	Cost	Source
Voxelotor		
Annual cost of voxelotor	£[redacted]	GBT, assumes a [redacted].
Adherence to treatment	[redacted]%	HOPE study clinical study report, table 38[100]
Adherence adjusted cost per bottle (90, 500 mg tablets)	£[redacted]	GBT
Adherence adjusted cost per day	£[redacted]	As per OXBRYTA SmPC: 1500 mg per day (3 tablets of 500mg each)[2]
Adherence adjusted cost per day, ESRD patients	£[redacted]	As per OXBRYTA SmPC[2]: 1000 mg per day (2 tablets of 500mg each)
Annual dispensary cost	£15.36	NHS proposed dispensing fee scales for GMS contractors, England and Wales, 2021[208]; model assumes 6 dispensaries per year at £2.56 per prescription.
Regular transfusion therapy		
Patients on SOC	[redacted]	Weighted average of simple (5%) and automated exchange transfusion costs (95%). Assumes that 19.2% and 44.3% of adults and adolescents, respectively, are on chelation therapy when on simple transfusion. Costs reported in Table 39.
Patients on voxelotor	[redacted]	Weighted average of simple (5%) and automated exchange transfusion costs (95%). Assumes that 18.3% and 44.2% of adults and adolescents, respectively, are on chelation therapy when on simple transfusion. Costs reported in Table 39.
Automated exchange transfusion costs		
Staff time	£41.00	NICE TA743[130] and NICE NG24[216] uses day ward nurse costs. Since day ward nurse is no longer reported, unit cost for day ward hospital-based nurse (costs include qualifications) was used (PSSRU Unit cost 2021, Band 5) [217]. The cost is per unit of blood transfused.

Disposables for first unit of blood	£13.78	Following NICE TA743 [130], Agrawal [218] was used as source for costs associated with disposables. £11.59 / £3.46 disposables for first / subsequent units of blood, inflated to 2020 yield £13.78 / £4.12 disposables for first / subsequent units of blood
Disposables for subsequent units of blood	£4.12	
Unit cost for blood	£234.52	Following TA743[130] unit cost for blood are taken from NHS Blood and Transplant price lists (2021-22)[219]. According to expert opinion/clinical guidelines,[66] 10 units are assumed to be required in ARCET.
Automated exchange transfusion, per transfusion (sum of above)	[redacted]	Following NICE TA743[130], £234.52 (unit of blood) * 10 + £41.00 (cost of staff time) *10 + +£13.78 (disposables for first units of blood) + £4.12 (disposables for subsequent units of blood) *9 = £2,806.02 per transfusion
Simple transfusion		
Simple transfusion unit cost	£608.38	NHS reference costs 2019/20[211] [Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over: £587; Single Plasma Exchange or Other Intravenous Blood Transfusion, 18 years and under: £785]
Chelation therapy		
On SOC	£2,687.48	Assuming 10.8% of patients are adolescents and a weighted average in Table 39.
On voxelotor	£2,578.01	Assuming 10.8% of patients are adolescents and a weighted average in Table 39.
Hydroxycarbamide		
Cost per packet	£9.54	UK eMIT[220], Packet of 100 capsules, 500 mg per capsule
Daily drug cost	£0.39	Assuming a dose of 35 mg/kg and a mean weight of 58.9 kg (based on expert opinion where a mean weight of 42kg is assumed for SCD patients age 12-17 and 61kg for those age 18+[209] with 11% of population assumed to be adolescents[165]), the drug cost per day is £0.39 ((58.95*35)/500)*(9.54/100).
Adherence	49.7%	Weighted average of Fogarty et al.[213] and Kang et al.[215]/Mathias et al.[214]. Fogarty et al.[213] explored adherence in 63 Irish SCD patients recruited at two tertiary referral centres in Dublin, Ireland (average age 19 years, 63% female). Self-reported average monthly adherence was 76% using a visual analogue scale. Kang et al.[215]/Mathias et al.[214].

		Fogarty et al.[213]. Report the medical possession ratio among 1,146 Medicaid patients (average age 18.3 years, 60% female). Reported adherence among SCD patients was 48.3%. Given the limitations of both estimates (using VAS vs US-based), a weighted average was assumed (49.7%).
Annual dispensary costs	£15.36	NHS proposed dispensing fee scales for GMS contractors, England and Wales, 2021[208]; model assumes six dispensaries per year at £2.56 per prescription.
eMIT, electronic market information tool; ESRD, end-stage renal disease; HbS, sickle haemoglobin; HC, hydroxycarbamide; MPR, medication possession ratio; NHS, National Health Services; NICE, National Institute for Health and Excellence; PSSRU, Personal Social Services Research Unit; RBC, red blood cell; SmPC, summary of product characteristics; SOC, standard of care; UK, United Kingdom		

B.3.5.1.5. *Symptomatic management costs*

Opioids costs

The proportion of SCD patients on chronic opioids was obtained from the expert panel (see Appendix U), where it was estimated that in the SOC arm, 43% of adults and 13% of adolescents use opioids chronically.[209] Upon switching from transfusions to voxelotor, it is expected that the chronic use of opioids will reduce by [redacted] and [redacted]%, respectively, for adults and adolescents. This results in [redacted]% and [redacted]% of adults and adolescents using chronic opioids.

The annual cost of opioids for adolescents and adults was calculated as a weighted average of the different opioids used in each class, as reported by the expert panel (see Appendix U), priced as per the BNF 2022,[212] as detailed in Table 41. Assuming that 11% of the model population are adolescents,[165] the weighted average cost of opioid use is £131.65 for those in the voxelotor arm and £187.79 for those on RTT. Note that the proportion of patients using each type of opioid may exceed 100% because some patients take more than one opioid.

Table 41. Chronic opioid costs, by age group

	% Using	Source†	Cost / Day	Source
Adults (assumes 61kg weight)[209]				
Morphine (60 mg/day) IV SC	[redacted]	Expert opinion[209]	£2.01	BNF (2022)[212]
Morphine sulfate (60 mg/day) IV SC	[redacted]		£2.01	
Oxycodone (35 mg/day)	[redacted]		£0.64	
Codeine (180 mg/day)	[redacted]		£0.20	
Dihydrocodeine (120 mg/day)	[redacted]		£0.20	
Tramadol (300 mg/day)	[redacted]		£0.21	
Tapentadol (250 mg/day)	[redacted]		£2.23	
Opioids annual cost – adults				[redacted]
Adolescents 12-17 years old (assumes 42kg weight)[209]				
Morphine (60 mg/day) IV or SC	[redacted]	Expert opinion[209]	£2.01	BNF (2022)[212]
Morphine sulfate (60mg/day) IV or SC	[redacted]		£2.01	
Oxycodone (35 mg/day)*	[redacted]		£0.64	
Codeine phosphate (180 mg/day) oral	[redacted]		£0.45	
Dihydrocodeine (120mg/day)*	[redacted]		£0.30	
Tramadol (300 mg/day) oral	[redacted]		£0.84	
Tapentadol (250 mg/day) *	[redacted]		£2.23	
Opioids annual cost - 12-17 years old				[redacted]

*Assumed same dosage as adults.
† see Appendix U
IV, intravenous; SC, subcutaneous.

Erythropoietin stimulating agent costs

According to the expert panel (see Appendix U), 5% of adult patients 2% of adolescents on SOC are chronically on erythropoietin stimulating agents (ESA). Experts estimate that upon switching to voxelotor, the proportion of adults and adolescents on ESA would decrease by [redacted]% and [redacted]%, respectively, resulting in 1.7% of adults and 0.9% of adolescents on chronic ESAs. The annual cost of ESA is £7,340.97 and £675.02 for adults and adolescents respectively, based on a weighted average of type of ESA, an average body weight of 61 kg for adults and 42 kg, assuming 10.8% of the population is adolescents (Table 42). The weighted average cost of ESA is £111.97 and £328.87, for patients in the voxelotor and SOC arm, respectively.

Table 42. Annual cost of erythropoietin stimulating agents, by age group

	% Using	Cost per day	Source
Adults			
Epoetin alfa (50IU/kg or 3,150IU per week)	[redacted]	£66.66	https://www.medicines.org.uk/emc/product/1193/smpc#gref
Epoetin beta (3*30IU/kg or 1,890IU per week)	[redacted]	£14.03	https://www.medicines.org.uk/emc/product/1538/smpc#gref
Darbepoetin alfa (6.75 mcg/kg, given once every three weeks)	[redacted]	£244.68	https://www.medicines.org.uk/emc/product/6958/smpc#gref
Annual cost - adults	[redacted]		
Adolescents 12-17 years old			
Epoetin beta (20IU/kg SC or 40IU/kg IV, 3 times per week, average 3780 IU/week*)	[redacted]	£31.58	https://www.medicines.org.uk/emc/product/1538/smpc#gref
Annual cost - 12-17 years old	[redacted]		

IV, intravenous; SC, subcutaneous.

*Dose may be increased if Hb increase is not adequate, price here reflects the lower bound price.

B.3.5.1.6. *Monitoring costs*

Routine haematological, renal, and hepatic monitoring costs for SCD were assumed based on the NICE evaluation of crizanlizumab.[130] Haematological (full blood cell count including reticulocyte count) monitoring was assumed to be six times per year, at a cost of £2.56, based on NHS reference (Table 43).[211] Renal (urea and electrolytes), hepatic (liver function test), lactate dehydrogenase test, and foetal haemoglobin were assumed to be monitored four times per year, at a cost of £1.20 each, based on NHS reference (Table 43).[211] No specific monitoring costs were considered for voxelotor.

Table 43. Monitoring frequencies and cost assumptions

Parameter	Cost	Source	Frequency per year	Source
Haematological (full blood cell count including reticulocyte count)	£2.56	NHS Reference[211]	6	NICE TA743[130]
Renal (urea and electrolytes)	£1.20		4	
Hepatic (liver function test)	£1.20		4	
Lactate dehydrogenase test	£1.20		4	
Foetal haemoglobin	£1.20		4	

B.3.5.2. Health-state unit costs and resource use

B.3.5.2.1. *Costs of acute and chronic complications*

The model assumes one-off costs for acute complications and annual costs for chronic complications (Table 44). Costs were sourced from published UK studies, as indicated. No cost for terminal care was considered in the model.

Table 44. Costs of acute and chronic complications

	Unit cost	Source
Acute complications (cost per event)		
Acute renal failure	£1,969.00	NHS 2019/20, weighted average of LA07H-LA07P, excluding elective and regular day and night admissions[211]
Arrythmia	£1,007.00	NHS 2019/20, [weighted average across EB07A to EB07E (Arrhythmia or Conduction Disorder, with CC score 0 to 13+) – Total HRG][211]
Cardiomegaly	£174.00	NHS 2019/20, WF01B, Cardiology, Consultant Led Non-Admitted Face-to-Face Attendance, First (National Average Unit Cost) [211]
Gallstones	£6,324.00	NICE TA743[130], Diagnosis: liver function test and ultrasound, as per NICE CG188104 NHS Reference Costs 2019/20 [DAPS04 Clinical Biochemistry] - £1.20 NHS Reference Costs 2019/20 [weighted average across RD40Z (Ultrasound Scan with duration of less than 20 minutes, without Contrast – Total HRG) to RD43Z (Ultrasound Scan with duration of 20 minutes and over, with Contrast) – Total HRG] - £45.24 NHS Reference Costs 2019/20 [weighted average across GA10H (Laparoscopic Cholecystectomy, with CC Score 4+) to GA10N (Open Cholecystectomy, with CC Score 0) – Total HRG] - £3581 NHS Reference Costs 2019/20 [weighted average across GB05F (Major Therapeutic Endoscopic Retrograde

		Cholangiopancreatography with CC Score 5+) to GB09F (Complex Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 0-1) – Total HRG] - £2697[130]
Leg ulcer	£8,381.59	Based on Guest et al.[180], a retrospective cohort analysis of the records of 505 patients in The Health Improvement Network (THIN) Database, aimed at estimating the patterns of care and annual levels of health care resource use attributable to managing venous leg ulcers in clinical practice by the UK's NHS and the associated costs of patient management. The estimated mean NHS cost of wound care was £7600 (2016£) per venous leg ulcer (VLU); overall, 53% of all venous leg ulcers (VLUs) healed within 12 months, and the mean time to healing was 3.0 months. Costs are inflated from 2016 to 2020 pounds.[180]
Osteomyelitis	£3,335.00	NICE TA743 [130] based on NHS 2019/20 [weighted average across HD25D (Infections of Bones or Joints, with CC Score 13+) to HD25H (Infections of Bones or Joints, with CC Score 0-1) – Total HRG][130]
Osteonecrosis	£1,355.00	NHS 2019/20, Weighted average of NHS Reference Cost 2019/2020 currencies HD24D-HD24H (Unit cost of total HRGs)[211]
Priapism	£4,368.02	NICE TA743[130], NHS 2019/20,[211] [weighted average across LB58C (Penile Disorder with Interventions) and LB58D (Penile Disorder without Interventions) – Total HRG] (£1,562). Added the cost of one automated exchange transfusion as per NICE TA743 (£2,895.58)
Sepsis	£5,223.02	NICE TA743[130], NHS 2019/20[211] [weighted average across WJ06A (Sepsis with Multiple Interventions, with CC Score 9+) to WJ06J (Sepsis without Interventions, with CC Score 0-4) – Total HRG] - (£2,417). Added the cost of one automated exchange transfusion as per NICE TA743 (£2,895.58)
Vaso-occlusive crisis	£2,524.65	VOCs in the model are assumed to include both simple VOCs and those complicating to ACS/ pneumonia (note: in the HOPE trail, ACS and pneumonia are a single endpoint given the challenge of distinguishing between the two.) VOC cost follows NICE TA743 £2,127.70.[130,211]. ACS/ pneumonia cost follows NICE TA743 and is calculated based on NHS 2019/20, considering a weighted average of costs for DZ11K-DZ11V (Unit cost of total HRGs) + cost of one automated exchange transfusion £5,223.02.[130,211] The proportion of VOCs complicating to ACS/pneumonia in the HOPE trial was 58/763 = 7.6%[3] As a result, the cost of VOC (when consider the proportion complicating to ACS/pneumonia): £2,127.70 + (7.6%* £5,223.02 = £2,524.65.
Chronic complications (annual cost)		
Chronic kidney disease	£462.57	Based on Kent et al.[221], an international patient cohort study using UK costing as per NICE costing guidance.

		Reported costs (includes hospital costs only) for CKD (Stages 1 to 3b, but predominantly 3b) were £403 (in 2014£). Diabetes and CVD related costs not considered to avoid double counting. Costs were inflated to 2020 pounds.
End stage renal disease	£18,852.12	Based on Kent et al.[221], an international patient cohort study using UK costing as per NICE costing guidance. Reported annual hospital costs (in 2014£) for CKD Stage 4 (£393, , n = 2,228), CKD Stage 5, n = 1,017), on functioning kidney transplant in the current annual period (£24,602, n = 994), on functioning kidney transplant from an earlier annual period (£1,148, n = 1,663), on maintenance dialysis initiated in the current annual period (£18,986, n = 1,362, on maintenance dialysis initiated in an earlier annual period (£23,326, n = 9,516) Costs assumed for ESRD are a weighted average of the six categories listed above (£16,424.45 in 2014£) inflated to 2020£. Outpatient costs were not included in Kent nor in the model as they are likely to be relatively low and values were not available. As noted in Willis et al.[222] kidney transplant in SCD patients is less frequent than in the general population. No adjustment was performed for that given the lack of information.
Heart failure, Year 1	£11,358.57	As noted in NICE NG106 [223] rehabilitation is recommended after hospitalisation with heart failure. As such, the condition is assumed chronic. Costs for the first year after heart failure are based on Murphy et al.[224], an Irish study of 1,292 consecutive patients admitted with a primary diagnosis of heart failure to a hospital based HF-DMP, categorised as HFpEF (EF≥45%) or HFrEF (EF<45%). Costs include hospitalisations, primary care, medications, and DMP workload. Murphy et al. focused on recently diagnosed patients and was therefore used for year 1. Value assumed for heart failure year 1 is the average of the reported costs with HFrEF (€13,011) and reported annual costs in patients with HFpEF (€12,206), converted into £ at a 2016 exchange rate of 1.2242 € = 1£ [225] and inflated to 2020 £.
Heart failure, Year 2	£5,605.90	Costs for the second year after heart failure are based on Hollingworth et al.[226], a retrospective analysis of patients who died of or with heart failure from the CPRD linked to HES and ONS mortality data. Reported mean annual healthcare costs were £4,884.00 in 2013/2014 inflated to 2020.
Pulmonary hypertension	£17,117.81	Exposto et al.[227] analysed a cohort that included 2527 patients (68.4% female; 63.6% aged ≥50 years), between 1 April 2012 to 31 March 2018, from the NHS Digital HES database. Associated costs, calculated using national tariffs inflation-adjusted to 2017, did not include pulmonary hypertension-specific drugs on the high-cost drugs list). Reported mean costs, including inpatient admissions, outpatient visits and A&E attendances were £3,833+£896+£123 (sum of £4,852 [2017£]. Costs were inflated to 2020£ (£5,213.12)

		Based on the price of pulmonary hypertension drugs from NHS A11/P/, 2014[228], and the number of pulmonary hypertension patients and prescriptions as reported in the Digital NHS 11th annual report from 20201[229], drug cost were calculated to be £11,904.69. Total costs are: £5,213.12+£11,904.69 = £17,117.81. Detailed calculations for drug costs and prescriptions per patient are provided in Appendix M.
Stroke, 0-6 mo	£10,648.79	Patel et al.[230] estimated 2014/2015 annual mean cost per person and aggregate UK cost of stroke for individuals aged ≥40 from a societal perspective. The mean annual cost per person from an NHS and PSS perspective in the first year post-stroke is £18,081. Annual NHS and PSS costs for subsequent years total £7,759. Year 1 cost inflated to 2020: £18,081*1.023+£2,805.58 (divided by two for months 0 – 6 and months 7 – 12) Year 2+ cost inflated to 2020: £7,759*1.023
Stroke, 7-12 mo	£10,648.79	
Stroke, Year 2+	£7,935.18	
ACS, acute chest syndrome; CC, complications and comorbidity; CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; HES, Hospital Episode Statistic; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HRG, Healthcare resource group; mo, month; NHS, National Health Services; NICE, National Institute for Health and Excellence; PH, pulmonary hypertension; PSS, Personal Social Services; SCD, sickle cell disease; VLU, venous leg ulcers; VOC, vaso-occlusive crises.		

B.3.5.3. Adverse reaction unit costs and resource use

B.3.5.3.1. *Transfusion related adverse event costs*

AEs related to regular transfusion were defined based on the Cochrane SLR protocol developed by Estcourt[141] in patients with SCD receiving regular long-term blood transfusion regimens. The protocol lists the most relevant serious AEs for patients on RTT (iron overload, alloimmunisation, infections from blood products, acute or delayed haemolytic transfusion reactions, increased complexity of compatibility testing, and procedural complications (such as device malfunction) and formed the basis of AEs to be included in the present economic analysis. Assumptions of costs of AEs related to RTT are shown in Table 45. Of note, following the assumption in NICE TA 473,[130] as patients receiving RTT are assumed to receive automated exchange transfusions, no iron overload incidences are considered. The proportion of patients on regular transfusions is 1.5% in the voxelotor arm and 28.0% in the SOC arm.

Table 45. Costs of AEs related to regular transfusion

Regular Transfusion related AE Cost	Cost	Source
Composite adverse events per year (cost already incorporates incidence of each event)	£24.60	The total expected additional cost of all AEs considered in the study, associated with each transfusion, already accounting for incidence of each AE, estimated by Spackman et al.[128] Table 2, is £1.69 per transfusion (£ 2011). 8.7 transfusions per year results were assumed. Cost inflated to 2020. The list of AEs considered by Spackman et al. (2014) is: Transfusion-related graft vs. host disease, Incorrect blood component transfused, Haemolytic transfusion reaction, Post-transfusion purpura, Transfusion-related acute lung injury, Fatal air embolism, Variant Creutzfeldt–Jakob disease, and infections (HIV, Human T-cell lymphotropic virus, Malaria, Hepatitis A, B and C)[128]
Alloimmunisation cost per transfusion	£4.53	The total expected additional cost associated with each transfusion adverse event estimated by Spackman (2014)[128] Table 2, is £1.69 per transfusion (£ 2011). Inflated to 2020 yields a total of £2.83. Kacker et al.[231] reports the cost of complications per transfusion unit, for those with and without alloimmunisation under different matching methods. Taking an average of the four different methods yields USD 0.6925 and USD 0.1825 for those with and without alloimmunisation, respectively. Since the present economic analysis assumes that 10 units are transfused per transfusion, the complication cost difference per transfusion, in those with and without alloimmunisation, is USD 6.925 -USD 1.825 = USD 5.1. This difference is assumed to be the cost of alloimmunisation per transfusion. According to the Bank of England 1 pound was worth USD 1.3605 on January 11, 2022. Therefore, the cost of alloimmunisation per transfusion is $5.1/1.3605 = £3.75. Inflating from 2012 yields £4.53.
AE, adverse event; RCT, randomised controlled trial; SCD, sickle cell disease; SAEs, serious adverse events; SLR, systematic literature review.		

B.3.5.3.2. *Voxelotor and hydroxycarbamide non-SCD related adverse events*

The incidence of grade 3 or greater AEs for voxelotor and HC not related to SCD were taken from the 72-week follow-up of the HOPE trial, where frequencies in at least 2% of

patients, in either arm, were reported[91]; AEs were valued assuming the NHS reference cost for inpatient care for each AE (Table 46).

Table 46. Incidence and cost of non-SCD related grade 3 or greater AEs for voxelotor and standard of care

AE	Incidence voxelotor	Incidence SoC	Cost	Source
Anaemia	0.020	0.029	£378.71	Other Haematological or Splenic Disorders, with CC Score 6+, with CC Score 3-5 and with CC Score 0-2. Weighted average of National Schedule of NHS Costs - Year 2019/20 codes: SA08G, SA08H, SA08J [211]
Reticulocytopenia	0.020	0.000	£378.71	Other Haematological or Splenic Disorders, with CC Score 6+, with CC Score 3-5, and with CC Score 0-2. Weighted average of National Schedule of NHS Costs - Year 2019/20 codes: SA08G, SA08H, SA08J [211]
Vision blurred	0.020	0.000	£392.12	Non-Surgical Ophthalmology with Interventions, Non-Surgical Ophthalmology without Interventions, with CC Score 5+, with CC Score 2-4, and with CC Score 0-1. Weighted average of National Schedule of NHS Costs - Year 2019/20 codes: BZ24D, BZ24E, BZ24F, BZ24G[211]
Abdominal pain upper	0.000	0.019	£649.11	Abdominal pain included abdominal pain, abdominal pain upper, and abdominal pain lower. Weighted average of National Schedule of NHS Costs - Year 2019/20 codes: FD05A, FD05B (abdominal pain with / without interventions)[211]
Pain	0.000	0.029	£1,051.94	Unspecified Pain with CC Score 1+ and with CC Score 0. Weighted average of National Schedule of NHS Costs - Year 2019/20 codes: WH08A, WH08B[211]
Pyrexia	0.000	0.029	£424.39	Fever of Unknown Origin with Interventions, with CC Score 4+ and with CC Score 0-3, Fever of Unknown Origin without Interventions, with CC Score 4+ and with CC Score 0-3. Weighted average of National Schedule of NHS Costs - Year 2019/20 codes: WJ07A, WJ07B, WJ07C, WJ07D[211]

Fatigue	0.000	0.019	£210.09	For costs that were sourced from the Oxford Outcomes report.[232] Cost year is 2012, inflated to 2020 using 1.20815450643777 multiplier.
Non-cardiac chest pain	0.020	0.019	£302.49	Unspecified Chest Pain with CC Score 11+, with CC Score 5-10 and with CC Score 0-4. Weighted average of National Schedule of NHS Costs - Year 2019/20 codes: EB12A, EB12B, EB12C[211]

B.3.6. Severity modifier

In the most recent updated methods published, NICE recognises that the severity of a disease is an important consideration in a health technology assessment.[161] In the cases of medicines being appraised for a severe disease, such as SCD, NICE considers the severity of the disease via absolute quality-adjusted life years (QALY) shortfall (AS) and proportional QALY shortfall (PS).

The calculation used to determine AS was as follows:

$$Absolute\ QALY\ shortfall = QALYs\ in\ SoC - \ QALYs\ in\ age\ and\ sex\ matched\ general\ population$$

The calculation used to determine PS was as follows:

$$Proportional\ QALY\ shortfall = \frac{Absolute\ QALY\ shortfall}{QALYs\ in\ age\ and\ sex\ matched\ general\ population}$$

Table 47 shows sex distribution and starting age for the analysis.

Table 47 summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	38% male, 62% female	B.3.2.1
Starting age	32	

Results of the calculation are shown in Table 48 and Table 49. In the base case analysis, with a mean age at baseline of 32 and a proportion of males of 38%, the AS estimated is [redacted]. This gives a severity modifier of [redacted]. Note that the values are calculated on the basis of discounted QALYs.

The only previous appraisal by NICE in SCD, the appraisal of crizanlizumab, did not include a QALY shortfall analysis. A breakdown by health state utility is not applicable due to the nature of the DES model.

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Table 48. QALY shortfall calculation results

Outcome	Total QALYs	Shortfall	
		Absolute	Proportional
General Population	[redacted]		
Disease Specific	[redacted]	[redacted]	[redacted]
QALY Multiplier		[redacted]	[redacted]
WTP Threshold		[redacted]	
QALY, Quality adjusted life year; WTP, Willingness to pay threshold			

Table 49 summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
[redacted]	[redacted]	[redacted]

GBT believes that this calculation does not fully capture the severity of SCD in L2+ patients who would be treated with voxelotor. SCD is a rare life-long genetic condition which may be clinically impactful from an early age.[7] The impact of SCD on patients and their carers is described in testimonies from patients in Appendix V. SCD is progressive and is associated with a wide range of acute and chronic complications, progressive organ damage, and a 20-30-year reduction in life expectancy even under modern treatment.[8] L2+ patients have high unmet with few treatment options, in a patient population that suffers from health and socio-economic inequalities. The baseline EQ-5D values taken from the HOPE study are likely to overestimate the utility of patients with SCD: they are very close to population norms for the UK and are higher than utilities reported in the literature for SCD patients.[192,199] In addition, the estimated mean age of death in the economic model under SOC is [redacted] years. This implies that patients living with a SCD experience a material loss in life expectancy versus the average age of the general population. However as SCD is not an end of life condition, and despite the material loss of life when compared to population norms, this loss is not large enough to drive qualification for the highest level of severity as set out by NICE in the most recent

methods guide. Therefore, despite SCD being acknowledged by patients, carers and physicians as a severe disease (see patient and carer testimonies in Appendix V), it does not meet the highest level of severity as proposed by NICE due to the nature of the NICE metric. In light of this, the company strongly believe that voxelotor should qualify for the highest level of severity, which reflects the 1.7 QALY weight, applied to medicines with a QALY short fall of 18 QALYs.[161]

B.3.7. Uncertainty

Several factors affect the ability to generate high quality evidence in SCD. SCD is a rare condition, so recruitment of large patient populations to RCTs or observational studies is difficult. Furthermore, it is associated with a wide range of possible complications and the clinical course varies widely between individuals. It is characterised by progressive organ damage that accumulates over time due to the continuous effect of red blood cell sickling, haemolysis and haemolytic anaemia. This progressive damage cannot fully be captured over the time-frame of randomised controlled trials. Voxelotor is indicated for the treatment of haemolytic anaemia, and its effect on Hb is expected to reduce the incidence of SCD-related events and complications over time, but direct evidence for this is difficult to generate over the course of an RCT. Nevertheless, high quality observational evidence is available for the link between Hb levels and outcomes (see Section B.3.3.3.1).

B.3.8. Managed access proposal

GBT is not submitting a managed access proposal at this juncture. GBT is committed to securing a positive routine commissioning decision for voxelotor. GBT is committed to working with all stakeholders throughout the process.

B.3.9. Summary of base-case analysis inputs and assumptions

B.3.9.1. Summary of base-case analysis inputs

A summary of key attributes and variables in the economic model are provided in Table 50.

Table 50. Summary of key model input variables

ATTRIBUTE OR VARIABLE	VALUE
Intervention	Voxelotor
Comparator	Treatment mix of: RTT HC RTT & HC Neither RTT & HC
Perspective	UK: NHS and Personal Social Services
Model type	DES
Currency	British pounds
Costing year	2020
Time horizon, years	100
Cohort size, n	50,000
Discount rate, costs (%)	3.5%
Discount rate, outcomes (%)	3.5%
Female, %	58%
Age, years, mean	32.7
DES, discrete event simulation; HC, hydroxycarbamide; UK, United Kingdom; RTT, regular transfusion therapy	

B.3.9.2. Assumptions

While every effort was made to source data to inform the economic model from the literature, some key assumptions were necessary, given the nature of the disease and the limited information available. These assumptions and their rationale are summarised in Table 51.

Table 51 Key modelling assumptions and rationale

Assumption	Rationale	Section
The efficacy data taken from the HOPE clinical trial is representative of the efficacy expected to be observed in L2+ patients in the real-world in the UK, when adjusted to reflect differences in HC use,	The HOPE trial population is broadly comparable with SCD patients in the UK (see Section B.2.12.2). The HOPE population is effectively a 2L population, as explained in the same section. Furthermore, the mean Hb change in the HOPE trial is similar to the Hb change observed with voxelotor in real world	B.2.12.2 B.2.6.9 B.3.3.1.1

Assumption	Rationale	Section
	data using data from the US (Section B.2.6.9); the US real-world population can also be considered 2L because US guidelines recommend that all patients are offered HC (B.3.3.1.1).[138]	
The incidence/prevalence of SCD-related events and complications is directly related to Hb level. The incidence/prevalence of events observed is dependent on demographics (gender, age), Hb level, VOCs frequency history, interplay between Hb and VOCs frequency history, treatment (HU and RTT) history and comorbidities history, all of which were evaluated at baseline.	SCD-related complications result from progressive organ damage over time, and could not be captured in the time-frame of the RCT. Risk of these events was therefore modelled using real-world evidence, based on Hb levels and the additional factors listed. The surrogacy relationship between Hb and SCD-related events and complications is biologically plausible and is supported by extensive observational evidence, including meta-analysis for some outcomes (Section B.3.3.3).	B.3.3.3
The link between the covariates evaluated and event occurrence is described sufficiently by an exponential TTE equation	An exponential survival distribution was used as there was no reason to believe there would be any temporal association between the hazard and time since the Hb assessment (other than age, the effect of which is captured as a covariate). Additionally, the relatively frequent recurrences of certain events e.g., VOC, meant that other survival functions might not be appropriate, since they would contain an assumption that the shape of the hazard function remains the same for subsequent events	B.3.3.3 Appendix Q
The impact of improved Hb on event occurrence (incidence and prevalence) in UK SCD patients can be calculated by changing the Hb level at baseline in TTE equations.	TTE event equations describe the relationship between Hb levels (together with demographics [gender, age], Hb level, VOCs frequency history, interplay between Hb and VOCs frequency history, treatment [HU and RTT] history and comorbidities history) and the occurrence of an event. There is strong evidence for the relationship between TTE and events – see above.	B.3.3.3 Appendix Q
Voxelotor discontinuation rates observed in the HOPE clinical trial are reflective of what is expected to occur in clinical practice in the UK	In the trial there was a statistically significant relationship between discontinuation and Hb response at week 24 (Section B.3.3.2 and Appendix O). Response rates for voxelotor in UK clinical practice are expected to be comparable with those seen in the trial (see above). Voxelotor discontinuation	B.3.3.2 Appendix O

Assumption	Rationale	Section
	rates in HOPE were not dependent on HC use (Appendix O), so any variation in HC use can be assumed not to affect discontinuation. For these reasons, it is reasonable to assume that discontinuation rates in UK clinical practice will be similar to those seen in HOPE in the voxelotor arm with and without HC.	
Voxelotor efficacy is assumed to be maintained as long as the patient stays on treatment	There is no evidence of a waning effect with voxelotor. The mean change in Hb remained stable up to 72 weeks in HOPE,[91] and up to 144 weeks in the open-label extension study.[92,106]	B.3.3.1.4
Hb levels have a positive and linear relationship with utility derived from EQ-5D.	Utility values by Hb level were obtained from the Patient Journey survey and analysed using linear models of utilities as a function of Hb including patient age as a covariate (see Section B.3.4.4.3 and Appendix T). The resulting estimated utility increment per 1g/dL increase in Hb was calculated to be [redacted]. The patient journey survey was used because a targeted literature review did not identify any suitable studies reporting this data in UK patients using EQ-5D and UK tariffs.	B.3.4.4.3 Appendix M
L2+ SoC patients in the UK are treated with a mix of RTT, HC and no treatment.	Derived from expert opinion via modified Delphi panel (see Appendix U)	B.3.2.5.2 Appendix U
Only in very rare cases (<1.5%) will Voxelotor be combined with RTT.	Derived from expert opinion via modified Delphi panel (see Appendix U)	B.3.2.5.2 Appendix U
In the base case no change in Hb levels among patients on RTT is explicitly modelled.	No data on the relationship between Hb levels and RTT could be found despite extensive searching. Given the absence of applicable data, in the base case no change in Hb levels among patients on RTT is explicitly modelled. However, RTT is included as a covariate in the TTE analysis and RTT therefore influences the incidence of complications within the model (see Section B.3.3.3). A scenario analysis which assumes a change of 0.8 g/dL in Hb following treatment with RTT was performed.	B.3.3.1.2
5.0% of patients who receive RTT discontinue annually.	While alloimmunisation, among other AEs, may ultimately result in the discontinuation of RTT, rates of alloimmunisation among patients on RTT reported in the literature vary	B.3.3.2.2

Assumption	Rationale	Section
	significantly. Given that SCD patients are recommended to receive matched blood donation [233] which reduces the risk of alloimmunisation, it was assumed that 5.0% of patients who receive RTT discontinue annually. As this assumption is highly uncertain, it was tested in scenario analyses.	
Patients not receiving voxelotor, HC or RTT (but who are in need of DMT treatment), are assumed to only receive symptomatic management.	Derived from expert opinion via modified Delphi panel (see Appendix U)	B.3.2.5.2 Appendix U
Utility values in SCD patients on RTT are same as those of thalassemia patients on RTT.	No data on the disutility associated with regular transfusions specific to SCD was identified; however, an NIHR HTA evaluation by Cherry et al. calculated such a disutility using data from thalassemia patients in a study by Osborne et al. This disutility was used in the present model, based on its prior use in an NIHR HTA evaluation in SCD.	B.3.4.4.2

B.3.10. Base-case results

B.3.10.1. Base-case incremental cost-effectiveness analysis results

In the model base case, considering a lifetime horizon, the total undiscounted life years (LYs) was [redacted] for voxelotor and [redacted] for SOC; total discounted LYs were [redacted] and [redacted], respectively (Table 52). Total undiscounted QALYs were [redacted] for voxelotor and [redacted] for SOC; total discounted QALYs were [redacted] and [redacted], respectively, with an incremental difference of 0.75 (Table 52). Total discounted costs were £[redacted] and £[redacted] for voxelotor and SOC, respectively, resulting in a difference of £[redacted]. The incremental cost effectiveness ratio was £[redacted] / QALY. The resulting incremental cost-effectiveness ratio (ICER) by the number of agents in the simulation is shown in

Figure 23.

Table 52. Cumulative discounted cost-utility results (£2020)

	Voxelotor	SOC	Difference
Total LYs (not discounted)	[redacted]	[redacted]	[redacted]
Total LYs (discounted)	[redacted]	[redacted]	[redacted]
Total QALYs (not discounted)	[redacted]	[redacted]	[redacted]
Total QALYs (discounted)	[redacted]	[redacted]	[redacted]
Patient QALYs (not discounted)	[redacted]	[redacted]	[redacted]
Patient QALYs (discounted)	[redacted]	[redacted]	[redacted]
Caregiver QALYs (not discounted)	[redacted]	[redacted]	[redacted]
Caregiver QALYs (discounted)	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Incremental cost effectiveness ratio	**£[redacted] / QALY**		
Net health benefit			
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
Net monetary benefit			
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	

LY, life years; QALYs, quality-adjusted life years; SOC, standard of care; WTP, willingness to pay

Figure 23. ICER by number of agents in the simulation for voxelotor vs SOC

ICER, incremental cost-effectiveness ratio
Solid line represents mean ICER, dashed lines are ±2%

B.3.10.2. Base-case health outcomes

The percentage of patients with one or more complication in the base case scenario is shown in Table 53. Treatment with voxelotor reduces the incidence of all complications, with the highest effect predicted to occur in terms of ESRD (difference of 4.6% compared with SOC)

Table 53. Patients experiencing one or more complication by the end of the simulation

	Voxelotor	SOC	Relative difference
ARF	[redacted]	[redacted]	[redacted]
Arrythmias	[redacted]	[redacted]	[redacted]
Cardiomegaly	[redacted]	[redacted]	[redacted]
CKD	[redacted]	[redacted]	[redacted]
ESRD	[redacted]	[redacted]	[redacted]
Gallstones	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]
Leg ulcer	[redacted]	[redacted]	[redacted]
Osteomyelitis	[redacted]	[redacted]	[redacted]
Osteonecrosis	[redacted]	[redacted]	[redacted]
Pulmonary hypertension	[redacted]	[redacted]	[redacted]
Priapism	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
VOC	[redacted]	[redacted]	[redacted]

ARF, acute renal failure; CKD, chronic kidney disease; ESRD, end stage renal disease; SOC, standard of care; VOC, vaso-occlusive crises

Incidence rates (events per person per year) of complications are shown in Table 54.

Table 54. Incidence rate (events per person per year)

	Voxelotor	SOC	Relative Difference
ARF	[redacted]	[redacted]	[redacted]
Arrythmias	[redacted]	[redacted]	[redacted]
Cardiomegaly	[redacted]	[redacted]	[redacted]
CKD	[redacted]	[redacted]	[redacted]
ESRD	[redacted]	[redacted]	[redacted]
Gallstones	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]
Leg ulcer	[redacted]	[redacted]	[redacted]
Osteomyelitis	[redacted]	[redacted]	[redacted]
Osteonecrosis	[redacted]	[redacted]	[redacted]
Pulmonary hypertension	[redacted]	[redacted]	[redacted]
Priapism	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
VOC	[redacted]	[redacted]	[redacted]

ARF, acute renal failure; CKD, chronic kidney disease; ESRD, end stage renal disease; SOC, standard of care; VOC, vaso-occlusive crises

B.3.10.3. Base-case cost outcomes

The breakdown of the cumulative discounted treatment costs and complication management costs is shown in Table 55. Increased treatment costs associated with voxelotor (£[redacted]) are partially offset by lower complication management costs (£[redacted]).

Table 55. SCD treatment and complication costs for voxelotor vs SOC (£2020)

	Voxelotor	SOC	Difference
SCD treatment costs	[redacted]	[redacted]	[redacted]
Voxelotor medication	[redacted]	[redacted]	[redacted]
Voxelotor administration	[redacted]	[redacted]	[redacted]
Hydroxycarbamide medication	[redacted]	[redacted]	[redacted]
Hydroxycarbamide administration	[redacted]	[redacted]	[redacted]
Top up transfusions	[redacted]	[redacted]	[redacted]
Regular transfusions	[redacted]	[redacted]	-[redacted]
Other medications	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Complication management	[redacted]	[redacted]	[redacted]
ARF	[redacted]	[redacted]	[redacted]
Arrythmias	[redacted]	[redacted]	[redacted]
Cardiomegaly	[redacted]	[redacted]	[redacted]
CKD	[redacted]	[redacted]	[redacted]
ESRD	[redacted]	[redacted]	[redacted]
Gallstones	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]
Leg ulcer	[redacted]	[redacted]	[redacted]
Osteomyelitis	[redacted]	[redacted]	[redacted]
Osteonecrosis	[redacted]	[redacted]	-[redacted]
Pulmonary hypertension	[redacted]	[redacted]	[redacted]
Priapism	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
VOC	[redacted]	[redacted]	[redacted]

ARF, acute renal failure; CKD, chronic kidney disease; ESRD, end stage renal disease; VOC, vaso-occlusive crises

B.3.11. Exploring uncertainty

A number of uncertainties affect the cost-effectiveness modelling. SCD is a complex disease involving both acute events and a large number of possible long-term complications. The magnitude of effect of voxelotor on long-term outcomes remains uncertain as long-term follow-up evidence is not yet available, so this had to be modelled indirectly via the effect on Hb. However, the evidence that Hb is linked to these outcomes is robust, having been confirmed in the two database analyses undertaken for this submission (Section B.3.3.1.3 and appendices P, Q and R), a meta-analysis and several smaller studies published since (Section B.3.3.3.1).

A discrete event simulation model was used to allow a large number of different outcomes to be modelled using a time to event approach, as this was considered to be the most effective way of modelling the complexity of SCD. In the SOC comparator arm, there is uncertainty over the effect of RTT on Hb levels in SCD due to a lack of data (see Section B.3.3.1.2). The uncertainty in the effect of RTT on different possible outcomes in SCD is addressed by keeping RTT as a covariate in time to event equations. Uncertainty around the effect of RTT was further explored in a scenario analysis. Unlike the Hb increase with voxelotor, which remains essentially constant whilst on treatment, the effect of transfusions on Hb decays over time, so that patients experience an initial boost to Hb but levels then gradually fall back until the next transfusion.[147] This means there is uncertainty around attributing a fixed Hb efficacy to transfusions (see Section B.3.11.3.1). Discontinuation rates for RTT are an additional source of uncertainty due to lack of available data and evidence.

Uncertainty was extensively explored in a range of sensitivity and scenario analyses, presented below. The key drivers of the economic model are voxelotor costs, RTT costs and discontinuation rates (Figure 26).

B.3.11.1. Probabilistic sensitivity analysis

The probabilistic sensitivity analysis draws values for each variable from its individual uncertainty distribution (see Appendix M). This is performed for all parameters simultaneously, and the resulting incremental results for each combination of probabilistic inputs are recorded. This constitutes one ‘simulation’. In total, 500

simulations of 10,000 patients were performed, which gives a distribution of incremental results, and consequently, an estimate of the overall uncertainty surrounding cost-effectiveness results.

Table 56 ICER from probabilistic sensitivity analysis

Incremental costs	Incremental QALYs	ICER
[redacted]	[redacted]	[redacted]
QALY, Quality adjusted life years; ICER, Incremental cost effectiveness ratio		

B.3.11.1.1. *Probabilistic sensitivity analysis results*

In all simulations treatment with voxelotor results in improved clinical benefit; while in most cases, this benefit comes at an increased cost, in about 5% of the simulations voxelotor is dominant (costs less and is more effective) (Figure 24).

Figure 24. Cost-effectiveness plane

[redacted]

QALY, quality-adjusted life year

At a willingness to pay (WTP) threshold of £[redacted], there is a [redacted]% chance that voxelotor is cost-effective (Figure 25). At a WTP threshold of £[redacted], the probability of being cost-effective is about [redacted]%.

Figure 25. Cost-effectiveness acceptability curve

[redacted]

QALY, quality adjusted life year

B.3.11.2. Deterministic sensitivity analysis

For this analysis, each model parameter was assigned an appropriate uncertainty distribution, where the mean of the distribution is typically equal to the point estimate. The standard error of the distribution is set according to any distributional information provided in the original source. If no distributional information is available, the standard error was assumed to be 25%. For event rates and utility values, a beta distribution has been used to restrict draws across the range of 0 to 1. For costs and

resource use estimates, a gamma distribution has been fitted to prevent values less than zero. The deterministic sensitivity analysis varies one parameter at a time to assess the subsequent impact on the outcomes. Each parameter is allocated a 'lower' value and an 'upper' value, which correspond to the lower and upper bound of the 95% confidence interval, respectively (see Appendix M). By adjusting each parameter one at a time, the sensitivity of the model results to that parameter are estimated.

B.3.11.2.1. *Deterministic sensitivity analysis results*

The key drivers of the economic model are voxelotor costs, RTT costs and discontinuation rates (Figure 26).

Figure 26. Deterministic sensitivity analysis tornado plot, ICER (£)

ARCET, automated red cell exchange transfusions; d/c, discontinuation; Hb, haemoglobin, HU, hydroxyurea (hydroxycarbamide); SOC, standard of care

B.3.11.3. Scenario analysis

Scenario analyses were performed exploring various inputs and combinations as described in Table 57.

Table 57. List of scenarios considered

Scenario	Scenario	Base case	Values assumed for the scenario analysis
Discount rate	1a	3.5% for costs and benefits	Costs discounted at 1.5%
	1b		No discount for costs of benefits
	1c		Costs and benefits discounted at 1.5%
RTT benefit	2	RTT is a covariate in the TTE equations; benefit of RTT on event incidence is implicit. No additional benefit assumed.	Assume 0.8 g/dL increase in Hb among patients on RTT
Discontinuations	3a	RTT: 5% / HC: 5%	Higher (25%) for both
	3b		Lower (1%) for both
	3c		RTT higher (25%)

			HC same as base case (5%)
	3d		RTT same as base case (5%) HC higher (25%)
Persistence	4	Persistence stratified by responder (13.5%) and non-responder (36.9%)	Assume responders don't discontinue
Time point of Hb evaluation	5a	At 24 weeks	At 72 weeks
	5b		Up to 72 weeks
Reimbursement population	6a	Reimbursement population is second line. Comparator is mix of HC, RTT, RTT+HC or nothing. No benefit on Hb is assumed	All patients treated with RTT; no benefit on Hb for those treated with RTT.
	6b		All patients treated with RTT and assume 0.8 g/dL increase in Hb.
Waning effect	7	Not included	Assume treatment waning of annual reduction in Hb level of 5%
RTT, regular transfusion therapy; Hb, haemoglobin; HC, hydroxycarbamide; TTE, time to event			

B.3.11.3.1. *Scenario analysis results*

Summary results for each scenario analysis described in Table 57 are shown in Table 58. The high-level overview allows for a clean picture of the impact of each parameter varied in sensitivity analysis on the key results measures. There are two important points to note regarding scenario 2, in which a 0.8 g/dL increase in Hb was assumed in patients on RTT, both of which bias the findings in favour of SOC and against voxelotor. Firstly, RTT is included as a covariate in the TTE analysis and RTT therefore influences the incidence of complications within the model even when no Hb efficacy for RTT is explicitly modelled (as in the base case); adding an explicitly modelled efficacy value therefore introduces an element of double-counting. Secondly, the waning of Hb levels between transfusions (see Section B.3.3.1.2) is not captured in the model. The scenario effectively assumes a constant relative difference of 0.8 g/dl for those on transfusion vs those not on transfusion. This is clearly a conservative assumption biasing against voxelotor.

Table 58. Summary of sensitivity analysis results (discounted, £2020)

	Difference (voxelotor versus comparator)			
	LY	**QALYs**	**Total cost**	**ICER/QALY**
Base case	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1a	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1b	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1c	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3a	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3b	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3c	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3d	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5a	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5b	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6a	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6b	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year

*Less costly, more effective

**Note that in this scenario, voxelotor is less costly and less effective (bottom left quadrant)

B.3.12. Benefits not captured in the QALY calculation

Unmet need in SCD

Despite the substantial clinical, humanistic and economic burden of SCD, there were no new treatments for over 20 years[234] until the recent regulatory approvals of voxelotor and crizanlizumab. Voxelotor is the first and only pharmacological treatment indicated specifically for the treatment of haemolytic anaemia in SCD. The EMA noted that there is a high unmet medical need for treatments for this manifestation of SCD, which affects all SCD patients to varying degrees.[6] In the SHAPE survey, 89% of patients with SCD (total N = 919) said that reducing their risk of anaemia/haemolytic anaemia was important to them.[48]

For patients who are intolerant, ineligible, unwilling to take or have an inadequate response to hydroxycarbamide, additional treatment options are currently limited to use of chronic transfusions. However, these are burdensome for patients and health services and carry risks of transfusion reactions, alloimmunisation and iron

overload.[79,235-237] Access to apheresis machines for automated exchange transfusions is limited, with some patients having to travel long distances to receive treatment.[56] Attending transfusion appointments is likely to involve absence from education and/or employment for patients and their carers. Patients also face high transport costs, and travel poses additional difficulties for patients who have mobility issues (e.g., resulting from stroke, bone damage or other complications of SCD). Thus, there is a significant need for new treatment options for these patients.[6]

Innovative nature of voxelotor

Voxelotor was the first treatment for SCD to be granted Promising Innovative Medicine (PIM) status by the MHRA,[238] and was selected for the Early Access to Medicines Scheme (EAMS) on 25 January 2022.[5] Additionally, voxelotor was granted Priority Medicines (PRIME) designation and orphan designation from the EMA. In the US, in recognition of the critical need for new SCD treatments, the FDA granted voxelotor Breakthrough Therapy, Fast Track, Orphan Drug and Rare Pediatric Disease designations for the treatment of patients with SCD.

Voxelotor was developed specifically for the treatment of SCD and is the only approved treatment that addresses the underlying molecular basis of SCD by inhibiting HbS polymerisation, which is the root cause of RBC sickling and the resulting cascade of pathology and acute and chronic symptoms and complications. By intervening at the beginning of the cascade of pathology, voxelotor is likely to improve both short- and long-term outcomes.

Voxelotor is associated with a rapid and sustained increase in Hb levels.[3,91] Over the longer term, increased Hb is associated with reduced risk of end-organ damage, including chronic kidney disease, pulmonary hypertension, stroke and mortality (see Section B.3.3.3 for further details).[16,18] Further, lower Hb levels are associated with increased risk of vascular complications of SCD, including stroke, leg ulcers, pulmonary hypertension, priapism, and renal failure.[10] Voxelotor also reduces the annualised incidence of VOCs (numerically in the phase 3 trial,[3,91] and significantly in real-world use).[96]

Voxelotor is an oral treatment that can be administered as monotherapy or in addition to hydroxycarbamide. Thus, it can be said to represent a step change in the management of SCD in patients who require a second-line treatment for haemolytic anaemia after hydroxycarbamide and might otherwise require chronic transfusions. (Voxelotor is not expected to replace transfusions in patients who require them for the prevention of stroke). Unlike the Hb increase with voxelotor, which remains essentially constant whilst on treatment, the effect of transfusions on Hb decays over time, so that patients experience an initial boost to Hb but levels then gradually fall back until the next transfusion. Patients on RTT may experience increased fatigue and other symptoms of anaemia in the period before their next transfusion.[147] Treatment with voxelotor provides a sustained increase in Hb without peaks and troughs, sparing patients from the negative effects on HRQoL associated with pre-transfusion troughs.

The other recently approved SCD treatment, crizanlizumab, is indicated for the prevention of recurrent VOCs, and acts by inhibiting adhesion between endothelial cells and blood cells to reduce the risk of vaso-occlusion. However, the SUSTAIN trial reported no significant differences in markers of haemolysis between high-dose crizanlizumab and placebo-treated SCD patients.[82] Thus crizanlizumab does not appear to prevent sickling or haemolysis or to address the broader pathology of SCD beyond VOCs. Voxelotor is the only pharmacological treatment that addresses the underlying molecular basis of SCD pathology, and thus is likely to improve both short- and long-term outcomes.

Benefits not captured by the QALY

Over the long term, the effects of voxelotor described earlier in this section have the potential to produce benefits that are not captured in the QALY calculation:

- Providing a simple oral treatment as an alternative to blood transfusions for some patients will have important benefits for patients by reducing the need for transfusion-related hospital visits (which are inconvenient and burdensome, particularly as patients must travel to specialist centres), and reducing anxiety over potential adverse effects from transfusions.

- Produce benefits for the NHS arising from reduced demand for blood transfusions in people with SCD. This would reduce the pressure on blood supplies, transfusion clinics and apheresis machine time, and reduce the incidence of transfusion-related complications.

- Increase patients' ability to study and work, which in turn would improve their economic situation and productivity and reduce indirect societal costs (e.g. social security benefits). SCD has a severe impact on education and employment[54,57] that prevents those affected (and often their carers) from fulfilling their full potential and ambitions, and reinforces existing socio-economic inequalities. A study in adult UK SCD patients with high unmet need (the population likely to benefit from new treatments such as voxelotor) found Total productivity loss due to healthcare admissions, attendances, consultations, and non-hospitalised sickness for patients with SCD and high unmet need was £[redacted] (mean £[redacted] and median £[redacted] per patient year) – see Section B.1.3.1.6).[58] Carers also suffer lost productivity: a survey of 43 carers for SCD patients in the UK using the WPAI:SHP Questionnaire (see Appendix S) found that average missed work hours per year was [redacted] resulting in a yearly mean productivity loss of £[redacted].[60]

- Reduce patients' anxiety about long-term progression of symptoms, from the knowledge that they are taking a disease-modifying treatment that acts on the underlying molecular basis of SCD.

B.3.13. Validation

B.3.13.1. Validation of cost-effectiveness analysis

The model has been extensively quality controlled, both internally by the model developers and externally by other modelling groups. However, in order to gain confidence in the model output, additional comparisons of model output were made either to the data underpinning the model (internal validation), or to the available literature (external validation).

B.3.13.1.1. *Effect of Hb*

Figure 27. Hazard ratio for each 1 g/dl increase in Hb derived from the Symphony TTE analysis weighted to HES-CPRD vs the HES-CPRD analysis*

[redacted]1 - result is not statistically significant in HES-CPRD analysis; 2 - result does not show beneficial hazard ratio for increase in Hb in HES-CPRD analysis.

TTE analysis was conducted as per described in Appendix Q. The covariate estimates for baseline Hb level were exponentiated to give the hazard ratio and plotted in Figure 27. There is a good agreement between the two datasets for most complications, which provides confidence that the link between Hb and complications is robust.

However, where the results of the HES/CPRD analysis are not statistically significant (i.e., arrythmias, leg ulcer, osteomyelitis, osteonecrosis, priapism, and stroke), the results diverge to an extent. It is predominantly for this reason, and because a greater proportion of patients have Hb levels reported in Symphony than in HES/CPRD, that the Symphony dataset is favoured over the HES-CPRD. It has greater power because of its larger population and is more able to detect the effect of Hb where the hazard ratio is closer to one.

B.3.13.1.2. *Effect on mortality*

General population mortality

All excess mortality in the model was removed from the model such that time of death was determined solely by the exponential rates classified by age and sex that were retrieved from the Office for National Statistics. By comparing the life expectancy of the mean age entering the model with that of the lifetables it is possible to determine whether the model is correctly estimating the baseline mortality (Table 59). All excess SCD mortality was removed from the model simulation for comparison purposes. Model results and settings are available in the model by selecting '**Validation 4: remove excess mortality**' from the scenario manager.

Table 59. Comparison of model predicted mean age at death versus the life expectancy for the same mean age at baseline in the ONS lifetables.

Baseline age	Model predicted mean age at death (with excess SCD mortality removed)	Life expectancy for 33 y/o*	Standardised mortality ratio
[redacted]	[redacted]	82.44	0.99
*Weighted by 58% female / 42% male y/o, year old			

Excess mortality

To assess whether the mortality predictions for persons with SCD are credible, the most recent and relevant report in the literature is that by Piel et al.[162] This is an analysis of mortality and complications in the UK SCD population using the HES/CPRD dataset. Piel et al.[162] stratify the overall SCD cohort into a crises cohort, transfusion cohort and all other SCD patients. The criteria for the crises cohort were to have experienced four VOCs in the two baseline years of the study (2009 to 2010), while for transfusions the requirement was six or more transfusions per year over the same period. It is possible to calculate an overall SMR from the data provided for each of the sub-cohorts and the overall population and to compare with the predicted SMR from our model. The model was run with two populations: (1) to match the RTT and HC proportions of the complete TTE analysis dataset [refer to 'Validation 3']; and (2) to match the base-case analysis dataset where RTT and HC proportions are defined by the results of the UK Delphi panel .[209] [Refer to 'Base case']

The predicted SMRs from the model are not directly comparable to any of the cohorts from Piel et al.[162] Both model populations are clearly less healthy than the entire SCD cohort, which is reflected in the predicted SMR of [redacted] and [redacted] vs [redacted] for model populations 1 and 2 respectively. Model population 2 is probably closer in terms of health to the crises/transfusion cohort ([redacted] vs [redacted]), although the model population was less restrictive than the crises cohort with regard to how many crises events were experienced: for the crises cohort, the mean number of crises was 4.5 per year and the median was 3 per year while in contrast the model predicts the mean number of VOCs per year to be [redacted] over the lifetime horizon. It should be expected then that the model SMRs falls between the bounds of the overall SCD cohort and the crises/transfusion sub-cohort, with model population (1) being closer

to the entire cohort and model population (2) being closer to the crises/transfusion cohort.

Table 60. Comparison of the predicted SMRs versus those observed in a HES-CPRD dataset by Piel[162]

Model predictions		Cohort (data from Piel et al.)				
Validation 3[a]	Base case[b]	Crises	Transfusion	Transfusion & crises	Other SCD	Entire SCD
[redacted]	[redacted]	8.92	8.80	9.48	3.20	3.56
[redacted]						

B.3.13.1.3. *Complication prevalence*

By running the model with a time horizon of seven years, we can compare the complication prevalence at seven years to that observed in the HES/CPRD dataset (see Appendix Q and R), where the mean follow-up time was approximately seven years. As such, for the Symphony TTE equations, this serves as external validation, while for the HES-CPRD TTE equations it serves as internal validation.

Symphony derived TTE dataset

Figure 28. Predicted complication prevalence using Symphony TTE equations versus HES-CPRD prevalence during study period (mean follow-up ~ 7 years)

[redacted]

Dashed lines represent ± 50% difference.
Refer to model scenario '**Validation 1: HES CT/HC proportions, 7 year time horizon**'

It is evident from Figure 28, that there is good agreement between the model predictions and HES-CPRD observations. There are several complications where the predictions are not as good, notably for sepsis, arrythmias, cardiomegaly, heart failure and ARF. The model appears to over-predict the seven year prevalence compared to the results of the HES/CPRD analysis. This suggests a difference in diagnosis/treatment rates between the UK and the US. This can be confirmed by running the model using the HES/CPRD derived TTE equations.

HES/CPRD derived TTE dataset

Using Figure 29 and with reference to the foregoing, it is clear that there is very good internal consistency between the results of the HES/CPRD dataset and the model predictions using TTE equations derived from the dataset. This presents something of a trade-off with respect to which underlying source to use for the model equations: the Symphony equations appear more robust with respect to the effect of Hb (indirectly the treatment effect), while the HES/CPRD equations appear to represent the baseline incidences of the UK SCD population better.

Figure 29. Predicted complication prevalence using HealthIQ TTE equations versus HES/CPRD prevalence during study period (mean follow up ~ 7 years)

[redacted]Dashed lines represent ± 50% difference.
Refer to model scenario '**Validation 8: HES CT/HC proportions; 7 years; HES TTEs**'

B.3.13.1.4. *Complication incidence rates*

The prevalence of complications does not give us the full picture of the model performance. There are multiple recurrent events within the mode which make estimation more complicated. There is a scarcity of good data on incidence rates in SCD in the literature, so only some complication incidence rates are validated here.

VOC

The HES/CPRD analysis (see Appendix R) in its Clinical Events section, reports a mean VOC incidence rate of 1.30 per year over 7 years of follow up. Using scenario '**Validation 1: HES CT/HC proportions, 7 year time horizon**', the model predicts a mean VOC incidence rate of [redacted], which is somewhat lower. However, the predicted VOC incidence rate is much closer to the median incidence VOC rate of [redacted] in the HES-CPRD analysis. This suggests that the distribution of VOC events is skewed to the right which is potentially why the TTE models as constructed are not able to properly represent the tail of the VOC distribution. This behavior occurs for both arms of the model and is not likely to be beneficial to voxelotor, because it reduces the overall rate of VOC which have substantial cost and utility impacts.

It is also possible to compare the (non-statistically significant) reduction in VOC incidence in HOPE[91] to a model simulation over two years which matches the HOPE proportions of HC and RTT (0% RTT / 65% HC. The incidence rate ratio for voxelotor vs placebo in HOPE was [redacted], while the model predicts a ratio of [redacted] [refer to

'**Validation 2**']. This suggests very close agreement between the best data available for the effect of voxelotor on VOC incidence and that indirectly obtained via the simulation model using the TTE analysis.

Stroke

As seen from Figure 30, the model over-predicts stroke in the all the age categories compared to the literature. It should be noted that the literature values represent a Californian SCD population from over the period 1998 to 2007,[167] and the confidence intervals are quite wide (Figure 30). Additionally, the populations are not matched, with the model restricting to a patient population described in Section 2.1 and the literature using the overall SCD population, which mean that the comparisons should not be over interpreted; the overall SCD population in the literature estimates is likely to be healthier than that chosen for the model. Model predictions were estimated for each age group by running the model for 15 [refer to **'Validation 5'**], 30 [refer to '**Validation 6'**] and 100 [refer to '**Validation 3**'] years respectively such that the mean age taken over the entire model time horizon matched the age grouping in the literature.

Figure 30. Model predictions for stroke incidence versus Strouse[167]

[redacted]

CKD

Yeruva et al.[239] used the Truven Health MarketScan Medicaid Databases in the US from 2007–2012 and estimated the annual incidence of CKD in the patients with a sickle cell diagnosis. The annual rate was 1.4 per 100 person years compared to the model which predicted an annual rate of [redacted] person years when the model time horizon was set to five years [refer to '**Validation 7**']. Again, the model and literature populations were not matched as the literature population was the overall SCD.

Osteonecrosis

Milner et al. [240] studied 2,690 persons with SCD over an average period 5.6 years in the US. Overall, the incidence rate of osteonecrosis was 3.50 per 100 person years in the 25-34 age category. This compares to a rate of in the model of [redacted], when the time horizon is set to five years [refer to '**Validation 7**']. Again, the model and

literature populations were not matched as the literature population was the overall SCD. The literature data are also very old, which might explain why the incidence rate is higher than the model predicts. The model can be considered conservative.

Leg ulcers

It is possible to calculate an incidence rate of new leg ulcers in the placebo population in the HOPE RCT ([redacted] person years).[93] We attempted a comparison to the model by matching the HOPE population (0% RTT / 65% HC) for which the model predicts a leg ulcer incidence rate over [redacted] person years [refer to **'Validation 2'**]. Although the model prediction is lower than that derived from the HOPE trial, it must be considered that population in HOPE was under clinical trial conditions and as such diagnosis rates of leg ulcers are likely higher than in the real world on which the model bases its TTE equations.

B.3.14. Interpretation and conclusions of economic evidence

Patients with SCD face considerable morbidity over their life time, and reduced life expectancy. Patients who are intolerant, ineligible, have an inadequate response to or are unwilling to take current first line treatment (hydroxycarbamide) have limited options, and high unmet need. Voxelotor would provide a new treatment option for these L2+ patients. This analysis found that voxelotor compared to SOC resulted in total incremental QALYs of [redacted], with incremental costs of £[redacted], resulting an ICER of £[redacted] / QALY.

Strengths of the modelling approach

The economic model has several important strengths. A DES approach was used in order to overcome the limitations highlighted in previous models of SCD submitted to NICE.[132] This allowed for a time-to-event approach (which was suggested as being a good option in SCD by the ERG in the crizanlizumab appraisal), modelling a large range of SCD-related events. The model was extensively validated and independently QC'd, and a range of deterministic and probabilistic sensitivity analyses were run to explore uncertainties.

Time to SCD-related events was modelled based on Hb levels (together with demographics [gender, age], Hb level, VOCs frequency history, interplay between

Hb and VOCs frequency history, treatment [HU and RTT] history and comorbidities history). This was informed by a large contemporaneous cohort of patients with SCD.

The evidence that Hb is linked to these outcomes is robust, having been confirmed in two database studies, a meta-analysis and several smaller studies published since. The use of the Symphony database to derive TTE data has the advantage of providing a larger sample with more complete recording of Hb levels than could be obtained from the UK source that was considered (the HES-CPRD database). To improve the applicability of Symphony to the UK SCD population, a matching-adjusted indirect comparison (MAIC) analysis was undertaken match the population to the UK SCD patient population characteristics found in HES-CPRD.

Limitations

As with all economic analyses, there are some limitations. Because of the long-term nature of the disease and the complications arising from it, the treatment effect of voxelotor on wider SCD outcomes had to be modelled indirectly via the improvement in Hb level. As noted above, there is strong evidence for this relationship. However, the results may not fully reflect the long-term benefits of voxelotor on the pathology of SCD. As voxelotor acts on the underlying molecular event in SCD (HbS polymerisation, which leads to sickling, haemolysis and the progressive organ damage that is characteristic of SCD, as illustrated in Section B.1.3.1.1), it has potential benefits beyond those which emerge from the modelling of Hb levels in SCD patients who are not receiving voxelotor. The magnitude of effect of voxelotor on long-term outcomes remains uncertain as long-term follow-up evidence is not yet available. There is also no evidence on the long-term efficacy of voxelotor past 144 weeks, though the evidence that is available does not suggest any waning of treatment effect over the time period studied.

The model population differs from that studied in HOPE due to the inclusion of a proportion of patients on RTT in the model (in line with the UK patient population). This creates uncertainty, because no direct head-to-head comparison is available between RTT and voxelotor. Given the absence of applicable published data despite the extensive search, in the base case no change in Hb levels among patients on RTT is explicitly modelled. However, RTT is included as a covariate in the TTE

analysis and therefore influences the incidence of complications within the model (see Section B.3.3.3). Furthermore, the waning of Hb levels between transfusions (see Section B.3.3.1.2) is not captured in the model for reasons of simplicity. A scenario analysis is presented which effectively assumes a constant relative difference of 0.8 g/dl for those on transfusion vs those not on transfusion. This is conservative assumption biasing against voxelotor. Similarly, there is a lack of good evidence on the rates of RTT discontinuation, which is a source of uncertainty. A conservative rate of 5% was assumed based on discussions with clinicians, but it is possible this is significantly higher in clinical practice and may vary due to variations in practice and in the services and resources available. Higher discontinuation of RTT would mean that under current SOC more patients are left without disease-modifying treatment (or with only inadequate response to hydroxycarbamide in those able to take it). These patients have very high unmet need and use of a low RTT discontinuation rate may overestimate efficacy in the SOC arm and thus bias against voxelotor.

There is also uncertainty about the health utility status of 2L SCD patients. The baseline EQ-5D values taken from the HOPE study are likely to overestimate the utility of patients with SCD: they are very close to population norms for the UK and are higher than utilities reported in the literature for SCD patients.[192,199] SCD patients have never known full health so they may value their default health state more highly than it would be valued by someone who had previously been healthy. The baseline utilities from HOPE were used to calculate the SCD-related utility decrement that was applied in the model. As all patients in both arms have SCD throughout the model time horizon, this will have a limited effect on the incremental QALY values. However, the baseline value in HOPE was also used to calculate the QALY shortfall for the severity modifier, and may have led to underestimation of the shortfall.

Conclusion

The use of a DES model incorporating time-to-event to a comprehensive range of SCD-related outcomes, informed by real-world data, provides a robust approach to modelling the effect of voxelotor in SCD. Voxelotor provides a gain in both life years and QALYs for patients with SCD ewho are intolerant, ineligible, unwilling to take or

have an inadequate response to, hydroxycarbamide). In the model base case, considering a lifetime horizon, the total undiscounted life years (LYs) was [redacted] for voxelotor and [redacted] for SOC; total discounted LYs were [redacted] and [redacted], respectively (Table 52). Total undiscounted QALYs were [redacted] for voxelotor and [redacted] for SOC; total discounted QALYs were [redacted] and [redacted], respectively, with an incremental difference of [redacted] (Table 52). The incremental cost effectiveness ratio was £[redacted] / QALY. Making voxelotor available on the NHS in England will provide an important new option for the treatment of haemolytic anaemia in SCD, in a population with high unmet need that faces a range of equality issues.

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B.5 Appendices list

A list of the appendices to the submission is given below. All appendices are supplied as separate documents.

Appendix	Content
C	SmPC and Public Assessment Report
D	Identification of evidence: Clinical SLR
E	Subgroup analysis
F	Adverse events
G	Published cost-effectiveness studies
H	HRQoL studies
I	Cost and HCRU studies
J	Clinical outcomes and disaggregated results from model
K	Price details of treatments
L	Checklist of confidential information
M	Model inputs: additional information
N	Hb response probabilities, HOPE
O	Time to discontinuation analysis, HOPE
P	HES/CPRD TTE analysis
Q	Symphony TTE analysis
R	HES-CPRD Symphony matching report
S	Caregiver burden survey
T	Patient journey report
U	Delphi panel report
V	Patient testimonies

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

July 2022

File name	Version	Contains confidential information	Date
		Yes	29 July 2020

Summary of new material provided

In addition to the responses document and confidentiality checklist, the following items have been supplied, and should be read in conjunction with the responses:

Appendix	Content
K	Price details of treatments – an updated version has already been sent to the EAG as requested
P	HES/CPRD TTE analysis (revised version)
Q	Symphony TTE analysis (revised version) + accompanying Excel workbook
R	HES-CPRD Symphony matching report (revised version)
W	Association between age and comorbidities (new appendix)
Addendum	Addendum containing updated modelling results
Reference pack	New references that were not contained in the reference pack to the original submission

An updated economic model has also been supplied, together with a supplementary file of patient history data (Patient History 50K base case).

Section A: Clarification on effectiveness data

A1.

Evidence provided by the company suggests that, for patients with SCD, higher Hb levels are associated with lower risks of specific complications. However, not all patients with high Hb levels experience low rates of these complications and not all patients with low Hb levels experience high rates of these complications. Voxelotor elevates Hb levels for some, but not for all patients. This could be because the biology of the patients who respond to voxelotor may be different to the biology of the patients who do not respond to voxelotor. Please provide clinical evidence to refute the interpretation that any patient who

responds to voxelotor may also be one who is less likely to experience complications, irrespective of their Hb level (or treatment with voxelotor).

The evidence from time-to-event analysis of the Symphony database (presented in CS Appendix Q) shows that higher Hb was statistically significantly associated with reduced risk for occurrence of ARF, arrythmias, cardiomegaly, CKD, gallstones, heart failure, leg ulcer, osteomyelitis, osteonecrosis, pulmonary hypertension, pneumonia or VOCs, priapism, sepsis, and stroke. In addition, at the median value for number of VOCs during the 12 months pre-index (zero), a [redacted]% proportionate reduction in the risk of pulmonary hypertension was found per unit increase in Hb (Appendix Q Section 3.3). The finding that higher Hb is associated with lower risk of complications is in line with published studies, including a meta-analysis.[1-4] Furthermore, the correlation between low Hb and increased risk of complications reflects the biology of SCD: sustained haemolytic anaemia causes progressive deterioration in tissue and organ function, through chronic reduction in oxygen supply and via inflammation and vascular damage caused by the products of haemolysis.[5,6]

As with almost all such correlations, the relationship between Hb and complications is not absolute but rather is based on increased risk. At any given Hb level, some patients will develop a given complication while others will not. Similarly, as with most medicines, voxelotor produces a response in some patients but not in all. Of note, 89% of patients receiving voxelotor 1500 mg/day in HOPE achieved a response at some time point by 72 weeks (ITT population).[7] To refute the interpretation that any patient who responds to voxelotor may also be one who is less likely to experience complications, it is useful to examine factors that are statistically associated with risk of complications and see whether they are also associated with likelihood of response to voxelotor.

Predictors of lower complication risk in Symphony

In the Symphony database analysis, higher Hb was associated with significantly reduced risk for the complications listed above. The only other patient characteristic consistently associated with a reduced risk of these complications was female sex (see Appendix Q, Table 3). Age showed a significant association with some complications but not all, and the direction of association varied, as might be expected

given that some are acute in nature and affect SCD patients throughout life, while some develop over time and are therefore more common in older patients. Thus, age was not an overall predictor in Symphony for the risk of developing these complications. In addition, the interaction between Hb and VOC count was significantly associated with increased complication risk in 9 of the 15 complications. In these complications, the magnitude of association between Hb and the complications is influenced by the number of VOCs. However, the effect from the interaction is much smaller than the effect attributable to Hb alone. In summary, higher Hb was the main predictor of lower complication risk.

Covariates were selected for inclusion in the analysis by a process of iterative elimination until all variables had p-values less than or equal to 0.05 (see Appendix Q for details of methodology). Additional covariates were then dropped if they were deemed irrelevant or immaterial or coefficient values were deemed to be implausible by a clinical expert. The regression analysis, undertaken on a large database, can therefore be expected to have captured all the patient-related characteristics (for which data were available) that have a significant influence on the risk of these complications. The complications for analysis were selected based on review of the literature and clinical expert opinion. Complications for which the analysis predicted an increased risk at higher Hb levels were not included in the economic model as the association was deemed to be implausible; the rationale for this is discussed under Question B4.

Predictors of response to voxelotor

In the HOPE trial,[8] pre-specified subgroup analyses were carried out to see whether baseline patient characteristics influenced likelihood of response (defined as a 1 g/dL increase in Hb at 24 weeks). All subgroups showed a statistically significant benefit for voxelotor (with the exception of baseline Hb < 7 g/dL, where, although the point estimate was similar to that for Hb ≥ 7 g/dL, small patient numbers [n=7 in each arm] led to a wide confidence interval whose lower bound was marginally below 0). There were no statistically significant differences in response rate between groups within any of the categories examined (age, sex, race, geographic region, VOC history, baseline hydroxycarbamide use and baseline Hb; see Figure 1), therefore none of these were predictive of response to voxelotor.

	Placebo		Voxelotor 1500 mg	
	N	Response Rate[a]	N	Response Rate[a]
ITT (Groups 1 and 2)	92	6.5%	90	51.1%
Age				
12 to <18 years	17	5.9%	14	57.1%
18 to 65 years	75	6.7%	76	50.0%
Sex				
Male	42	9.5%	32	56.3%
Female	50	4.0%	58	48.3%
Race				
Arab or Middle Eastern	20	5.0%	20	55.0%
Black or African American	63	4.8%	59	52.5%
Geographic Region				
North America	35	11.4%	34	52.9%
Europe	18	0%	19	36.8%
Other	39	5.1%	37	56.8%
VOC History (prior 12 months)				
1 episode	39	5.1%	35	60.0%
≥2 episodes	53	7.5%	55	45.5%
Baseline HU Use				
No	34	8.8%	32	43.8%
Yes	58	5.2%	58	55.2%
Baseline Hb				
<7 g/dL	7	14.3%	7	57.1%
≥7 g/dL	85	5.9%	83	50.6%

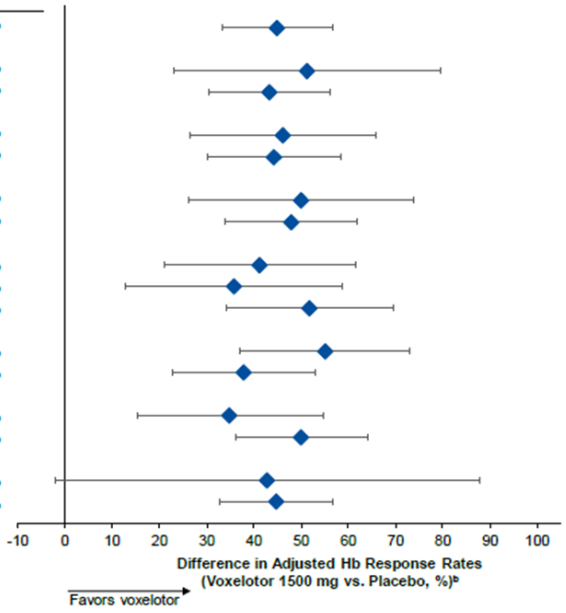


Figure 1 Hb response at week 24 by subgroup (voxelotor 1500 mg vs placebo)

Source: EMA EPAR[9]

Additional subgroup analysis for change from baseline in Hb with voxelotor was undertaken using both individual patient-level data from HOPE and real-world data from US patients in Symphony who were receiving voxelotor (see CS Section B.3.3.1.1, results in Table 28). Across most subgroups, differences in treatment effects were again not statistically significant. However, in Symphony the mean increase in Hb was significantly greater in individuals with lower baseline Hb (≤7.5 g/dL vs >7.5g/dL). Additionally, the mean increase in Hb was significantly greater in patients with 1 VOC in the last 12 months as compared to 2-3 VOCs (HOPE data analysis), but the trend was not observed in patients with ≥4 VOCs: the effect on patients with ≥4 VOCs was similar to those with only one VOC. The analysis of the Symphony data did not indicate any differences in treatment effect by VOC history.

These data again indicate that none of the patient groups analysed had a significantly greater increase in Hb with voxelotor, with the exception that in real-world use, patients with lower Hb (who would be expected to be at greater risk of developing complications) had a larger response to voxelotor than those with higher Hb. In

summary, no patient groups– either in HOPE or in real-world use of voxelotor in Symphony – have an increased likelihood of response to voxelotor than other groups.

Effect of voxelotor on complications vs placebo

Some placebo-controlled data on the effect of voxelotor on complications is available from the HOPE study. Patients treated with voxelotor 1500 mg had numerically lower annualised adjusted incidence rate of VOC than in the placebo group (2.37 vs 2.79) at 24 weeks. Patients receiving voxelotor in HOPE open label extension had low annualised VOC rates across all former HOPE treatment arms, at 1.3 (95% CI: 1.1-1.4) events per year (median duration of treatment 69.9 weeks; CS Section B.2.6.8.4). A published post hoc analysis at 72 weeks suggests that voxelotor has clinical benefits for leg ulcers, with more voxelotor-treated patients experiencing improvement or resolution of leg ulcers compared with placebo, and fewer developing new ulcers (CS Section B.2.6.7).[10] These placebo-controlled data support the assertion that voxelotor is a disease-modifying treatment that is expected to reduce the incidence of SCD complications.

Conclusions

Subgroup analyses from the HOPE trial show that none of the patient characteristics analysed significantly influence either a patient's likelihood of responding to voxelotor or the mean change from baseline in Hb obtained with voxelotor. The majority of patients do respond to voxelotor (89% by 72 weeks).[7] In the Symphony database, a comprehensive set of regression analyses was carried out to identify patient characteristics that were significantly associated with risk of complications, and baseline Hb was the only consistent predictor found (apart from female sex, which is not predictive of response to voxelotor). In the HOPE trial, voxelotor was associated with numerical benefits for VOC incidence and leg ulcers compared with placebo. Together, these results refute the interpretation that patients who respond to voxelotor have characteristics that also reduce their risk of complications regardless of Hb level or treatment, based on the characteristics for which data are available. Furthermore, increased Hb level has been shown to be associated with reduced risk of SCD complications in the literature,[1-4] and was the only characteristic found to consistently predict lower risk of complications in Symphony.

A2. Priority question

The company states in Appendix Q (page 4) that "Patients in the Symphony database were weighted so that their aggregate baseline characteristics matched those reported by HealthIQ in their analyses of the CPRD/HES database using matching-adjusted indirect comparison (MAIC) methods":

- ***Please describe in further detail the MAIC approach which has been used to match patients in the Symphony database with patients in the GPRD/HES database.***

The MAIC was conducted using procedures initially described by Signorovitch et al.[9] MAIC is a form of propensity score weighting, applicable where IPD are available in one population and aggregate data in another. Individuals in the IPD population are weighted by the inverse of their propensity score, to balance the covariate distribution with that of target aggregate population. [10] Whereas conventional propensity score methods use logistic regression to estimate propensity scores, MAIC requires a novel approach – i.e., "method of moments" – due to IPD only being available in one of the two populations.[10] The calculation of MAIC weights were conducted using the MAIC package in R.[11] MAIC weights were standardised by dividing unstandardised weights by the mean value of the unstandardised weights (so that the mean of standardised weights equals 1.0). Descriptive statistics for the MAIC weights were generated including mean, SD, mode, percentiles and a histogram. Covariates included in the calculation of weights are described below AFT regressions were conducted using SAS Proc Lifereg. The MAIC weights were incorporated using the WEIGHTS statement. In the Lifereg procedure, the WEIGHT variable multiplies the contribution to the log likelihood for each observation.

- ***Please confirm the list of patient characteristics that were included in the MAIC which were used to estimate weights for patients in the Symphony database.***

Patient characteristics used in the calculation of the MAIC weights included the following:

- Mean age at baseline (y)
- Female (%)
- Mean Baseline Hb (g/dL)
- Number of VOCs during 12 months pre-index, 0, 1-2, 3, 4, 5+ (%)
- Prior treatment with hydroxyurea (%)
- Prior treatment with chronic transfusion (%)

- History of Acute Renal Failure (%)
- History of Arrhythmias (%)
- History of Cardiomegaly (%)
- History of CKD (%)
- History of ESRD (%)
- History of Any Kidney Failure (%)
- History of Gallstones (%)
- History of Heart failure (%)
- History of Leg Ulcer (%)
- History of Osteomyelitis (%)
- History of Osteonecrosis (%)
- History of Pulmonary Hypertension (%)
- History of Priaprism (%)
- History of Sepsis (%)
- History of Stroke (%)

For age and baseline, only the first moment (mean) was included

- ***Please explain the process used to identify the list of patient characteristics considered to be relevant for inclusion in the MAIC.***

The covariates included in the matching were similar to those employed in the AFT regressions for predicting the time to event distributions for clinical events. These included demographic variables (age and sex), baseline Hb (mean), history of VOCs (categorical variable), history of treatment with hydroxyurea (%), history of chronic transfusion therapy (%), and history of various potential complications of SCD (%). These were the same events as considered in the model. These characteristics were hypothesised as being potentially prognostic for the events of interest, and were in line with subgroups analysed in the HOPE trial, with some additional clinically relevant covariates.

- ***Please explain the method used to calculate the weights for patients in the Symphony database.***

As noted above, the calculation of MAIC weights were conducted using the MAIC package in R.[11] MAIC weights were standardised by dividing unstandardised weights by the mean value of the unstandardised weights (so that the mean of standardised weights equals 1.0). Descriptive statistics for the MAIC weights were generated including mean, SD, mode, percentiles and a histogram. Covariates included in the calculation of weights are described above.

- ***Please explain how the weights have been incorporated into the accelerated failure time (AFT) regression models.***

As noted above, AFT regression was conducted using the flexsurvreg function in the flexsurv package in R. In flexsurv, the MAIC weights were incorporated using the "weights" option, which multiplies each observation's contribution to the log likelihood by the variable specified in the weights option. In weighted analyses, patients with very small weights (<.0001) were dropped from the regressions to ensure that valid solutions could be obtained (although there were no weights <.0001, so this screen was not applied).

- ***Please describe the impact of weighting patients in the Symphony data by providing an interpretation of the results obtained from the weighted AFT regression models (secondary analyses) and please also provide a narrative comparison of the weighted AFT regression model results versus the unweighted AFT regression model results.***

Results of the AFT regressions with patients MAIC weighted to match patients in the CPRD/HES dataset were qualitatively similar to those for the unweighted sample: the signs on the coefficient were the same in both analyses for virtually all covariates, and the coefficient for Hb was generally similar (+/- 30% relative difference) for the weighted and unweighted samples.

- ***Please confirm whether it was possible to include any additional patient characteristics in the MAIC to match patients in the Symphony database to patients in the CPRD/HES database.***

As noted above, the covariates included in the matching were similar to those employed in the AFT regressions for predicting the time to event distributions for clinical events. While there are many additional patient characteristics that could theoretically be included in the MAIC, the variables included were considered sufficient to effectively match the patients in Symphony to those in CPRD/HES on the key prognostic characteristics available in the two datasets. The Symphony database did not have information on ethnicity or IMD deprivation status, so these variables were not included in the calculation of the MAIC weights. Opioid dependence was not included as it was not possible to identify this in the CPRD/HES database. History of the events that were dropped from the AFT regressions because of noncredible coefficient estimates (i.e., cellulitis, depression, retinopathy) was also not included in the weighting.

A3. Priority question

The company states in Appendix Q (page 4) that: "Patient characteristics were eliminated iteratively starting with the covariate with the highest p-value until all variables had p-values less than or equal to 0.05. Additional covariates were then dropped if they were deemed irrelevant or immaterial or coefficient values were deemed to be implausible by a clinical expert". Where possible, for each outcome listed in Table 9 (Appendix Q):

a. Please confirm why a saturated AFT regression model (i.e., without using elimination methods) which includes all patient characteristics, for both unweighted and weighted Symphony data was not fitted.

Regression models were initially fit with all covariates of interest (i.e., "saturated" regression models). However, as saturated regression models frequently did not converge (e.g., with the revised weights, the regression models converged only for four events: cardiomegaly, gallstones, osteonecrosis, and sepsis), regression models with covariate selection were explored. For those saturated regression models that did converge, the saturated regression models yielded similar results to the regression models with covariate selection. For consistency, regression models with covariate selection were used for all events in the economic model.

b. Provide a narrative comparison of the results obtained from the saturated AFT regression models fitted as a response to Question 3a with the results presented in Tables 3 and 9 in Appendix Q, including an assessment of model fit.

As noted above in the response to Question 3a, the weighted regression models based on the revised weights prepared for this response converged for only four events: cardiomegaly, gallstones, osteonecrosis, and sepsis. For these events, the coefficients that were estimated for both the saturated and unsaturated models were qualitatively similar. The signs of the coefficients were the same for all the models, except for the covariate for VOC count for gallstones, which was negative for the saturated model and positive for the model with covariate selection. The coefficient for the covariate for Hb was similar (+/-5% relative difference) for all outcomes except osteonecrosis, for which the coefficient was 63% greater with covariate selection than without [redacted] vs. [redacted]).

A4.

The company states in Appendix Q (page 4) that: "In weighted analyses, patients with very small weights (<.0001) were dropped from the regressions." Please provide a summary of the rescaled weights obtained from the MAIC analysis reported in Appendix Q, including:

- ***Mean and median values.***
- ***Minimum and maximum values as well as lower and upper quartiles.***
- ***The proportion of patients with weights less than 0.0001.***
- ***A histogram of the distribution of weights.***

The requested summary outputs from the MAIC are provided in Appendix Q, page 56 onwards. Note that there were no weights <.0001, so this screen was not applied.

A5.

Regarding the summary patient characteristics of the CPRD/HES database based on 2,106 patients, please explain the discrepancies observed in Table 4 (Appendix P) versus Table 8 (Appendix Q) for the following characteristics:

- ***The proportion of patients who have received either current or prior hydroxyurea treatment [Table 4, Appendix P: n=229 (10.87%) versus Table 8, Appendix Q: n=[redacted] ([redacted])].***

Thank you for identifying the mismatches. For the bullet above, both values are incorrect. Values reported in Table 4 of Appendix P are the sum of "current" and "prior" but the two are not mutually exclusive. As such, the total number (percentage) of patients ever on hydroxyurea treatment (including current and prior) in the HES/CPRD database is n=[redacted] ([redacted]%). Table 4 of Appendix P and Table 8 in Appendix Q have been updated accordingly. Moreover, the MAIC was redone after correcting for the errors identified.

One additional correction was performed before rerunning the MAIC, as follows: The codes used to define the variable "chronic transfusion" were not exactly matching in the HES/CPRD database and the SYMPHONY database. Codes in SYMPHONY have been adjusted to exactly match the ones used in the HES/CPRD analysis. For further details, please see revised Appendix Q.

In addition, it should be noted that an error was identified in the TTE analysis of the HES/CPRD database whereby the covariates treatment history with hydroxycarbamide (HC) and RTT were being considered at point instead of up to baseline. The analysis has therefore been redone and an updated Appendix P is provided (specifically, Table 3 has been updated). The HES/CPRD based equations are used (only) for validation purposes in the economic model. As such, that section of the model has been updated accordingly.

All of the corrections identified above have been incorporated into the economic model and are reflected in the revised results supplied in the Addendum document.

- ***The proportion of patients who have a history of end stage renal disease (ESRD) [Table 4, Appendix P: n=[redacted] versus Table 8, Appendix Q: [redacted].***

Thank you for identifying the mismatch. The correct values are those in Table 4 of Appendix P.

- ***The proportion of patients who have a history of any kidney failure [Table 4, Appendix P: [redacted] versus Table 8, Appendix Q: [redacted].***

Thank you for identifying the mismatch. The correct values are those now in Table 8 in the updated Appendix Q.

A6.

Table 9 (Appendix Q) reports results for MAIC weighted patients; please explain why the effective sample size (ESS) after matching is identical to the total number of patients for the following outcomes: acute renal failure (ARF), arrythmia, cardiomegaly, chronic kidney disease (CKD), ESRD, gallstones, heart failure, leg ulcer and osteomyelitis.

In Table 9 (Appendix Q) there was a transcription error of some of the ESS numbers for some events. All of these transcription errors have now been corrected in the amended Appendix Q that has been submitted with the CQ responses. The transcription error had no impact on the analysis, which was run using the correct values. Thank you for raising this clarification question.

Section B: Clarification on cost-effectiveness data

B1. Priority question

The EAG is not able to carry out a comprehensive check of the submitted company model as it is not possible to follow individual patient experiences and/or check how costs and QALYs accumulate over time. As a priority, please provide a more transparent version of the model that would enable the EAG to carry out the necessary checks.

The company has submitted a revised version of the model with increased functionality to output raw data from VBA code to Excel sheets. Two new functions have been added.

The first summarises overall QALYs and costs over time and outputs the data to the sheet 'COST_QALY_OUT' and is presented in graphical form at the bottom of the main results tab.

The second new feature of the model allows the user to optionally output the event history of all agents in the model. For each agent this includes 4 rows of data: (1) the event label; (2) the event time (in months); (3) the cumulative QALYs at each corresponding event time; and (4) the cumulative costs at each corresponding event time. Initial checks have been made on a simulation of 100 patients that the mean LYs and mean QALYs match those output on the results tab. It is possible to output the results of all 50,000 patients in the model, but this is very data intensive and requires Excel to work very hard to calculate summary data, so it is advised to perform verification checks on smaller numbers of agents. To activate this mode, the user can switch a toggle on the settings tab and re-run the simulation. A step-by-step guide can be supplied on request; please notify the company if the EAG would like the guide.

B2. <u>Priority question</u>

Some of the values in CS Table 32 and CS Table 33 are implausible. Please check and correct, if necessary, all values in these two tables.

Thank you for identifying this issue. Some of the values in CS Table 32 and CS Table 33 were implausible due to a transcription error. In addition, the row label for the

duration of follow-up was labelled in years when the correct duration is months not years. These reporting errors had no impact on the analysis, which was run using the correct values. The table has been revised in the amended Appendix Q, Table 3.

B3. Priority question

Please explain why the mean patient utility values in the model (approximately 0.3 regardless of treatment) are so low.

Utility values were calculated in the model by first applying an SCD utility decrement of [redacted], which was meant to capture the impact of living with an SCD diagnosis as well as that of any complications not captured in the model. This follows the approach used in NICE clinical guidance 143 (CG143)[12] where an SCD utility decrement of 0.198 was applied.

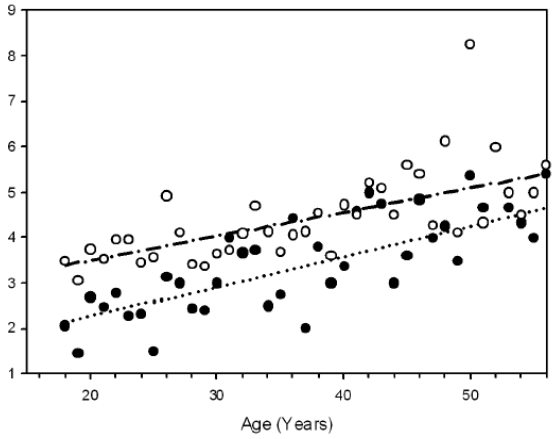
Utilities in the model evolve over time according to three factors: Hb levels, occurrence of complications, and regular transfusion therapy (RTT), as detailed in the company submission documents.

Since the SCD decrement was calculated based on baseline utility values from the HOPE trial[8] and utility values of age and gender matched population norms, it is possible that double counting may have occurred, if at baseline HOPE participants had some of the conditions modelled in the economic model. However, given that the mean baseline utility in the HOPE trial is very high compared to values published in the literature for SCD patients, this possible double counting is unlikely to be a major factor contributing to the overall low mean utility over time (see Section below entitled Utility values in patients with SCD).

The main driver for the low average lifetime utility in the model is the additive assumption made for comorbidity decrements. SCD is a systemic disease where multi-comorbidities are frequent and increase with age.[13,14] In the well-established Comprehensive Sickle Cell Centers Clinical Trial Consortium (CSCC), data from 1046 adults indicates that at the age of 31 (standard deviation 11.8) most adults had experienced more than one SCD-related complication (mean 3.8 ± 2.0, median 4), and more than one affected organ system (mean 3.3 ± 1.5, median 3).[13] Moreover, there is a positive association between age and comorbidities which contributes further to a

low mean lifetime average utility in a modelled cohort of patients with “mean age” of [redacted] years old.[1]

Figure 2: Relationship between age and mean number of complications per individual (Dampier 2011)



As part of your explanation, please provide the following information:

- ***For patients with multiple co-morbidities, are utility values additive? If yes, what evidence do you have to support the validity of this approach?***

Yes, an additive approach was followed for patients with multiple comorbidities. To our knowledge, only two publications simultaneously consider utilities and a wide variety of common complications in SCD[13,14] and unfortunately, none of them looks into the question of how utilities are influenced by multiple simultaneous comorbidities beyond the basic question of whether an increase in the number of comorbidities is associated with a decrease in utility, which as expected, it is.

There is therefore, to our knowledge, no evidence to support the validity of the additive assumption – or any other approach – in SCD patients. There is nonetheless, a precedent of the additive method being preferred by NICE in its 2016 update of CG143 which assessed pain management of SCD patients hospitalised with acute painful sickle cell episode (Appendix F Full health economic report):[12]

[1] Mean age at model start: 32.85; mean age at death: 62.19.

"Application of multiple decrements

It should be clear, from the above, that a proportion of each modelled cohort is subject to multiple utility decrements (…). A recent review by the NICE Technology Appraisal Programme's Decision Support Unit (DSU) noted that there is currently no consensus on the best method for combining multiple utility decrements and provided an interim recommendation that a multiplicative method may be preferred.[15] However, this approach is only mathematically tractable where utilities are constrained to be positive. In our model, negative utility values are possible, and it is not clear how a multiplicative method could be applied. For this reason, and also because we believed it was important to capture very substantial fluctuations in short-term HRQoL for people who may be in excruciating pain, we used an additive method to combine decrements."

Current recommendations by the DSU[16] acknowledge that there is currently no consensus on the most appropriate technique, and the standard methods used to adjust for comorbidities generate very different values. In this context the recommendation is "*In the interim period, to facilitate consistency and thus comparison of results we would recommend the multiplicative method, using adjusted baselines, is used*."

It should nevertheless be noted that all nonparametric methods (including the multiplicative method) produce biased results when estimating utilities for 3 or 4 joint comorbidities.[17] As described above, this is a common situation among patients with SCD, especially when focusing on second line patients as is the case with voxelotor.

Moreover, as noted by Thompson 2019,[18] it is also possible that due to potential synergy (whereby an assessment is made as to whether the combined disutility for a set of conditions is greater than the sum of the disutilities expected for each individual condition), the additive method is in itself conservative. As noted by Thompson 2019,[18] evidence of synergies, using EQ-5D-3L index, have been found in individuals experiencing stroke and cardiovascular disease simultaneously.

Given all of the above, the additive method was initially assumed in the company submission. But face validity is a key component of any economic model and while the true lifetime mean utility values of the population with multiple complications modelled

is unknown, the research performed in the context of these EAG clarifying questions does suggest that a mean lifetime utility of 0.3 is possibly too low (see Section below entitled Utility values in patients with SCD).

As such, and despite all its limitations, the company has decided to adjust its base case by removing the initial SCD decrement and by applying the multiplicative method to multi-comorbidities. A revised model along with a results addendum are included in the response to EAG questions.

In the revised model, the mean lifetime utility is [redacted] in the standard of care arm. This is a modelled population with average age of [redacted] years (over the course of the model), representing second line patients, [redacted] of whom are on regular transfusion therapy (RTT) which is known to be associated with increased disease severity.[19] The mean lifetime utility estimated by the revised model in this population is supported by available evidence in the literature (see Section below entitled Utility values in patients with SCD).

Utility values in patients with SCD

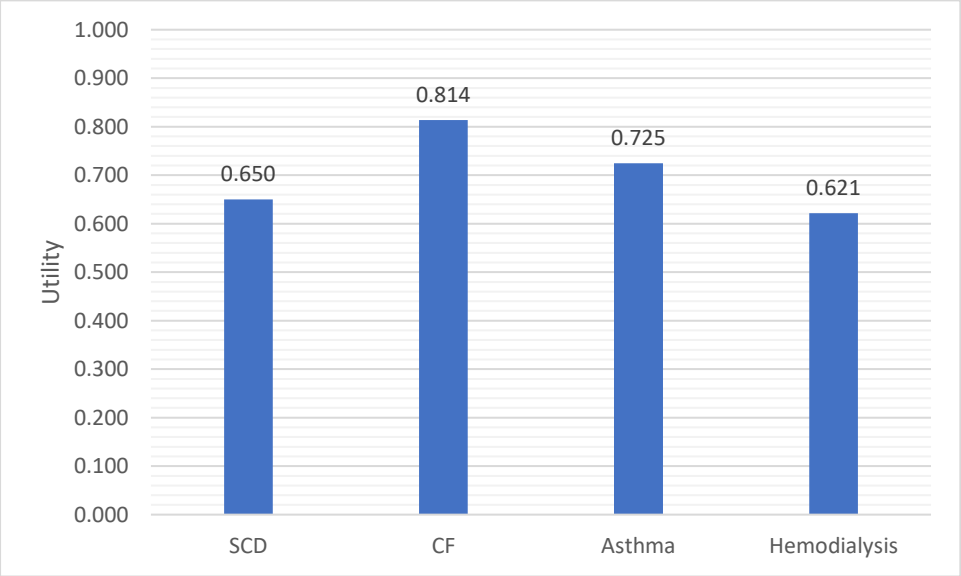
SCD versus other diseases

McClish et al. (2005)[20] administered the Medical Outcomes Study 36-item Short-Form to 308 patients from Virginia USA, participating in the Pain in Sickle Cell Epidemiology Study (PiSCES) to assess HRQoL. The majority were female (60.4%). The mean age was 33, ranging from 16 to 64 with 17.5% being over 45 years old. To assess the relative HRQOL in SCD patients, comparison groups from published reports representing three different cohorts of patients with chronic diseases including asthma,[21] cystic fibrosis[22] and hemodialysis[23] patients were included. These comparison groups were selected to be similar in age and gender to the PiSCES cohort.

Applying the mapping developed by Ara 2008[24] to map SF-36 aggregate results into EQ5D utility estimates, the analysis by McClish et al. (2005)[20] suggests that there is a 25% decrement in utility versus the general population in a cohort with 62% female (as in the economic model; 0.648 versus 0.868, for PiSCES and general population norms, respectively). Moreover, when comparing utilities for SCD patients to those of patients with cystic fibrosis, asthma and hemodialysis, those of SCD patients are found

to be 20%, 10% and 5% lower, respectively (Figure 3). However, other studies have reported different estimates for utilities in patients with the above-mentioned conditions. For example, in a multicenter study of patients with CF in the UK, Bradley (2013)[25] collected HRQoL data using EQ-5D in a sample of 94 patients, mean age 28.5, 51.1% of which were male, and reported that EQ-5D utility index means (95% CI) were 0.85 (0.80–0.89), 0.79 (0.67–0.91) and 0.60 (0.44–0.76) for no, mild and severe pulmonary exacerbations, respectively. The cross-study comparison results by McClish et al. (2005) are mentioned here not to argue that SCD patients have a worse HRQoL than those of other diseases, but rather to highlight that SCD is indeed a disease with a significant impact on HRQoL.

Figure 3: Utility values for patients with SCD, cystic fibrosis, asthma, and haemodialysis (data from McClish 2005)[20]



Abbreviations: SCD: sickle cell disease; CF: cystic fibrosis

Utility of UK SCD patients

GBT has been actively involved in generating primary data that will help understand the burden of SCD. Some of the studies financially supported by GBT include generating HRQoL data measured using EQ-5D. All individual patient level data available from UK patients were merged to estimate the association between age and utility values among UK SCD patients. Details of that analysis are provided in Appendix W - Association between age and comorbidities.

As presented in Table 1, the predicted mean utility at the age of 45 and 50 years is [redacted] and [redacted], respectively in the fixed effects model; and [redacted] and [redacted], respectively, in the random effects model.

Table 1: Predicted utility by age, fixed effects and random effects models

Age	Predicted utility value Fixed effects lowest BIC model	Predicted utility value Random effects lowest BIC model
15	[redacted]	[redacted]
20	[redacted]	[redacted]
25	[redacted]	[redacted]
30	[redacted]	[redacted]
35	[redacted]	[redacted]
40	[redacted]	[redacted]
45	[redacted]	[redacted]
50	[redacted]	[redacted]
55	[redacted]	[redacted]
60	[redacted]	[redacted]
65	[redacted]	[redacted]

To compare utility in SCD UK patients with that of the UK population norms, the equation provided by Ara & Brazier 2010[26] was applied to the company's UK sample of SCD patients and then plotted against the predicted utility based on EQ-5D answers from the sample. Figure 4 highlights the impact of SCD on HRQoL versus the general population.

Figure 4: Utility by age among SCD patients versus UK general population norms (GBT data on file, see Appendix W)

[redacted]

Utility values reported in the literature for SCD patients

A review of the literature was performed in the context of the EAG clarification questions to ascertain the face validity of the mean utility values estimated by the model. The search was performed on June 30th, 2022 in PubMed using the terms "health related quality of life" and "sickle cell disease". Of the 172 hits, 28 were deemed relevant based on abstract screening. Full text screening allowed for the identifications

of 7 additional primary studies in adults with SCD. Table 2 summarises the evidence available considering only full-text primary real-world studies using EQ-5D or SF-36 as instruments, no more than one study per cohort, and reporting data for overall sample (not just subgroups).

Table 2: Mean utility of SCD patients reported in the literature.

Reference	Sample size, Mean* age, % female	Mean utility value	Instrument/Mapping	Country
McClish 2005[20]	308, 33, 60.4%	0.650	SF-36->EQ-5D (Ara 2008)[24]	US
Adam 2017[27]	141, 34.2 ,57%	0.671	SF-36->EQ-5D (Ara 2008)[24]	US
Ahmed 2015[28]	629,28.8, 59.6%	0.587	SF-36->EQ-5D (Ara 2008)[24]	Saudi Arabia
Anie 2002[29]	96, 30.1, 66.7%	0.636	SF-36->EQ-5D (Ara 2008)[24]	UK
Anie 2012[30]	510, 28.9, 60%	At admission: 0.39, 1-week post discharge: 0.75	EQ-5D - hospital admission for pain	UK
Lubeck 2019[31]	NR. Based on 3 SCD cohorts reporting pain	severe pain: 0.437 moderate pain: 0.492 mild pain: 0.557	Based on the algorithm reported by Anie 2012[30] which mapped VAS pain score to utility	
Dampier 2011[13]	1046, 28.0, 52%	0.458	SF-36->EQ-5D (Ara 2008)[24]	US
Ojelabi 2019[14]	200, 27.9, 58.5%	0.65	SF-6D (Derived from SF-36), UK value set (brazier 1998)[32]	Nigeria
Karafin 2018[33]	99, 30, 65%	0.637	SF-36->EQ-5D (Ara 2008)[24]	US
Khaled 2020[34]	107, 25, 79%	0.678	SF-36->EQ-5D (Ara 2008)[24]	Saudi Arabia
Shafrin 2021[35]	301, 34.4, 73.4%	0.738	EQ-5D, US value set	US
Vilela 2011[36]	25, 68%	0.584	SF-36->EQ-5D (Ara 2008)[24]	Brazil
Santos 2013[37]	32, 32, *65.6%*	0.463	SF-36->EQ-5D (Ara 2008)[24]	Brazil

*or median if mean not reported

- ***For the voxelotor and SoC arms of the model, please provide details of the annual proportion of patients requiring chronic/regular transfusions each year, and the average annual number of chronic/regular transfusions received.***

For each patient in the model receiving regular transfusion therapy, [redacted] transfusions are assumed for a full year. For example, with reference to *Figure **5**, at the end of year 4 in the SoC arm of the model, [redacted]% of are receiving regular transfusion therapy which equates to an average of [redacted] transfusions per patient.

[redacted]Figure 5 Proportion of patients on regular transfusion therapy

- ***For the voxelotor and SoC arms of the model, please provide a breakdown of the base case QALY results according to QALY losses due to (i) the Hb level of the patient, (ii) the patient having SCD and (iii) patient chronic/regular transfusions separately. In addition, for each complication, please provide results from an analysis to show where the QALY gains/losses occur.***

The information requested is shown in Table 3.

Table 3 Breakdown of base case QALY results

Results breakdown: patient utilities (discounted)			
	Voxelotor	**SoC**	**Difference**
Baseline QALYs (before adjustment)	[redacted]	[redacted]	[redacted]
QALYs after adjust. for SCD, Hb CTT	[redacted]	[redacted]	[redacted]
Utility adjustments			
General sickle cell disease	[redacted]	[redacted]	[redacted]
Hb	[redacted]	[redacted]	[redacted]
RTT	[redacted]	[redacted]	[redacted]
Utility Decrements	[redacted]	[redacted]	[redacted]
ARF	[redacted]	[redacted]	[redacted]
Arrythmias	[redacted]	[redacted]	[redacted]
Cardiomegaly	[redacted]	[redacted]	[redacted]
CKD	[redacted]	[redacted]	[redacted]
ESRD	[redacted]	[redacted]	[redacted]
Gallstones	[redacted]	[redacted]	[redacted]
Heart Failure	[redacted]	[redacted]	[redacted]
Leg Ulcer	[redacted]	[redacted]	[redacted]
Osteomyelitis	[redacted]	[redacted]	[redacted]
Osteonecrosis	[redacted]	[redacted]	[redacted]
Pulmonary hypertension	[redacted]	[redacted]	[redacted]
Priapism	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
VOC	[redacted]	[redacted]	[redacted]
Overall patient QALYs	[redacted]	[redacted]	[redacted]

- ***For the voxelotor and SoC arms of the model, please provide the raw data for the mean undiscounted QALYs and mean undiscounted life years for each of the 50,000 simulations.***

Output for 50,000 patients in the base case is contained within the revised model for each model arm (sheets 'HISTORY_VOX_OUT' and 'HISTORY_SOC_OUT''. For each patient there are 4 rows of data: event label, event time, cumulative QALYs at event time, and cumulative costs at event time. The data for the 50,000 patients are supplied in a separate file (Patient History 50K base case), as having these data within

the model slows the running down significantly. In the version supplied, output is shown for only 100 patients.

- ***For the voxelotor and SoC arms of the model, please provide the average time to first complication and the average time to chronic/regular transfusion.***

The mean time to first complication is [redacted] months for the voxelotor arm and [redacted] months for the SoC arm. The average time to transfusion is [redacted] weeks. Note that each transfusion is not considered as an event. A patient is either on regular transfusions or not. If they are on regular transfusion, they incur costs amounting to [redacted] transfusions per year and a 0.03 QALY decrement.

B4. Priority question

Information provided in the CS (Table 30) shows that some events were not included in the model due to 'uncredible direction of effect'. Please explain the meaning of this phrase.

A small number of complications (cellulitis, depression, myocardial infarction, myocardial injury and retinopathy) were excluded from the economic modelling because preliminary analysis in the Symphony database suggested an association between higher Hb level and an increased risk of these complications.

This is the opposite to the direction of effect seen for the majority of complications in Symphony (in the majority, higher Hb was associated with reduced risk) and in the literature.[1-4] No plausible biological explanation for the direction of association suggested in Symphony is apparent. The direction of effect was therefore deemed to be non-credible, and the complications were excluded. The complications in question had relatively low numbers of events. If the EAG would like to see a scenario in which these events are added in to the model, this can be provided at technical engagement stage; it was not feasible to run the scenario during the CQ timeframe.

Section C: Textual clarification and additional points

C1. <u>Priority question</u> Please provide the following documents:

a. The HOPE trial protocol.

b. The HOPE trial statistical analysis plan.

These have now been provided (provided prior to delivery of the CQ responses).

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	AOFAC Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Anthonia Oyindamola Folakemi Afelumo Coshare (AOFAC) Foundation is a charity registered in England and Wales, we are a patient advocacy group in the area of Thrombotic Thrombocytopenic Purpura (TTP) with interest in Sickle Cell Disease and Lupus SLE.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	**We normally gather information from Groups and patients that are linked with the disease.**

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with = Tiredness which means physical task are difficult, pain, stress, Anxious/depress mood, draining financially and physically – to work is difficult. Carers experience = Big live adjustment, stress

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	No Comment
8. Is there an unmet need for patients with this condition?	No Comment

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	No Comment

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	No Comment

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No Comment

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No Comment

Other issues

13. Are there any other issues that you would like the committee to consider?	NA

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• The more options of medications for treatment the better • • •

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Cianna's Smile
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Cianna's Smile supports families affected by Sickle in the UK and reduce isolation, raise awareness of the condition and the challenges those affected by it face and offer education.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Yes GBT £7546 To produce 3 books to help families affected by Sickle Cell. A nutritional guide and recipe book for Sickle Cell, A transition guide for young people moving from paediatric to adult care and a children's illustrated book about Sickle Cell .
4c. Do you have any direct or indirect links	no

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	A carers focus group and I am carer also.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The condition can be very debilitating as it is unpredictable and symptoms can be spontaneous. Many people with Sickle Cell find themselves isolated and sacrificing social activities, education and employment due to the many factors and challenges they face because of Sickle Cell. Hospital admissions, cost of repeat prescriptions for adults and the financial burdens due Sickle Cell. The isolation and pressure to be well to attend school/work can trigger stress which can in turn trigger a Sickle Cell crisis. Because Sickle Cell is very much misunderstood by healthcare professionals, employees and education providers people with Sickle Cell have the additional pressures of having to prove their pain and health complications because of this lack of awareness and education. To be able to reduce such challenges is extremely important. Carers often find themselves juggling caring for someone, work, studies, hospital admissions, sleep deprivation, social isolation, lack of support from professionals and family and friends and more.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	It is still apparent that the quality of care depends on where you live, the knowledge healthcare professionals hold and openness to work with patients and take on board their opinions. For children in particular the treatment available is extremely limited.
8. Is there an unmet need for patients with this condition?	Yes particularly children. There is currently only one approved drug for Sickle Cell to help reduce symptoms and does not work for everyone. The other treatment in bone marrow transplant which is not readily available and will only be considered for people in very few people that have additional complications.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	It gives hope and choice to those that currently are not eligible for or able to use existing treatment.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	It has age restrictions which means some children will not be able to receive the treatment.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Sickle Cell affects each individual differently and it is important that the necessary access to resources, training and education is provided to relevant healthcare professionals regardless of how many Sickle Cell patients they see or area in which they live in.

Other issues

13. Are there any other issues that you would like the committee to consider?	There is a enormous lack of education, awareness, research, funding and treatments available for people with Sickle Cell. With Sickle Cell being the fast growing genetic condition globally it is crucial that changes are made to improve the quality of life for those affected by it.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• New treatment for Sickle Cell is overdue and people are suffering because of the lack of treatment available • Reducing symptoms can make a significant difference to the individual with Sickle Cell and also their support network • Decreasing isolation experienced by individuals and carers can be reduced if people have the opportunity to be more in control of their condition • Empowering individuals with choice, resources and support is key to the much needed shift in busting the myths and stigmas attached to Sickle Cell due to misinformation and lack of empathy towards the severity and complexity of how Sickle Cell can affect each person differently. •

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Single Technology Appraisal

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

Patient Organisation Submission

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Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	The Essenelle Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	A mental health charity that supports those impacted by Sickle Cell Disease and their families. We receive funding through corporate grants/partnerships, including public, corporate and pharma. We also raise money through public fundraisers and community building. Our team is made up of four people and we serve over 10,000 people across the UK.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Yes. The Essenelle Foundation received two grants totalling £17,000 from GBT in the last two years. These are detail below: <u>Grant one</u> Educational and Emotional Well-being Programme June 2021 - £7,000 The purpose of the grant is to improve the emotional wellbeing events for the community along with resources and workshops that implement policies and care plans that exist within hospitals, schools and employment spaces. <u>Grant two</u> Educational and Emotional Well-being Programme February 2022 - £10,000 The purpose of the grant is to improve the emotional wellbeing events for the community along with resources and workshops that implement policies and care plans that exist within hospitals, schools and employment spaces.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We continually explore and collect insights on the impact SCD has on patients and their families via our portfolio of programmes and services, as well as regular surveys. In the context of the upcoming NICE appraisal of voxelotor, we conducted a series of questionnaires, interviews and community workshops that discussed the impact of SCD and the perspectives and preferences regarding treatment and care that were important to patients and their families.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Sickle Cell Disease starts impacting patients and the family from diagnosis at birth (often through genetic screening for new parents - the journey begins then for them and immediately at birth of the child). Children begin experiencing crisis and symptoms from as young as 5 months old - their young bodies are impacted by SCD literally from the moment they are born. Living with sickle cell disease is an emotionally, physically and mentally destroying experience for both the patient and their caregivers. SCD is a life-threatening condition with no cure and very few meaningful treatment options. Patients are left in severe pain and agony while their bodies slowly deteriorate. Patients and carers both experience high levels of anxiety, panic and depression. PTSD is a common experience within the community where many experiences include repeated trauma and near-death experiences. From a carer's perspective, there is also guilt and exhaustion of having to navigate a condition that you know nothing about, and there is little direction given to you to help navigate. Your life is forever changed from the moment your child is born, your career will never be the same again and you live each day knowing that your child is gravely unwell and it's a case of when will the next crisis hit rather than if it will. You exist, you don't live. The nature of the disease means there is no clear pattern of decline in health. Attacks can come at any moment which can be small or fatal. This means most carers live in absolute panic and fear of crisis. As families we miss out in every important part of life, birthdays, Christmas or other religious holidays. As both patients and carers, we are frequently needing to miss out on education and work which often results in loss of employment. Loss of earnings. Parents and carers are often forced into unemployment - not thought choice, but by needing to navigate care and appointment for our patients. We literally help to keep them alive and caregiving becomes our primary unpaid occupation.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	There are not enough treatment options to address the multifactorial nature of the disease. Specifically, here are the treatment gaps - we have some medication which targets the symptoms of the disease, especially so in the management of acute pain. There is virtually nothing currently available which tackles the underlying cause of the disease though and one of the major concerns we hear from our community is that the damage is being done to the SCD patient's body from the moment they are born. Anything which can tackle, prevent or delay the damage being done in the first place would be welcomed by the community, who often feel isolated and let down by an imperfect health care system. Here is some evidence from the work we carried out…….
8. Is there an unmet need for patients with this condition?	Yes, Mental Health, Finance and general welfare are commonly ignored needs of both patients who have Sickle Cell Disease and their families. This is a life-long and life-limiting condition. The mental burden of this disease is huge - on the patient who lives with the silent but deadly damage being done daily to their bodies, but also on the caregiver who feels trapped in a world they didn't choose, but who is powerless to create any meaningful change other than supportive care and love.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We think that the new technology can alleviate a lot of physical traumas associated with other treatment options.. Reducing the need for blood transfusions will improve attendance in school/ colleges and work. Because the treatment is managed at home, it will improve the overall quality of life for patients and cause less disruption for families and their daily. It will also reduce costs of transport to and from hospitals for treatment. It can be used in conjunction of other existing technologies and we believe from the clinical trial data we have seen that there may be some interesting evidence relating to the reduction in organ damage. We think that if this were followed through to its natural conclusion that it may therefore have a positive impact on life expectancy too, if less organ damage occurs. All of this mean that as an organisation, we support the availability of the product for those who may derive a benefit from it.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	It is not available for people under the age of 12. Patients may find it difficult to remember to take 3 pills a day, in a world where they have not previously been used to having treatments, other than blood transfusions and painkillers, available to them. Generally though, we think this would be true of all new treatments in SCD and we're are confident that the community feel ready and enthused about possible new treatment options.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who will not benefit from this technology are those under 12. This is because it is not cureently licenced for them. Given the mode of action of this technology, we very much hope that there may be clinical trials ongoing which could make this treatment available to much younger SCD patients. Those receiving regular blood transfusions and those patients who are resistant to other treatments may find this incredibly useful. Regular blood transfusions cause a lot of issues for patients from vascular necrosis, long days spent in hospital and continued interference in daily life. Patients and caregivers equally miss out on a huge amount of school or employment. There is significant trauma from repeated medical procedures and often, patients and their families become distrusting because of poor experiences. They will be able to potentially substitute that experience with taking tablets at home and being in more control of their condition. We believe this could be incredibly empowering and welcomed by the community.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	SCD is a condition which disproportionately affects people of colour. We know from the APPG Report entitled 'No one's listening' that there are many social, health and societal inequalities which SCD patients and caregivers experience. We know that 48% of those who enter the NHS through A & E are drawn from the two most socio-economically deprived groups of people. Yet this is a community who is still paying for their prescriptions unlike other long-term conditions such as diabetes and cystic fibrosis. It's time for this to change and giving access to this new technology for eligible patients could mean a huge amount to patients and their families. It could also mean that in our lifetime, we see more new treatments being developed and made available to SCD patients.

Other issues

13. Are there any other issues that you would like the committee to consider?	Change is desperately needed in the SCD community. We need to be able to have trust and faith in systems and processes after so many have been let down for such a long time. Giving access to this treatment will make a positive step of intent that our community matters just as much as the next one does, that our voices are being heard and that we deserve meaningful change just like other disease areas have seen over time too.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	● It is important that the committee should consider the mental, emotional and physical and psycho-social impact the condition has on the patients, caregivers and their families. Too many miss out on significant chunks of education and employment as the disease is so pervasive. ● There is an urgent and significant need to have more options on technologies available for a community who have not had many positive options in the last 50 years ● This disease is doing damage from the moment a child is born with SCD. Anything that could slow or reduce that damage has to be welcomed by the community and healthcare system. ● SCD has been left behind with a lack of new treatment options in recent times - we're still overly reliant on symptomatic control versus tackling the root cause of the problem in the first place. We believe that if you can slow down the disease, you have the potential to change health outcomes too. ● This new technology is an effective and safe treatment option, which SCD patients have a right to be able to get benefit from. Choice of treatment is important given the heterogeneity of the disease.

Thank you for your time.

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About you

1.Your name	[redacted]
2. Name of organisation	Sickle Cell Society (UK)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Sickle Cell Society is the only national charity in the UK that supports and represents people affected by sickle cell disorder (more affectionately known as Warriors) to improve their overall quality of life. The organisation became a registered charity in 1979. We work closely with the sickle cell community, health care professionals, other stakeholders such as NHS England, Public Health England, NHS Blood and Transplant, Industry and other stakeholders. The Sickle Cell Society is funded by unrestricted and restricted grants from Trusts and Foundations eg National Lottery – Reaching Communities Fund. As part of our fundraising activity we also receive donations from individuals, churches, schools and other organisations. Our total operating income for the financial year ended 31 March 2022 was £871,741
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	We have received £7,755 in the financial year ended 2021/2022 from the company (Global Blood Therapeutics) bringing the treatment for NICE evaluation. This was a grant towards the Society's annual children's holiday, which the Society has been running for decades. Our beneficiaries are people who live with sickle cell disorder (children, adults and families). We also a received a grant of £10,000 in the financial year ended 2021/2022 towards operating the secretariat of the Sickle Cell and Thalassaemia All Party Parliamentary Group, from Novartis, who as a company have been in the space of sickle cell for many decades. The Sickle Cell Society also contributes to the funding of the secretariat.

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We work with people who live with sickle cell and their families every day. In the case of Voxelotor, we actively assisted NHS Sickle Cell Centres enrol patients in the clinical trials. We held patient education days about participating in trials to understand the experiences of patients and carers. We are also fielding two patient representatives as part of the evaluation process, one of whom has direct experience of being on the Voxelotor clinical trial. We have also been closely reviewing the published evidence from the trials with our clinical advisers.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Sickle Cell disorder is a genetic blood disorder of the haemoglobin. It is a debilitating condition from childhood, continuing throughout adolescence and adulthood. Whilst severe painful crises are a common complication, sickle cell also affects multiple organs within the body causing additional acute complications such as strokes, priapism (for men), organ damage, retinopathy, avascular necrosis of the hip and leg ulcers. In relation to severe painful crises, sickle cell is for example, in the top 20 of all causes for hospital admissions in London. Furthermore, the psychological impact on mental health well- being is also significant. The recent Covid19 pandemic also heightened these impacts evidenced by work/surveys the Society has undertaken with people living with the condition and families during the pandemic. The complications of sickle cell lead to early mortality when compared to the general population. The burden of sickle cell is significant. It has a profound impact on quality of life and affects all daily living activities including school, further education, work and relationships. With regard to carer experiences a recent global survey, the Sickle Cell Health Awareness Perspectives and Experiences (SHAPE), which included over 200 sickle cell patients from the UK showed that the impact of the condition is not limited to those living with the disease. It also significantly affects the lives of their carers. More than half of those surveyed who look after someone with sickle cell disorder stated their ability to attend and succeed at work/school(56%), long term health(55%), earning potential (54%), overall wellbeing (53%) and mental health (52%) are impacted.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Frankly, patients and carers and indeed the Sickle Cell Society are not impressed with the range of current treatments and the care afforded to patients particularly in accident and emergency department and general wards. Currently, hydroxycarbamide is the standard treatment to reduce the incidence of painful crisis. It is a chemotherapy drug which has been up until November 2021, the only licence treatment available in England. We know from studies like the Baby Hug study that it is effective. However, we also know from conversations with patients and indeed healthcare professionals, that this is not a treatment for everyone. Some patients cannot tolerate it or have contraindications. In addition, the carcinogenic properties of hydoxycarbamide have lead over the years to myths and misconceptions about its safety. As a result, whilst effective, the uptake hydroxycarbamide is lower in England and similarly in other parts of the world. In November 2021, NICE/NHS England authorised another treatment; Crizanlizumab under a managed access scheme. Work is currently taking place on the latter under the managed access scheme but it is important not to lose sight of the fact that this is only the second licensed treatment for sickle cell in nearly 30 years. It is striking and in our view as a patient advocacy organisation, unacceptable that there is such limited choice of treatments for sickle cell disorder when compared to like conditions, with smaller numbers of people and mainly affecting the anglo-saxon white communities. We make this point to highlight one of the serious health disparities affecting people living with sickle cell disorder. The optics are that sickle cell disorder mainly affects people of African or Caribbean heritage. The condition has been known about medically for over a century yet in 2021 there are only two available treatments. Contrast that to Haemophilia or Cystic Fibrosis which mainly affect a different demographic, but there is a significantly wider range of choice of treatments for these conditions. With regard to care available on the NHS, the Sickle Cell Society in collaboration with the Sickle Cell and Thalassemia All Party Parliamentary Group published the Group's Inquiry report –No One's Listening, in November 2021. The Inquiry was Parliamentary Select Committee style, taking oral and written evidence from patients living with sickle cell and family members from across the country together with evidence from health care professionals and other stakeholders. The report highlighted 5 main themes; 1. Sub- standard care on general wards and in accident and emergency departments 2. Failures in the NHS in providing joined up sickle cell care 3. Low awareness of sickle cell among healthcare professionals and inadequate training

	4. Negative attitudes towards sickle cell patient (including racial bias) 5. Inadequate investment in sickle cell care. 31 recommendations have been made to various policy institutions including NICE for urgent change ad improvement.
8. Is there an unmet need for patients with this condition?	There is without question a high unmet need for choice of effective additional disease modifying treatments for sickle cell, as evidenced by the All Party Parliamentary Group's inquiry report on the serious health inequalities associated with this condition, as well as the recent global SHAPE survey and other recent surveys.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Voxelotor has already been licensed in the USA (2019). We have therefore looked at data on the effectiveness of this technology- Real World effectiveness of Voxelotor for treating sickle cell disease in the US: a large claims data analysis (https://doi.org/1080/17474086.2022.2031967). The evidence from this study shows that patients living with sickle cell disorder aged 12 years and older who started with Voxelotor had significant increase in Hb levels as well as a significant decrease in vaso-occlusive – crises (VOCs). In this respect what patients and carers want to see is more choice of safe and effective treatments for sickle cell disorder. One of our patient members who will be present at the NICE meeting in December 2022, will speak from her own experience of the advantages. The anecdotal feedback we have received has been positive in reducing painful crises. Any treatment that reduces the incidence of painful crises and the significant burden of the condition is a step forward.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	We are aware of possible side effects such as headache, diarrhea and nausea. From studies (Long term safety and efficacy of Voxelotor for patients with sickle cell disease: an open – label extension of the phase 3 HOPE trial) it appears that the benefits of Voxelotor outweigh any disadvantages.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Please see section 7 above. There are serious health inequalities experienced by people with SCD. Recently the NHS through its Chief Executive and the Secretary of State for Health and Social Care have accepted these inequalities exist and are real. As a first, they have launched a national awareness/education campaign targeted at health care professionals. Limited access to new safe and effective treatments for SCD only serve to widen health inequalities for the SCD community.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• SCD is the fastest growing genetic blood disorder in the UK • There has been a lack of innovation and investment in NHS SCD services, for many decades evidenced by only 2 licenced treatments; one of which has only been available from February 2022 • There is very limited choice of safe and effective disease modifying treatments • The burden of SCD is significant. It affects all aspects of a person's quality of life • The NHS experience of people living with SCD is generally poor, particularly in accident and emergency and in general wards • Healthcare professionals understanding and knowledge of SCD is patchy at best. The lack of understanding and knowledge has contributed to avoidable deaths of people with SCD

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Single Technology Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	[redacted] on behalf of Royal College of Pathologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? No A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	Tertiary referral centre for patients with sickle cell disorder. Chair of regional and national MDTs on treatment of patients with sickle cell disorder. NHS funded – partially via specialist commissioning
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve outcome and relieve symptoms of sickle cell disorder. Voxelotor has a unique ability to keep oxygen bound to haemoglobin which results in less cell destruction and improvement of anaemia as well as rate of haemolysis. Some of the long-term morbidities in sickle cell disorder are directly related to the degree of anaemia and/or haemolysis and voxelotor has the option to target both. The reduced strain on bone marrow can also improve fatigue and quality of life for people with this chronic disorder
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An improvement in haemoglobin by 10-15 g/dL or more; reduction of venous ulcers; improvement of priapism; improvement of fatigue; a reduction in heart rate at rest by 20 beats / minute; an improvement of LAVI of 20-25% by echocardiography; a reduction of direct bilirubin by 15% or more; reduction of blood transfusion (transfused units) by 20% or more
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There is a need for an alternative treatment that can improve haemoglobin and haemolysis is sickle cell disorder. Hydroxycarbamide has the potential to improve both to a similar level as voxelotor, but a number of people do not tolerate hydroxycarbamide or are ‘non-responders’. Because of concerns about fertility and fears of using an anti-cancer drug, patients are sometimes reluctant and prefer to opt out of treatment for these reasons. Blood transfusion (exchange or top up) will also improve these parameters, but is more invasive than an oral treatment. There is a risk of iron overload in the more anaemic sickle cell patients. Some patients become hard to transfuse due to the development of allo-antibodies. A number of sickle cell patients are members of Jehova’s Witness communities and do not wish to receive blood products. Voxelotor fulfils the need for disease-modifying treatment in these groups.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Hydroxycarbamide or blood transfusion are the currently available standard treatments Crizanlizumab does not target the haemolytic anaemia aspect of sickle cell disorder and has been left out of the comparison.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease A British Society for Haematology Guideline 06 May 2018 Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion. 18 November 2016
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined and is monitored by dedicated specialist centres and coordinating centres. There are national audits on compliance with guidelines and there is a peer-review system in place for assessment of services against the national standards of care.
9c. What impact would the technology have on the current pathway of care?	It will offer a new and specific target for treatment in a subgroup of sickle cell people
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is already used via an Early Access to Medicines Scheme
10a. How does healthcare resource use differ between the technology and current care?	Funding
10b. In what clinical setting should the technology be used? (For example,	Specialist clinics only

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment required
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – for a subgroup of patients for whom there is currently no alternative
11a. Do you expect the technology to increase length of life more than current care?	Possibly. Current follow up data insufficient to suggest a survival benefit, but on theoretical grounds a patient who responds well to voxelotor may have a better life expectancy due to lower risk of eg heart failure or pulmonary hypertension.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, supported by long-term follow up data
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Only appropriate for patients with sickle cell disorder

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	In comparison with hydroxycarbamide: somewhat easier. Fewer concerns about toxicity (blood counts) and certain side effects. With voxelotor no concerns about male fertility and sperm freezing not required In comparison with blood transfusion / exchange transfusion: easier. No venous access required; no day unit infrastructure / specialist teams / apheresis machine
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. The same decision rules as currently in place for the EAMS scheme, which will also be outlined in a national SOP in development. No additional tests required.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
16a. Is the technology a 'step-change' in the management of the condition?	Yes – hydroxycarbamide will remain first treatment of choice
16b. Does the use of the technology address any particular unmet need of the patient population?	Please see question 8
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The tolerability and side effects profile based on phase 3 studies are reassuring.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the key trials were partially performed in the UK

18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	See question 7 - yes
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Haemoglobin rise too high
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
21. How do data on real-world experience	Comparable

compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Novel treatment for a disorder with historically very few available options • Alternative for people who do not respond or tolerate first-line treatment with hydroxycarbamide • Alternative for people who cannot or will not receive blood transfusions • Potentially very beneficial for a subgroup of sickle cell disorder with primarily haemolysis-driven symptoms • Few side effects and long term concerns

Thank you for your time.

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Single Technology Appraisal

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

NHS organisation submission (CCG and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England and NHS improvement
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for a CCG or NHS England in general? Yes ~~or No~~ Commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? Yes ~~or No~~ Responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ~~Yes or~~ No An expert in treating the condition for which NICE is considering this technology? ~~Yes or~~ No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ~~Yes or~~ No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England and NHS Improvement – specialised commissioning team are the commissioners with responsibility for the commissioning of Sickle Cell services.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	N/A.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	N/A – unable to comment, unable to provide opinion
8. What impact would the technology have on the current pathway of care?	The impact of the implementation could increase the workload of the sickle cell haemoglobinopathy teams.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	N/A
10. Will the technology be used (or is it already used) in the same way	N/A

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	N/A
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment should be used in a specialist haemoglobinopathy clinic
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Unable to quantify
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	N/A
11. What is the outcome of any evaluations or audits of the use of the technology?	N/A

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Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	The treatment is for people living with sickle cell disease, which predominately affects people from Black and ethnic backgrounds. This treatment would only be the second new treatment for this patient cohort in 20 years. As such it is vital that this is give due consideration to address equality issues.
12b. Consider whether these issues are different from issues with current care and why.	Please see as above

Thank you for your time.

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135619

Completed 15th September 2022

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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

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Contributions of authors:

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervision of the final report
James Mahon	Critical appraisal of the economic model
Katherine Edwards	Critical appraisal of the clinical evidence
Angela Boland	Critical appraisal of the clinical and economic evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence
Rebecca Harvey	Critical appraisal of the statistical evidence
Rachel Houten	Critical appraisal of the economic model
Yenal Dundar	Critical appraisal of the company's search strategies
Joanne McEntee	Critical appraisal of the company submission
Joseph Sharif	Clinical advice and critical appraisal of the clinical evidence

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ACS	acute chest syndrome
AE	adverse events
AFT	accelerated failure time
AgD	aggregate data
BSC	best supportive care
BSH	British Society of Haematology
CFB	change from baseline
CGIC	Clinical Global Impression of Change
CI	confidence interval
CKD	chronic kidney disease
CPRD	Clinical Practice Research Database
CS	company submission
CSR	clinical study report
DES	discrete event simulation
EAG	External Assessment Group
EAMS	Early Access to Medicines Scheme
EQ-5D-5L	EuroQol-5 Dimension 5 level
ESA	erythropoietin stimulating agent
ESRD	end stage renal disease
ESS	effective sample size
g/dL	grams per decilitre
Hb	haemoglobin
HbF	foetal haemoglobin
HbS	sickle β-globin haemoglobin
HbSβ^0	haemoglobin Sβ^0
HbSβ+	haemoglobin Sβ+
HbSC	haemoglobin SC
HbSD	haemoglobin SD
HbSS	homozygous sickle β-globin haemoglobin
HC	hydroxycarbamide (hydroxyurea)
HES	Hospital Episode Statistics
HOPE	the main trial discussed in the company submission
HRQoL	health-related quality of life
ICER	incremental cost effectiveness ratio
IPD	individual patient data
ITT	intent-to-treat
K-M	Kaplan-Meier
LS	least squares
MAIC	matching adjusted indirect comparison
MHRA	Medicines & Healthcare products Regulatory Agency
mITT	modified intention-to-treat
MMRM	mixed model for repeated measures

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OLE	open-label extension
PH	pulmonary hypertension
PSA	probabilistic sensitivity analysis
PSS	Personal Social Service
QALY	quality adjusted life year
RCT	randomised controlled trial
RDI	relative dose intensity
RR	response rate
RTT	regular transfusion therapy
SCD	sickle cell disease
SCDSM	sickle cell disease severity measure
SD	standard deviation
SE	standard error
SLR	systematic literature review
SOC	standard of care
TEAE	treatment-emergent adverse-event
TSAP	trial statistical analysis plan
TTE	time-to-event
VOC	vaso-occlusive crisis
WTP	willingness to pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Section 1.6 outlines the key cost effectiveness issues identified by the EAG.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of key issues

Issue	Summary of issue	Report sections
Issue 1	The company's positioning of voxelotor as a 'second-line treatment' is problematic	Section 3.2.1 and Section 4.7
Issue 2	It is unclear if an increase in Hb of >1g/dL is clinically meaningful for SCD patients with haemolytic anaemia	Section 4.3.2 and Section 4.7
Issue 3	The impact of voxelotor on long-term complications is unknown	Section 4.7
Issue 4	Methods used by the company to generate TTE probabilities are not robust	Section 6.2 and Appendix 8.2
Issue 5	The modelled impact of treatment with voxelotor on HRQoL is not supported by trial evidence	Section 6.3.2
Issue 6	Inappropriate regular transfusion therapy rates	Section 6.3.3
Issue 7	The company model generates clinically implausible individual patient simulations	Section 6.3.5

g/dL=gram per decilitre; Hb=haemoglobin; HRQoL=health-related quality of life; SCD=sickle cell disease; TTE=time to event

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained.

Overall, the main company model assumption that has the biggest effect on costs and QALYs is the proportions of patients in the voxelotor and standard of care (SoC) arms and who receive regular transfusion therapy (RTT) ([redacted]% and [redacted]% respectively).

The EAG highlights that the company model generates clinically implausible individual patient simulations and therefore lacks face validity. The EAG considers that the company model outputs should not be used to inform decision making

1.3 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 The company's positioning of voxelotor as a 'second-line treatment' is problematic

Report section	Section 3.2.1 and Section 4.7
Description of issue and why the EAG has identified it as important	The company plans to position voxelotor as an option for patients requiring second-line treatment after HC, i.e., adults and paediatric patients aged 12 years or older with SCD who are ineligible for, intolerant of or unwilling to take HC, or for whom HC alone is insufficiently effective. The EAG considers that the company's positioning of voxelotor as only a 'second-line treatment after HC' is not appropriate. Clinical advice to the EAG is that it should be considered for all patients with low Hb, regardless of whether they are taking/have previously taken HC. In the HOPE trial, 64% of patients in the voxelotor arm and 63% of patients in the placebo arm were taking HC at baseline. Therefore, the HOPE population is not patients who are receiving voxelotor as a second-line treatment after HC. In the CS, the company justifies the proposed positioning of voxelotor by stating that it is reasonable to assume that in the HOPE trial, patients who were not receiving HC at baseline had previously been offered treatment with HC and had either stopped treatment, declined treatment, or were ineligible for treatment with HC. The EAG highlights that the MHRA EAMS indication supports the use of voxelotor as a monotherapy or in combination with HC and does not limit the use of voxelotor to after HC.
What alternative approach has the EAG suggested?	The company should re-consider the positioning of voxelotor as a 'second-line' treatment.
What is the expected effect on the cost-effectiveness estimates?	None.
What additional evidence or analyses might help to resolve this key issue?	None.

CS=company submission; EAG=External Assessment Group; Hb=haemoglobin; HC=hydroxycarbamide; MHRA EAMS=Medicines & Healthcare products Regulatory Agency Early Access to Medicines Scheme; SCD=sickle cell disease

Issue 2 It is unclear if an increase in Hb of >1g/dL is clinically meaningful for SCD patients with haemolytic anaemia

Report section	Section 4.3.2 and Section 4.7
Description of issue and why the EAG has identified it as important	HOPE trial results showed a statistically significant difference in favour of voxelotor over placebo in the numbers of patients who experienced an Hb response (defined as an increase of 1g/dL) at Week 24 (51.1% and 6.5% respectively). It is unclear whether this level of Hb increase is clinically meaningful. In the CS, the company states that it selected an increase of 1g/dL as an outcome measure because it achieves a Hb increase equivalent to that achieved by infusing one unit of blood. Clinical advice to the EAG is that is not known whether an increase of 1g/dL is clinically meaningful; however, the European Medicines Agency considers that treatment with voxelotor has resulted in a beneficial effect in terms of reduction in haemolysis and an increase in Hb, which are considered of clinical relevance to patients.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Further consultation with clinical experts regarding the clinical significance of this increase in patient Hb level.

CS=company submission; EAG=External Assessment Group; g/dL=grams per decilitre; Hb=haemoglobin; SCD=sickle cell disease

Issue 3 The impact of voxelotor on long-term complications is uncertain

Report section	Section 4.7
Description of issue and why the EAG has identified it as important	The company has provided clinical effectiveness data from the HOPE/OLE trial for a maximum of 144 weeks. The available trial data do not provide evidence for the long-term impact of treatment with voxelotor on the development of SCD complications (for example, stroke, ESRD and heart failure) over a patient lifetime.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The HOPE OLE is an ongoing study with an expected completion date of October 2024. The study aims to assess the frequency of sickle cell complications associated with long-term voxelotor use, and may provide additional clarity on the long-term impact of the drug.

EAG=External Assessment Group; ESRD=end-stage renal disease; OLE=open-label extension; SCD=sickle cell disease

1.4 The cost effectiveness evidence: summary of the EAG's key issues

Issue 4 Methods used by the company to generate TTE probabilities are not robust

Report section	**Section 6.2 and Appendix 8.2**
Description of issue and why the EAG has identified it as important	The company carried out AFT regression analyses to link patient Hb levels with SCD complications over the model time horizon. The EAG considers that: • there are several discrepancies between the baseline characteristics and regression coefficients presented in the main body of the CS and those presented in Appendices • the process used by the company to match patients in the Symphony database to those in the CPRD-HES dataset (matching the most important factors for which data were available in both sets) may not have accounted for all confounding factors. It is however, not possible to account for all factors in the patient matching process • acknowledging that the company compared the regression results on the matched Symphony dataset and directly on the HES-CPRD dataset, further sensitivity analyses to explore the effect of uncertainty around AFT regression results could have been considered
What alternative approach has the EAG suggested?	The company should carefully review analysis methods and reporting in light of the EAG concerns
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Updated company analyses and results

AFT=accelerated failure time; EAG=External Assessment Group; CS=company submission; CPRD-HES=Clinical Practice Research Datalink-Hospital Episode Statistics; SCD=sickle cell disease; TTE=time to event

Issue 5 The modelled impact of treatment with voxelotor on HRQoL is not supported by trial evidence

Report section	Section 6.3.2
Description of issue and why the EAG has identified it as important	The EQ-5D data collected during the HOPE trial showed no statistically significant difference between patients in the voxelotor and SoC arms in terms of the improvement between baseline and Week 72. At Week 72, patients in the SoC arm had experienced a numerically larger improvement in utility than patients in the voxelotor arm, therefore, the EAG considers that there is no direct evidence that treatment with voxelotor improves HRQoL compared with SoC, when measured using the EQ-5D-5L questionnaire
What alternative approach has the EAG suggested?	The EAG considers that in the absence of evidence of difference it should be assumed that voxelotor and SoC have the same impact on patient HRQoL
What is the expected effect on the cost effectiveness estimates?	Removing the assumption that, compared with SoC, treatment with voxelotor improves HRQoL will increase the company base case ICER per QALY gained. The EAG has not implemented this change due to serious concerns about the company model
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; EQ-5D=EuroQol-5 Dimensions; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; SoC=standard of care

Issue 6 Uncertainty around the proportions of patients receiving regular transfusion therapy

Report section	Section 6.3.3
Description of issue and why the EAG has identified it as important	There is no evidence from the HOPE trial that treatment with voxelotor reduces the need for RTT. To prohibit the confounding effects of transfusions on Hb endpoints, the HOPE trial explicitly excluded patients who were regularly receiving RTT or who had received a RBC transfusion for any reason within 60 days of signing the informed consent form (CS, Table 5); the EAG therefore considers that, at baseline, the SoC arm of the company model should not include RTT as a treatment
What alternative approach has the EAG suggested?	The company should have assumed the same proportions of patients were receiving RTT in both arms or, preferably, modelled the risk of having RTT
What is the expected effect on the cost effectiveness estimates?	Removing RTT from the start of the model or assuming the same RTT rate would increase the company base case ICER per QALY gained. The EAG has not implemented this change due to serious concerns about the company model
What additional evidence or analyses might help to resolve this key issue?	None

CS=company submission; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; RBC=red blood cell; RTT=regular transfusion therapy; SoC=standard of care

Issue 7 The company model generates clinically implausible individual patient simulations

Report section	Section 6.3.5
Description of issue and why the EAG has identified it as important	Individual runs of the company model generated patient experiences that were often clinically implausible
What alternative approach has the EAG suggested?	None. The EAG considers that the current version of the company model should not be used to inform decision making
What is the expected effect on the cost effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	The company should re-consider the structure and parameterisation of their model

EAG=External Assessment Group

1.5 Other key issues: summary of the EAG's view

Not applicable

1.6 Summary of EAG's preferred assumptions and resulting ICER

The EAG has not been able to generate any reliable ICERs per QALY gained. However, the evidence provided by the company only demonstrates that treatment with voxelotor leads to an increase in haemoglobin (Hb) level. Effect on health-related quality of life (HRQoL), reduced complications or the need for RTT has not been demonstrated. The EAG therefore considers that treatment with voxelotor may be dominated by SoC, i.e., costing more than SoC but not delivering any additional QALYs. The EAG further considers that even if the improvement in Hb level arising from treatment with voxelotor did result in improved HRQoL, the size of this improvement is likely to be small and therefore the ICER per QALY gained would be significantly higher than the company base case ICER per QALY gained ([redacted]).

2 INTRODUCTION AND BACKGROUND

This appraisal focuses on the use of voxelotor (Oxbryta®) for treating haemolytic anaemia in people with sickle cell disease (SCD). In this EAG report, the term 'company submission' (CS) refers to the company's document B, which is the company's full evidence submission. Documents provided by the company as part of the clarification process are referenced separately.

2.1 Sickle cell disease

SCD is a group of inherited conditions that affects the production of Hb.[1] The most common type of SCD is HbSS (also known as sickle cell anaemia, or SS disease).[2] People with HbSS have two sickle cell genes encoding an abnormal form of Hb, sickle β-globin haemoglobin (HbS).[1] People with other types of SCD for example, HbSC, HbSD, HbSβ^0 thalassaemia, and HbSβ+ thalassaemia have one sickle cell gene and an abnormal Hb gene of a different type.[1] HbSS and HbSβ^0 thalassaemia are the most severe types of SCD, however, there is variation in severity of clinical presentation between individuals.[3,4] HbSS and HbSC are the most frequently diagnosed types of SCD in the UK.[5] SCD is mainly found in people of African or African-Caribbean genetic origin, but it also occurs in people whose families originate from the Middle East, parts of India, the Eastern Mediterranean and South and Central America.[2]

Approximately 12,500 to 15,000 people in England have SCD.[2] SCD is one of the most commonly diagnosed genetic conditions in people in England.[2] In 2018/19, the NHS screening programme for SCD and thalassaemia identified 290 babies in England with SCD.[6] The NHS offers screening for SCD to pregnant women living in geographical areas of high SCD prevalence and all babies are screened for SCD in the new born blood spot (heel prick) test.[7]

Sickle cell genes cause the body to produce HbS.[1] Red blood cells that make HbS switch from being a bi-concave disc to a sickle shape (sickling) when they release oxygen into tissues.[4] High levels of sickling are triggered by conditions that lead to low blood oxygen, including cold, infection, dehydration, hard physical exercise, pregnancy and stress.[1] Sickle cells do not pass easily through blood vessels and they also tend to stick to other blood cells and to blood vessel walls, resulting in blockages and preventing normal blood flow.[8]

The most well-known and obvious complication of SCD is severe acute episodes of pain known as vaso-occlusive crises (VOCs).[9] VOCs occur when sickled red blood cells block blood flow to the point that tissues become deprived of oxygen.[10] The frequency of VOCs varies between individuals, and many patients will not experience a VOC in any given year.[11,12]

Consequences of VOCs include acute chest syndrome, severe anaemia, stroke, splenic sequestration, priapism, acute kidney injury and increased risk of infection.[2]

Over time, the sickling and subsequent breakdown (haemolysis) of red blood cells leads to haemolytic anaemia, blood vessel damage and vaso-occlusion (including VOCs). This can result in reduced oxygen delivery to the tissues, and inflammation, which contribute to a range of acute and severe complications.[13,14] Chronic complications of SCD increase with age, and include lung damage, pulmonary hypertension, kidney dysfunction, retinopathy and leg ulcers.[2]

The severity of SCD varies between individuals, as do the frequency and onset of acute and chronic complications.[2] Life expectancy for people living with SCD varies depending on treatment and co-morbidities.[15] Authors of a single centre UK study[16] published in 2016 (n=712), estimated the median survival of 450 patients with HbSS and HbSβ^0 thalassaemia as 67 years (confidence interval [CI]: 55 to 78 years). A statistically significant difference in median survival was noted between the HbSS/HbSβ^0 thalassaemia and HbSC subgroups, with survival favouring the latter subgroup ($p<0.001$).[16] In 2020, life expectancy for the general population in England was 82.6 years for females and 78.6 years for males.[17]

2.1.1 Haemolytic anaemia in sickle cell disease

The breakdown of red blood cells is termed haemolysis. Repeated sickling leads to abnormally high levels of haemolysis including excessive haemolysis in blood vessels. The lifespan of sickle cells is reduced by ≥75% compared with normal red blood cells (20 to 30 days versus 120 days).[2] As a consequence, patients with SCD have chronic haemolytic anaemia, although the degree of anaemia varies between patients.[18] Haemolytic anaemia is linked to progressive deterioration in tissue and organ function.[13]

2.2 Voxelotor

Voxelotor is a HbS polymerisation inhibitor (CS, Table 2). Inhibiting polymerisation increases the ability of Hb to retain oxygen, maintains red blood cells in their normal shape and helps to prevent haemolysis and associated anaemia. Polymerisation of HbS is the underlying molecular event that causes sickling, haemolysis and the resulting cascade of pathology.[3] Voxelotor is administered orally.[19]

Voxelotor became available to NHS patients via the Medicines and Healthcare products Regulatory Agency Early Access to Medicines Scheme (MHRA EAMS) in January 2022.[20] The EAMS[20] indication for voxelotor is for the treatment of haemolytic anaemia in adult and paediatric patients 12 years and older with SCD. Voxelotor can be administered alone or in

combination with hydroxycarbamide (HC). Voxelotor was granted marketing authorisation by the MHRA in July 2022.[21]

Voxelotor was approved by the US Food and Drug Administration agency in November 2019.[22] Healthcare records for patients with haemolytic anaemia due to SCD, including 3,128 patients who are treated with voxelotor are available from the Symphony Health Solutions Integrated Dataverse Database (known as the 'Symphony database').[23] The Symphony database contains healthcare data derived from medical, hospital and prescription claims for >317 million patients.

2.3 Company's overview of current service provision

The company highlights that there is no NICE clinical pathway of care for patients with SCD. The company identified NICE guidance and guidelines relevant to individual aspects of care for NHS patients with SCD, and four sources of UK-based guidelines relevant to the treatment of SCD (Table 1).

Table 1 Published guidelines and guidance relevant to the treatment of SCD in the NHS

NICE guidance and guidelines relevant to SCD	UK clinical guidelines relevant to SCD
National Institute for Health and Care Excellence. Sickle cell disease: managing acute painful episodes in hospital. CG143 2012[24]	Guidelines for the use of HC in children and adults with sickle cell disease: A British Society for Haematology Guideline. 2018[25]
National Institute for Health and Care Excellence. Spectra Optia for automatic red blood cell exchange in people with sickle cell disease. MTG28 2016[26]	Sickle Cell Society. Standards for clinical care of adults with sickle cell disease in the UK. Sickle Cell Society. 2018[4]
National Institute for Health and Care Excellence. Crizanlizumab for preventing sickle cell crises in sickle cell disease. TA743 2021[27]	Clarity Informatics Ltd for National Institute for Health and Care Excellence. Clinical Knowledge Summaries - Sickle Cell Disease. 2021[2]
	Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. 2017[28] Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion. 2017[29]

Source: External Assessment Group

2.3.1 Available treatments for SCD

There are currently no pharmacological therapies apart from voxelotor that are indicated for the treatment of haemolytic anaemia in SCD (CS, p32). The company lists the available treatments for SCD as best supportive care (BSC), HC, blood transfusions, crizanlizumab and allogenic stem transplant. Current SoC for the treatment of haemolytic anaemia is BSC, HC and blood transfusions. The company highlights (CS, Section B.1.3.2.2) that voxelotor is the only therapy specifically indicated for the treatment of haemolytic anaemia due to SCD.

As noted by the company (CS, p32), the 2018 report 'Standards of Care of Adults with SCD in the UK' published by the Sickle Cell Society[4] sets out the goals for management of SCD as improving survival, reducing acute and chronic complications and improving quality of life.

Best supportive care

BSC for patients with SCD is lifestyle advice, vaccinations, prophylactic antibiotics, pain medicines, blood transfusions and management of co-morbidities (CS, p31).

HC

HC (also known as hydroxyurea) received European Union marketing authorisation[30] in 2007 for the prevention of recurrent painful VOCs (including the development of acute chest syndrome [ACS]) in adults, adolescents and children older than 2 years with symptomatic sickle cell syndrome. HC is administered orally at a starting dose of 15mg/kg. There is no NICE recommendation for the use of HC to treat SCD.

HC is a cytotoxic drug that increases levels of foetal Hb (HbF), improves blood flow and reduces vaso-occlusion.[25] HC also reduces the inflammation associated with SCD.[25] The effect of HC on HbF levels differs between individuals, partly due to genetic variation.[25] Clinical advice to the EAG is that the efficacy of HC may decrease as patients age. Clinical advice to the EAG is that treatment with HC does not typically improve overall Hb levels and many patients treated with HC continue to experience progressive organ damage.

The British Society for Haematology (BSH) recommends[25] that all patients with SCD are offered HC. Clinical advice to the EAG is that in the NHS approximately 30% of eligible patients are treated with HC. The company states (CS, p33) that 24% of patients in the second-line setting (the proposed position of voxelotor – see Figure 1) currently receive HC. There are many reasons for the low uptake, including toxicity and side effects of treatment. Some patients, particularly those with mild phenotype SCD, consider that they do not need HC and/or have concerns about taking a cytotoxic/chemotherapy drug. HC causes impairment in spermatogenesis in men and, being genotoxic, is therefore not suitable for use in patients who are planning to start a family.[30]

Regular transfusion therapy

Clinical advice to the EAG is that, in-line with BSH guidelines,[28,29] regular transfusion therapy (RTT) is used to treat patients with SCD who have a serious clinical need. For example, transfusions are used as a primary prevention measure for children assessed as being at high risk of stroke, and as a secondary prevention measure for adults who have had a stroke. Patients who have recurrent episodes of acute VOCs despite treatment with HC, or patients with specific sickle-related end-organ damage, may also be offered RTT. Clinical advice to the

EAG is that the mode of RTT is usually automated red cell exchange to replace sickle cells with normal red blood cells. A smaller proportion of patients may receive regular simple 'top up' transfusions to improve anaemia, however, this may result in iron overload and hyperviscosity. Clinical advice to the EAG agrees with the company (CS, p34) that blood transfusions pose the risk of transfusion reactions, alloimmunisation and iron overload.

2.3.2 Number of patients eligible for treatment with voxelotor

The company estimates (CS, Document A, Table 12) that voxelotor would be a suitable treatment for [redacted] patients in Year 1, rising to [redacted] patients in Year 5.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

A summary of the final scope[19] issued by NICE, the decision problem addressed by the company, and EAG comments are presented in Table 2. Each parameter is discussed in more detail in the text following Table 2 (Section 3.1 to Section 3.7).

Table 2 Comparison between NICE scope and the company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Population	People with sickle cell disease	Patients requiring second-line treatment after HC, i.e., adults and paediatric patients aged 12 years or older with SCD who are ineligible for, intolerant of or unwilling to take HC, or for whom HC alone is insufficiently effective This positioning reflects where voxelotor will be used in clinical practice and therefore is of most relevance to HTA decision making. This positioning has also been validated by UK clinical experts (see Appendix U), who have confirmed that voxelotor would be used as a second-line treatment after HC in the NHS, consistent with BSH guidelines that HC should be offered to all SCD patients	The population discussed in the CS is patients aged ≥12 years with haemolytic anaemia due to SCD. This is in line with the population indicated in the title of the final scope[19] issued by NICE: voxelotor for treating haemolytic anaemia in people with sickle cell disease The company plans to position voxelotor as an option for patients requiring second-line treatment after HC, i.e., adults and paediatric patients aged 12 years or older with SCD who are ineligible for, intolerant of or unwilling to take HC, or for whom HC alone is insufficiently effective. The EAG considers that the company's positioning of voxelotor as only a 'second-line treatment after HC' is not appropriate. Clinical advice to the EAG is that it should be considered for all patients with low Hb, regardless of whether they are taking/have previously taken HC. In the HOPE trial, 64% of patients in the voxelotor arm and 63% of patients in the placebo arm were taking HC at baseline. Therefore, the HOPE population is not patients who are receiving voxelotor as a second-line treatment after HC. In the CS, the company justifies the proposed positioning of voxelotor by stating that it is reasonable to assume that in the HOPE trial, patients who were not receiving HC at baseline had previously been offered treatment with HC and had either stopped treatment, declined treatment, or were ineligible for treatment with HC.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
			The EAG highlights that the MHRA EAMS indication supports the use of voxelotor as a monotherapy or in combination with HC and does not limit the use of voxelotor to after HC.
Intervention	Voxelotor	Voxelotor	As per scope
Comparator (s)	Established clinical management without voxelotor including: • HC • blood transfusions (exchange and top-ups) • best supportive care	Established clinical management (termed standard of care [SOC]) without voxelotor in second-line treatment of haemolytic anaemia in patients who are ineligible for, intolerant of or unwilling to take HC, or for whom HC alone is insufficiently effective. This includes supportive care and also HC and/or blood transfusions (exchange and top-up) for a proportion of patients	The company has presented clinical effectiveness evidence for voxelotor from the HOPE trial. The HOPE trial compares the efficacy of voxelotor+SoC versus placebo+SoC (where SoC does not include RTT). The company and EAG agree that it is inappropriate to compare voxelotor+SoC versus HC+SoC or voxelotor+SoC versus RTT+Soc.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Outcomes	• changes to haematological parameters (haemoglobin levels) • number and severity of sickle cell crises • complications arising from sickle cell disease • markers of haemolysis • mortality • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • changes to haemoglobin level • Impact of Hb, VOCs and Hb*VOC (interaction) on the following complications: acute renal failure (ARF), Arrythmias, Cardiomegaly, chronic kidney disease (CKD), end-state renal disease (ESRD), Gallstones, Heart Failure, Leg Ulcer, Osteomyelitis, Osteonecrosis, Pulmonary hypertension, Priapism, Sepsis, Stroke, VOC (as defined in HOPE, that is, joint endpoint which includes uncomplicated and complicated to ACS/Pneumonia) • "Impact" is measured by: 1) Proportion of patients experiencing each complication by the end of the simulation; 2) Incidence rate (events per person per year) for each complication • mortality • adverse effects of treatment • health-related quality of life	Direct clinical effectiveness evidence is available from the HOPE trial (treatment up to 72 weeks) for the follow outcomes: <u>Changes to haematological comparators</u> • number of patients with an increase in Hb >1g/dL from baseline at Week 24 (primary) • CFB in Hb at Week 24 (secondary) at Week 48 (exploratory) and at Week 72 (exploratory) • incidence of severe anaemic episodes (Hb<5.5 g/dl) (secondary) <u>Number and severity of sickle cell crises</u> • time to first ACS, pneumonia or transfusion (exploratory) • annualised incidence rate mortality of VOC (secondary) <u>Complications arising from SCD</u> • incidence of leg ulcers at 72 weeks (post-hoc analysis) <u>Markers of haemolysis</u> • change and percentage change in unconjugated bilirubin, reticulocyte percentage, absolute reticulocytes, and lactate dehydrogenase at Week 24 (secondary), at Week 48 (exploratory) and at Week 72 (exploratory) • AEs at Week 72 • HRQoL up to Week 72 for CGIC, EQ-5D-5L and up to Week 24 for SCDSM (all exploratory) Mortality data from the HOPE trial are not presented in the CS but are available from the trial publication[31]

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
			The HOPE open label extension (OLE[32]) study provides data for 144 weeks of treatment with voxelotor for the outcomes of: • CFB in Hb g/dL • CFB in haemolysis measures (indirect bilirubin, reticulocyte count) • annualised incidence rate of VOCs • AEs To inform the economic model, the company has performed a time-to-event analysis using evidence from the US Symphony database and UK CPRD-HES database to determine the impact of Hb levels on complications arising from SCD
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective		As per scope

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Subgroups	If the evidence allows, the following subgroups will be considered: • subgroups defined by combination treatment with/without HC • subgroups defined by genotypes of sickle cell disease		The company has provided the results from a pre-specified subgroup analysis of the clinical effectiveness of voxelotor in patients who were and were not taking concomitant treatment with HC The EAG agrees with the company that the HOPE trial was not powered to provide robust results of subgroup analyses based on SCD genotype and that limited patient numbers in the HbSC and HbSβ+ genotypes do not allow for subgroup analysis

ACS=acute chest syndrome; AE=adverse event; CFB=change from baseline; CGIC=Clinician Global Impression of Change; EQ-5D-5L=EuroQol 5 Dimensions-5 levels; CS=company submission; EAG=External Assessment Group; EAMS=early access to medicines scheme; g/dL=grams per decilitre; Hb=haemoglobin; HbSβ+=haemoglobin Sβ+; HbSC=haemoglobin SC; HC=hydroxycarbamide; CPRD-HES=Clinical Practice Research Database-Hospital Episode Statistics; HRQoL=health-related quality of life; MHRA=Medicines and Healthcare products Regulatory Agency; OLE=open-label extension; RTT=regular transfusion therapy; SCD=sickle cell disease; SCDSM=Sickle Cell Disease Severity Measure; SoC=standard of care; US=United States of America; VOC=vaso-occlusive crises
Source: CS, adapted from Table 1

3.1 Source of clinical effectiveness data

The company identified one phase 3, international, double-blind, placebo-controlled randomised controlled trial (RCT) (the HOPE[33] trial) that provided data for the efficacy and safety of voxelotor+SoC versus placebo+SoC (from now on referred to as voxelotor versus placebo). The EAG reiterates that, in the HOPE trial, SoC did not include RTT.

Patients recruited to the HOPE trial (n=472) had a diagnosis of SCD, a Hb concentration of 5.5 to 10.5 g/dL and had experienced between one and ten VOCs in the year prior to randomisation. Stratification factors were HC use (yes or no), geographic region (North America, Europe or other) and age (adolescent [12 years to 17 years] or adult [≥ 18 years]). The primary endpoint of the trial was the percentage of patients with an increase in Hb of >1g/dL from baseline to 24 weeks. The treatment period was 72 weeks. The HOPE open label extension (OLE[32]) study provides data for 144 weeks of treatment with voxelotor. The HOPE trial included three treatment arms, voxelotor 900mg per day (n=90), voxelotor 1500mg per day (n=90) and placebo (n=92). As the licensed dose of voxelotor is 1500mg per day, the outcomes for patients treated with voxelotor 900mg are not discussed in this EAG report.

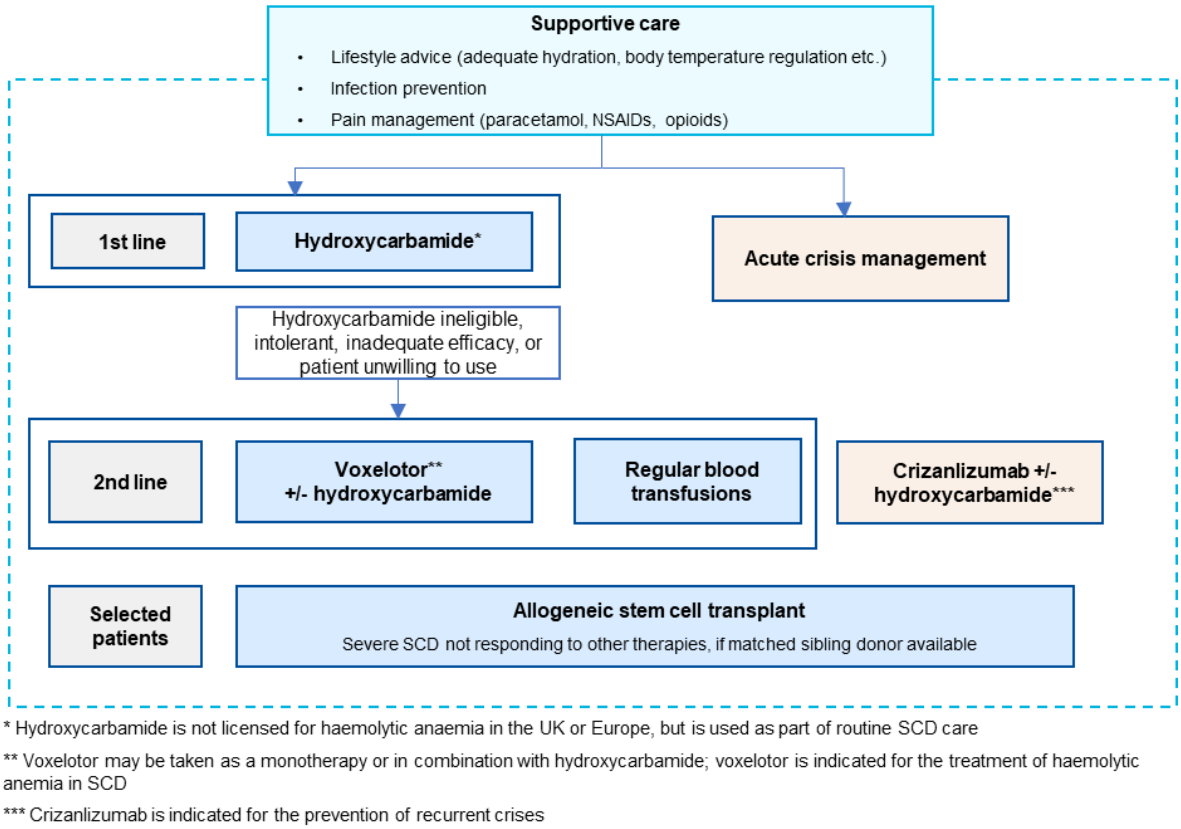
3.2 Population

The population described in the final scope[19] issued by NICE is people with SCD. However, the indication for voxelotor is referred to in the title of the final scope as 'voxelotor for treating haemolytic anaemia in people with sickle cell disease,' in line with the licensed indication.

3.2.1 Positioning of voxelotor

The company's proposed positioning of voxelotor (Figure 1) is as a treatment for patients requiring second-line treatment after HC, i.e., adults and paediatric patients aged 12 years or older with SCD who are ineligible for, intolerant of or unwilling to take HC, or for whom HC alone is insufficiently effective (CS, p12). In patients with SCD, HC and voxelotor can prevent red blood cells changing shape.[34,35] In addition, voxelotor improves the ability of Hb to hold on to oxygen.[35] Clinical advice to the EAG is that, as the two drugs deliver different benefits, it is not appropriate to only position voxelotor after HC. The HOPE trial provides evidence to support use of voxelotor in combination with HC (approximately 64% of the baseline population). The company has assumed that patients who were not receiving HC at baseline (approximately 36% of patients) had previously been offered treatment with HC and had either stopped treatment, declined treatment, or were ineligible for treatment with HC; therefore, some of these patients would have been receiving second-line treatment with voxelotor after HC whilst others would have been receiving voxelotor as a first-line treatment. The company does not report the proportions of patients who were not taking HC because they were

unwilling to, were ineligible for treatment or had stopped treatment. The EAG considers that the company's positioning of voxelotor as a 'second-line treatment after HC' is not appropriate.



* Hydroxycarbamide is not licensed for haemolytic anaemia in the UK or Europe, but is used as part of routine SCD care

** Voxelotor may be taken as a monotherapy or in combination with hydroxycarbamide; voxelotor is indicated for the treatment of haemolytic anemia in SCD

*** Crizanlizumab is indicated for the prevention of recurrent crises

Figure 1 Company's positioning of voxelotor

Source: CS, Figure 3

3.2.2 Generalisability of HOPE trial results

The company reports (CS, p88) that, at baseline, 64% of patients in the voxelotor arm and 63% of patients in the placebo arm were receiving treatment with HC. Clinical advice to the EAG is that, currently, approximately 30% of NHS patients with SCD are receiving HC. HOPE trial subgroup analysis results for patients in the voxelotor arm treated with and without concomitant HC at baseline show a consistent treatment benefit. Therefore, it appears that the difference in HC use between NHS and HOPE trial patients is not important.

Two notable patient groups were excluded from the HOPE trial:

- patients who were receiving RTT (clinical advice to the EAG is that between 10% and 30% of SCD patients treated in the NHS receive RTT)
- patients who had not experienced a VOC in the previous year and patients who had experienced >10 VOCs in the previous year.

Other patient populations excluded from the HOPE trial were patients aged >65 years, patients who had received a blood transfusion within 2 months of the start of the trial, patients with liver dysfunction and women who were pregnant or breastfeeding. There is therefore no evidence from the HOPE trial for the clinical effectiveness of voxelotor for patient in any of these groups.

3.3 Intervention

Voxelotor is a first-in-class Hb oxygen-affinity modulator.[36] It is an HbS polymerisation inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to red blood cells. By increasing the affinity of HbS for oxygen, voxelotor inhibits red blood cells from sickling, leading to a decrease in haemolysis and improvement of haemolytic anaemia (CS, Table 2). Voxelotor is administered orally and is available as 500mg tablets. The licensed dose is 1500mg daily.

Voxelotor (Oxbryta®) became available to NHS patients via the MHRA EAMS in January 2022.[20] The MHRA EAMS[20] indication for voxelotor for the treatment of haemolytic anaemia due to SCD in adults and paediatric patients 12 years of age and older as monotherapy or in combination with HC.

3.4 Comparators

The comparators listed in the final scope[19] issued by NICE are HC, blood transfusions (exchange and top-ups) and best supportive care.

In the HOPE trial, the comparator to voxelotor was placebo. All patients received SoC. SoC included pain control, HC, L-glutamine, and blood transfusions (except for RTT as patients receiving RTT were not eligible) (CS, Table 4). Clinical advice to the EAG is that SoC used in the HOPE trial was in line with SoC provided in the NHS, except that NHS patients may now also be treated with crizanlizumab to prevent recurrent VOCs if aged 16 years or over.[37]

Clinical advice to the EAG is in line with the company's comments on the draft NICE scope[38] for this appraisal, i.e., that NHS SoC treatments are used independently or in combination to treat SCD. The EAG agrees with the company that it is not appropriate to compare voxelotor+SoC versus HC+SoC, nor is it appropriate to compare voxelotor+SoC versus RTT+SoC.

3.5 Outcomes

The company has presented clinical effectiveness evidence from the HOPE trial for all outcomes, except mortality, listed in the final scope[19] issued by NICE. Definitions of the outcomes are provided in in the CS (Table 7). The results for the primary outcome of the HOPE trial (proportion of patients with Hb response of >1g/dL from baseline) and the

secondary outcomes of measures of haemolysis and change in Hb levels and are reported at 24 weeks. Results of exploratory analyses at 48 and 72 weeks are presented for the change in Hb level and measures of haemolysis (CS, Section B.2.6).

Data relevant to the complications of SCD derived from the HOPE trial are: overall VOC events, time to first ACS, time to first episode of pneumonia, time to first transfusion therapy and the incidences of leg ulcers (CS, Section B.2.6).

HRQoL outcomes are available at 24 weeks and 72 weeks for the Global Clinical Impression of Change scale (CGIC[39]) and the EuroQoL 5-Dimension 5-Level (EQ-5D-5L[40]) measures, and at 24 weeks for the Sickle Cell Disease Symptoms Measure (SCDSM[41]). Adverse event (AE) data from the HOPE trial are available in the CS (Section B.2.10).

Data are available from the HOPE trial OLE[32] (144 weeks), for the outcomes of change in Hb from baseline, change from baseline in markers of haemolysis, annualised incidence rates of VOCs (CS, Section B.2.6.8) and AEs (CS, Section B.2.10).

The HOPE trial was not designed to show an effect of treatment with voxelotor on chronic complications of SCD (CS, p86). Using data from the US-based Symphony database (see Section 2.2), the company conducted an analysis to explore associations between Hb concentration and several chronic complications of SCD. The specific complications are listed in the CS, Table 30. The EAG has serious concerns about the reliability of this analysis and considers that results should not be used to inform decision making. A full critique of the methods used by the company to undertake these analyses is provided in Section 6.2 of this EAG report.

3.6 Economic analysis

As specified in the final scope[19] issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per QALY gained. Outcomes were assessed over a lifetime horizon and costs were considered from an NHS and Personal Social Service (PSS) perspective.

3.7 Subgroups

The final scope[19] issued by NICE states that, if the evidence allows, the following subgroups will be considered:

- subgroups defined by combination treatment with and without HC
- subgroups defined by genotypes of SCD.

The results of the company's pre-specified subgroup analyses of baseline HC use (yes or no) are (appropriately) presented in the CS (Section B.2.7).

The company does not consider that subgroup analyses based on SCD genotype are relevant. (CS, Table 1). The company argues that the marketing authorisation for voxelotor is not restricted by SCD genotype and, that the HOPE trial was not powered to provide analyses by SCD genotype. The EAG agrees with the company that the HOPE trial was not powered to provide results based on SCD genotype and that limited patient numbers in the HbSC and HbSβ+ genotypes do not allow for subgroup analysis.

4 CLINICAL EFFECTIVENESS

4.1 Critique of review methods

Full details of the methods used by the company to identify and select clinically relevant evidence to demonstrate the effectiveness of voxelotor are presented in the CS (Appendix D). The EAG assessed the extent to which the review was conducted in accordance with the LR*i*G in-house systematic review checklist (Table 3). The EAG conducted its own searches and did not identify any new studies relevant to the clinical effectiveness of voxelotor. Overall, the EAG considers that the systematic review methods used by the company were appropriate. However, the EAG highlights that the company's systematic literature review (SLR) was broad and was aimed at identifying all treatments for patients with SCD and not specifically voxelotor (CS, Appendix D).

Table 3 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D.1.6, Table 5
Were appropriate sources searched?	Yes	CS, Appendix D.1.1 and D.1.5
Was the timespan of the searches appropriate?	Yes	CS, Appendix D.1.2 and D.1.3
Were appropriate search terms used?	Yes	CS, Appendix D.1.4
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix D.1.6, Table 5
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix D.1.7
Were data extracted by two or more reviewers independently?	Yes	CS, Appendix D.1.8
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	CS, Appendix D.3
Was the quality assessment conducted by two or more reviewers independently?	Yes	CS, Appendix D.3
Were attempts to synthesise evidence appropriate?	N/A	N/A

CS=company submission; EAG=Evidence Assessment Group; N/A=not applicable
Source: LR*i*G in-house checklist

4.2 EAG summary and critique of clinical effectiveness evidence

4.2.1 Included trials

The company presented clinical effectiveness evidence for the efficacy and safety of voxelotor from the following:

- a phase 3 RCT, the HOPE[33] trial
- long-term follow-up[31] data from the HOPE trial
- the open-label extension (OLE)[32] study of the HOPE trial

The primary source of clinical effectiveness evidence for voxelotor is the HOPE trial (a phase 3 RCT). HOPE trial efficacy and safety data are available up to 24 weeks, and long-term follow-up data are available up to 72 weeks.[31] The HOPE OLE[32] study was published following completion of the company SLR. Therefore, the company provided a descriptive summary of the outcomes from the HOPE OLE[32] study, but did not include the data from the study in their economic model.

This EAG report summarises the data from the HOPE trial, including long-term follow-up data[31] (Section 4.2.2 to Section 4.5). A descriptive summary of the HOPE OLE study[32] is presented in Section 4.6.

4.2.2 Characteristics of the HOPE trial

The HOPE trial was a phase 3, international, multicentre, double-blind, placebo-controlled RCT of voxelotor (1500mg and 900mg) versus placebo for adolescents and adults with SCD. The HOPE trial was conducted across 60 study sites in 12 countries, including the UK ([redacted] UK patients). The key characteristics of the HOPE trial are summarised in Table 4.

Table 4 Key characteristics of the HOPE trial

Trial parameter	The HOPE trial (NCT03036813)
Design	• Phase 3, multicentre, double-blind, placebo-controlled RCT • 60 sites in 12 countries (UK, Canada, USA, France, Italy, Netherlands, Turkey, Egypt, Lebanon, Oman, Kenya and Jamaica) • Three phases: screening ([redacted]); treatment ([redacted]) and end of trial follow-up visit ([redacted] after the last dose)
Patient population	• Patients aged 12 to 65 years with confirmed sickle cell disease (homozygous Hb S, sickle Hb C disease, Hb Sβ-thalassemia, or another variant) • Had a Hb level between 5.5 and 10.5 g/dL during screening • Had had between 1 to 10 VOCs in the past 12 months
Exclusions	• ≥10 VOC episodes in last 12 months • Received regular RBC transfusion therapy, or had received a transfusion in the last 60 days since signing the ICF • Hospitalised for VOC in last 14 days since signing the ICF • Hepatic dysfunction (ALT >4 times the normal upper limit) • Severe renal dysfunction • Received or required erythropoietin or HGF in 28 days of signing ICF • Pregnant or breastfeeding
Interventions	• Patients were randomised 1:1:1 to receive either 1500mg QD of voxelotor (n=90), 900mg[i] QD of voxelotor (n=92), or placebo (n=92)
Primary outcome	• Number of patients with an increase in Hb (>1g/dL) from baseline to Week 24
Secondary outcome(s)	• CFB in Hb level at Week 24 • CFB in haemolysis measures at Week 24 • Annualised incidence rate of VOC
Concurrent meditation	• All approved treatments for SCD were permitted (i.e., pain control, HC, L-glutamine and blood transfusions*) • Other commonly used medications (penicillin, folic acid and codeine) • HC was permitted if patients were on a stable dose for at least 90 days prior to the trial

[i] the marketing authorisation for voxelotor is for the 1500mg QD dose only
* except patients receiving regular transfusion therapy
ALT=alanine aminotransferase; CFB=change from baseline; CS=company submission; CSR=clinical study report; g/dL=grams per decilitre; Hb=haemoglobin; HC=hydroxycarbamide; HGF=hematopoietic growth factors; ICF=informed consent form; mg=milligrams; QD=once-daily; RBC=red blood cell; RCT=randomised controlled trial; SCD=sickle cell disease; VOC=vaso-occlusive crises
Source: CS, Table 5, HOPE trial CSR[42] and Vichinsky et al 2019[33]

4.2.3 Characteristics of patients in the HOPE trial

The baseline characteristics of patients recruited to the HOPE trial are presented by the company (CS, Table 6). The EAG agrees with the company (CS, p46) that the baseline characteristics of patients were generally well-balanced between the treatment arms. The majority of patients in the voxelotor and placebo arms were adults aged 18 to 65 years (84.4% and 81.5% respectively), female (64.4% and 54.3% respectively), black (65.6% and 68.5% respectively), and from North America and Europe combined (58.8% to 57.6% respectively). In the voxelotor and placebo arms, the predominant genotype was homozygous Hb SS (67.8% and 80.4% respectively), and nearly two-thirds of patients had between two and ten VOCs in

the past 12 months (61.1% and 57.6% respectively). Clinical advice to the EAG is that there is a slightly higher proportion of females in the trial, whereas in NHS practice there is a more even distribution of males and females; however, this is not a cause for concern. Clinical advice to the EAG is further that, while there is a slight imbalance between the voxelotor and placebo arms in the proportions of patients with the SCD genotype homozygous HbSS, this is no cause for concern as generally all patients with SCD are treated with the same standard measures regardless of genotype. The generalisability of HOPE trial results to NHS SCD patients with haemolytic anaemia has been discussed in Section 3.2.2.

4.2.4 Quality assessment of the HOPE trial

The company conducted a quality assessment of the HOPE trial using the NICE checklist for RCTs[43] which is based on the University of York Centre for Reviews and Dissemination guidance.[44] The results of the quality assessment are presented by the company (CS, Appendix D, Table 19). The EAG agrees with the company assessment of the quality of the HOPE trial and considers that the trial was well designed and well conducted.

4.2.5 Statistical approach for analysing the HOPE trial data

The EAG extracted information relevant to the statistical approach taken by the company to analyse the HOPE trial from the clinical study report (CSR, which is based on the 22 November 2019 database lock),[42] the most recent version of the trial protocol[31] and the trial statistical analysis plan (TSAP, version 5.0, dated 3 January 2019).[31] A summary of the EAG checks of the pre-planned statistical approach used by the company to analyse data from the HOPE trial is provided in the Appendix (Section 8.1, Table 31). The EAG considers the company's pre-planned statistical approach was appropriate.

4.3 Efficacy results from the HOPE trial

The efficacy results presented in this section are based on data from the 22 November 2019 database lock.

4.3.1 Participant flow in the HOPE trial

The company presented data on participant flow in all three treatment arms of the HOPE trial (CS, Table 16).

In the intent-to-treat (ITT) population, the majority of patients in both the voxelotor and placebo arms completed treatment at Week 72 (70.0% and 71.7% respectively). A similar proportion of patients in the voxelotor and placebo arms discontinued the study early (30.0% and 28.3% respectively). In the voxelotor arm, the most common reason for treatment discontinuation

was due to an AE (12.2%). In the placebo arm, the most common reason for treatment discontinuation was withdrawal of consent (9.8%).

4.3.2 Haemoglobin outcomes

Change from baseline in haemoglobin response: intent-to-treat population

The primary outcome of the HOPE trial was the number of patients with an increase in Hb >1g/dL from baseline to Week 24. For the ITT population, the number of patients who experienced a Hb response from baseline to Week 24 for each of the treatment arms is summarised in Table 5. Hb response was defined as an increase in Hb of >1g/dL (CS, Table 7). The company states (CS, p84) that an Hb increase of >1g/dL was used as it is equivalent to the intended effect of one unit of transfused blood. Clinical advice to the EAG is that it is not known whether an increase of 1g/dL is clinically meaningful; however, the European Medicines Agency considers that treatment with voxelotor has resulted in a beneficial effect in terms of reduction in haemolysis and an increase in Hb, which are considered of clinical relevance to patients.[18]

In the ITT population, the proportion of patients who had a Hb response (>1g/dL) at Week 24 was higher for voxelotor (n=46/90, 51.1%) than placebo (n=6/92, 6.5%); this difference was statistically significant (p<0.001).

No exploratory analysis was conducted for patients with a Hb response at Week 48 or Week 72.

Table 5 Proportion of HOPE trial patients with a Hb response (increase of >1g/dL) at Week 24: ITT population

	Placebo (n=92)	**Voxelotor 1500mg (n=90)**
Hb increase of >1g/dL, n (%)	6 (6.5)	46 (51.1)
p-value (vs placebo)	-	**p<0.001**

Results highlighted in bold are statistically significant
CS=company submission; g/dL=gram per decilitre; Hb=haemoglobin; ITT=intent-to-treat; vs=versus
Source: CS, Section B.2.6.1

Change from baseline in Hb levels: intent-to-treat population

A secondary outcome of the HOPE trial was the change in Hb levels from baseline to Week 24. The company also performed an exploratory analysis of the change in Hb levels from

baseline to Weeks 48 and 72. Results for the change in Hb levels for all three endpoints and treatment arms are summarised in Table 6.

In the ITT population, patients in the voxelotor arm had an adjusted (least square [LS] mean change in Hb from baseline to 24 weeks of 1.13g/dL compared with -0.10g/dL in the placebo arm (p<0.001). Change in Hb levels continued to show a statistically significant difference in favour of voxelotor compared to placebo at [redacted] Week 72.[42]

Table 6 Summary of the HOPE trial CFB in Hb levels: ITT population

	Placebo (n=92)	Voxelotor 1500mg (n=90)
Week 24‡		
LS mean (SE) g/dL	-0.10 (0.132)	1.13 (0.132)
p-value (vs placebo)	-	**p<0.001**
Week 48Φ		
LS mean (SE) g/dL	[redacted]	[redacted]
p-value (vs placebo)	-	[redacted]
Week 72Φ		
LS mean (SE) g/dL	0.02 (0.148)	1.02 (0.149)
p-value (vs placebo)	-	**p<0.001**

‡ Secondary endpoint
Φ Exploratory endpoint
Results highlighted in bold are statistically significant
CFB=change from baseline; CS=company submission; CSR=clinical study report; g/dL=grams per decilitre; ITT=intent-to-treat; LS=least squares; SE=standard error; vs=versus
Source: CS, Table 9, Howard et al 2021[31] and CSR (Table 25)[42]

4.3.3 Haemolysis measures

HOPE trial results for four haemolysis measures are summarised for each of the treatment arms at Week 24, Week 48 and Week 72 (Table 7); analyses were carried out using the mixed model repeated measures (MMRM) approach (CS, Table 7).

In the ITT population, patients who received voxelotor showed a statistically significant reduction against placebo for indirect bilirubin levels (-29.1 versus -3.2 respectively) and percentage of reticulocytes (-19.9 versus 4.5 respectively) at Week 24. At Week 72, a statistically significant reduction was maintained in patients receiving voxelotor in indirect bilirubin levels (p<0.001) and percentage of reticulocytes (p<0.05). These are biological markers for haemolytic anaemia that are reviewed by treating clinicians when making treatment decisions. Patients who received voxelotor showed an improvement compared to placebo for absolute reticulocyte count and lactate dehydrogenase levels, but these differences were not statistically significant at any timepoint.

Table 7 Summary of the HOPE trial haemolysis outcomes: ITT population

	CFB in LS mean (95% CI)	
	Placebo (n=92)	**Voxelotor 1500mg (n=90)**
Indirect bilirubin levels (%)		
Week 24‡	-3.2 (-10.1 to 3.8)§	-29.1 (-35.9 to 22.2)** §
Week 48Φ	3.4 (-4.5 to 11.3)	-26.2 (-34.2 to -18.3)**
Week 72Φ	2.7 (-7.0 to 12.3)	-23.9 (-33.5 to -14.3)**
Percentage of reticulocytes (%)		
Week 24‡	4.5 (-4.5 to 13.6)§	-19.9 (-29.0 to -10.9)** §
Week 48Φ	1.8 (-9.5 to 13.0)	-3.6 (-15.1 to 7.8)
Week 72Φ	11.0 (0.2 to 21.8)	-7.6 (-18.5 to 3.3)*
Absolute reticulocytes (%)		
Week 24‡	3.1 (-7.0 to 13.2)§	-8.0 (-18.1 to 2.1)§
Week 48Φ	0.8 (-11.5 to 13.0)	10.0 (-2.5 to 22.4)
Week 72Φ	9.1 (-3.3 to 21.5)	3.4 (-9.2 to 15.9)
Lactate dehydrogenase (%)		
Week 24‡	3.4 (-4.0 to 10.9)§	-4.5 (-11.9 to 2.8)§
Week 48Φ	2.1 (-3.3 to 7.5)	-4.8 (-10.2 to 0.7)
Week 72Φ	-3.8 (-2.5 to 10.0)	-1.1 (-7.5 to 5.3)

‡ secondary endpoint
Φ exploratory endpoint
§ The values reported here are consistent with those reported in Vichinsky et al 2019,[33] but different to those reported in the EPAR and CSR;[18] the reasons for the difference between these values are not clear
* p<0.05
** p<0.001
CFB=change from baseline; CI=confidence interval; CS=company submission; EPAR=European Public Assessment Report; ITT=intent-to-treat; LS=least squares
Source: CS, Table 10

4.3.4 Vaso-occlusive crisis: modified intent-to-treat population

The annualised incidence rates of VOCs for patients receiving voxelotor and placebo were assessed in the modified ITT (mITT) population. The mITT population was defined as all patients who were randomised to a treatment arm and received at least one dose of the study drug.[42] VOC events were modelled using a negative binomial model with treatment arm as an independent variable (CS, Table 7). A summary of on-treatment VOC events in each of the three arms of the HOPE trial is presented in Table 8.

In the mITT population, numerically fewer patients in the voxelotor arm experienced a VOC event compared to the placebo arm (69.3% versus 76.9% respectively). Similarly, the total number of VOC events was numerically fewer in the voxelotor arm compared to the placebo arm (219 versus 293 respectively). Overall, the adjusted annualised incidence rate was numerically lower for the voxelotor treated patients compared to placebo (2.37 versus 2.79 respectively); this difference was not statistically significant. The EAG highlights that the HOPE

trial was not powered to assess this outcome, therefore it is not appropriate to use these results for decision making.

Table 8 Summary of HOPE trial on-treatment VOC events: mITT population

	Placebo (n=91)	Voxelotor 1500mg (n=88)
Patients with any VOC event, n (%)	70 (76.9)	61 (69.3)
Total number of VOC events	293	219
Adjusted annualised incidence rate, events/year (95% CI)	2.79 (2.19 to 3.56)	2.37 (1.84 to 3.07)

CI=confidence interval; CS=company submission; mITT=modified intent-to-treat; VOC=vaso-occlusive crises
Source: CS, Table 11

4.3.5 Other exploratory outcomes

The company presented additional results from the HOPE trial for exploratory time-to-event outcomes in the mITT population, including time to first ACS or pneumonia, and time to first red blood cell transfusion (CS, Section B.2.6.5.2, Table 12). Kaplan-Meier (K-M) methods were used to assess time-to-event endpoints (CS, Table 7). The incidence of severe anaemic episodes and acute anaemic episodes were also presented as secondary endpoints.

Acute chest syndrome or pneumonia

The median time to first ACS or pneumonia was not reached in either treatment arm due to events occurring in fewer than 50% of patients (CS, p57). In the mITT population, a [redacted] of patients experienced ACS or a pneumonia event in the voxelotor arm compared to the placebo arm ([redacted] versus [redacted] respectively), though the total number of ACS events was slightly higher for voxelotor than placebo ([redacted] versus [redacted] respectively) (CS, Table 12). Overall, the annualised incidence rate was similar in patients receiving voxelotor compared to placebo ([redacted] versus [redacted]).

Time to first red blood cell transfusion

The median time to first red blood cell transfusion was not reached in any treatment arm due to events occurring in fewer than 50% of patients (CS, p58). In the mITT population, a similar proportion of patients in the voxelotor arm and placebo arm received a transfusion (36% for each) (CS, Table 12). The total number of red blood cell transfusions was [redacted] between the voxelotor arm and placebo arms ([redacted] and [redacted] respectively). Overall, the annualised adjusted incidence rate was similar in patients treated with voxelotor compared to placebo ([redacted] versus [redacted] respectively). The EAG highlights that the trial population on which these results are based consisted of patients who did not receive RTT or had not received a transfusion in the 60 days prior to the start of the trial because of the confounding effect of transfusions on Hb endpoints.

Incidence of severe anaemic episodes and acute anaemic episodes

The company reports that the incidence of severe anaemic episodes (defined as a Hb level of <5.5 g/dL) was low for voxelotor and placebo ([redacted] patients in each arm) (CS, Section B.2.6.2.2). The incidence of acute anaemic episodes (defined as a decrease in Hb of at least 2 g/dL from baseline) was lower in patients who received voxelotor compared to placebo ([redacted] and [redacted] respectively).

4.3.6 Post-hoc analyses

Incidence of severe anaemic episodes and acute anaemic episodes

A post-hoc analysis of HOPE trial data showed the annualised incidence rate of acute anaemic episodes was three times lower in patients receiving voxelotor (0.05 episodes per year) compared to those receiving placebo (0.15 episodes per year) at Week 72.[31]

Incidence of leg ulcers

The company additionally report the results of a post-hoc analysis on the incidence of leg ulcers in the HOPE trial until Week 72 (CS, Section B.2.6.7). Among the patients with leg ulcers, all of the patients (n=5/5) who received voxelotor showed an improvement or resolution of the leg ulcer by Week 72 compared to 63% (n=5/8) of patients receiving placebo. In the treatment period (up to 72 weeks), new leg ulcers were reported in only one patient (0.01%) receiving voxelotor and in five patients receiving placebo (0.05%).

4.3.7 Subgroup analyses

The company performed subgroup analyses based on patient demographic information (age, sex and race), geographic region, baseline HC use (yes or no), baseline VOC history (1 or ≥1), and baseline Hb level (5.5 to <7 g/dL or ≥7 g/dL) for the outcomes of Hb response (at Week 24) and change from baseline in Hb level (up to Week 72). The company also presented subgroup analyses of the on-treatment incidence rate of VOCs based on baseline VOC history (1 or ≥2 prior events) and prior opioid use (yes or no). The company results from the subgroup analyses for Hb response at 24 weeks are presented in the CS (Figure 19); these are reproduced below in Figure 2.

The subgroup analyses showed that treatment with voxelotor had a favourable effect compared to placebo for Hb response at Week 24 for all subgroups explored (RR, range: voxelotor 36.8% to 60.0%, placebo 0% to 14.3%) (CS, Figure 19).

The subgroup analysis of the on-treatment incidence rate of VOCs by baseline VOC history showed that patients who experienced one VOC in the previous year had a similar annualised incidence rate of VOCs if they received voxelotor ([redacted]) or placebo ([redacted]

[redacted]). Among patients who experienced more than one VOC in the previous year, there was a numerically lower incidence rate in those who had received voxelotor ([redacted]) compared to placebo ([redacted]) (CS, Appendix E). Rates of post-baseline opioid use were similar between voxelotor and placebo for patients with and without prior opioid history (CS, Appendix E).

	Placebo		Voxelotor 1500 mg	
	N	Response Rate[a]	N	Response Rate[a]
ITT (Groups 1 and 2)	92	6.5%	90	51.1%
Age				
12 to <18 years	17	5.9%	14	57.1%
18 to 65 years	75	6.7%	76	50.0%
Sex				
Male	42	9.5%	32	56.3%
Female	50	4.0%	58	48.3%
Race				
Arab or Middle Eastern	20	5.0%	20	55.0%
Black or African American	63	4.8%	59	52.5%
Geographic Region				
North America	35	11.4%	34	52.9%
Europe	18	0%	19	36.8%
Other	39	5.1%	37	56.8%
VOC History (prior 12 months)				
1 episode	39	5.1%	35	60.0%
≥2 episodes	53	7.5%	55	45.5%
Baseline HU Use				
No	34	8.8%	32	43.8%
Yes	58	5.2%	58	55.2%
Baseline Hb				
<7 g/dL	7	14.3%	7	57.1%
≥7 g/dL	85	5.9%	83	50.6%

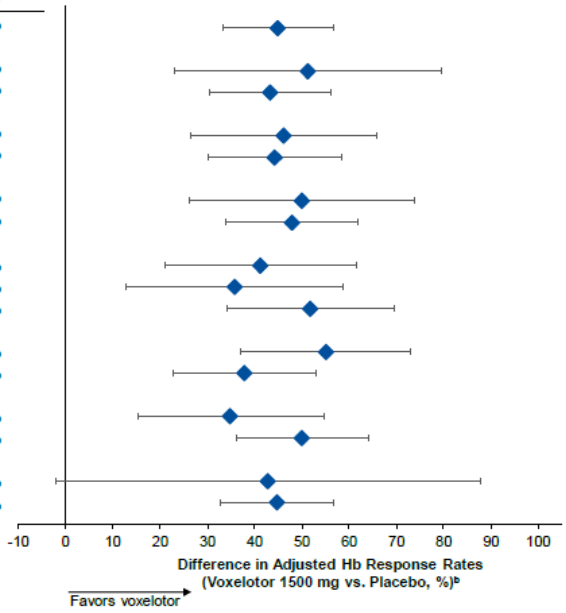


Figure 2 Hb response by subgroup at Week 24

Hb=haemoglobin; HC=hydroxycarbamide; HU=HC; ITT=intent-to-treat; VOC=vaso-occlusive crises
Source: CS, Figure 19

4.4 Patient reported outcomes from the HOPE trial

HRQoL data were collected during the HOPE trial using the CGIC[39] questionnaire, the SCDSM,[41] and the EQ-5D-5L[40] questionnaire. The HRQoL outcomes are exploratory endpoints.

The CGIC scale[39] is a 7-point scale completed by the treating physician. The items on the scale range from 'very much improved' to 'very much worse'. Assessments were completed on [redacted] (CSR Section 9.5.1.1. Table 3).

The EQ-5D-5L questionnaire[40] is a standardised instrument for measuring health outcome. The EQ-5D-5L questionnaires were administered on [redacted] (CSR Section 9.5.1.1. Table 3).

The SCDSM is a self-administered questionnaire developed by the company. The SCDSM consists of 9 items that include measures of pain, fatigue and mental acuity that are rated on a 4-point response scale. Outcomes from the questionnaire at week 24 are presented in the CS (p59). All patients completed the SCDSM questionnaires at baseline.

The results of the HRQoL outcomes are summarised in Table 9. The company highlights (CS, p59):

- CGIC results at Week 72 showed that 74% of patients in the voxelotor arm were rated as 'Moderately' or "Very Much Improved' compared with 47% of patients in the placebo arm
- EQ-5D-5L results at Week 24 and Week 72 showed no meaningful changes from baseline in either the voxelotor or placebo arms
- SCDSM results showed no difference in reported disease severity between the voxelotor and placebo arms at Week 24. The company highlights that SCDSM data are difficult to interpret due to low baseline scores and high variability in symptom scores

Table 9 Company summary of HRQoL outcomes from the HOPE trial

	Placebo n=92	Voxelotor 1500mg n=90
CGIC, 'Moderately Improved' or 'Very Much Improved' n/N (%)		
Week 24	[redacted]	[redacted]
Week 72	[redacted][§]	39/58 (73.6)
EQ-5D-5L Index, mean (SD)		
Baseline	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Week 72*	[redacted]	[redacted]
Change from baseline to Week 24[ł]	[redacted]	[redacted]
Change from baseline to Week 72[ł]	[redacted]	[redacted]
EQ-5D-5L VAS, mean (SD)		
Baseline	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Week 72**	[redacted]	[redacted]
Change from baseline to Week 24[ł]	[redacted]	[redacted]
Change from baseline to Week 72[ł]	[redacted]	[redacted]
SCDSM, mean (SD)		
Baseline	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Change from baseline to Week 24[ł]	[redacted]	[redacted]

*based on less than 20% of respondents
** based on 30% of respondents
[§] reported as 39/53 (47.1%) in the CS, Table 13
[ł] not clear how the company calculated these results
CGIC=Clinical Global Impression of Change; CS=company submission; EQ-5D-5L=EuroQol 5-Dimension 5-Level; EPAR=European Public Assessment Report; HRQoL=health-related quality of life; SCDSM=Sickle Cell Disease Activity Measure; SD=standard deviation; VAS=visual analogue scale
Source: CS, Table 13 and EPAR[18]

4.5 Safety and tolerability results from the HOPE trial

The CS presents safety and tolerability data from the HOPE trial (Section B.2.10). Safety analyses were based on the safety analysis set, which comprised all patients who received at least one dose of trial medication (CS, p48). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.03[45]), and coded using the Medical Dictionary for Regulatory Activities (MedDRA®, version 22.0[46]).

All AEs were treatment-emergent adverse events (TEAEs), which were defined as [redacted][42] TEAEs were categorised as being or not being related to SCD. SCD-related TEAEs were SCD morbidities and complications, including sickle cell anaemia with crises, acute chest syndrome, pneumonia, priapism and osteonecrosis (CS, Table 10).

4.5.1 Exposure to study treatment

Treatment exposure data for the safety population in the HOPE trial are summarised by the company (CS, Table 15). The median duration of treatment exposure was similar between the treatment arms (voxelotor: [redacted] weeks [range: [redacted] to [redacted] weeks] and placebo: [redacted] weeks [range: [redacted] to [redacted]]).[42]

4.5.2 SCD-related adverse events

Overview of SCD-related TEAEs

A summary of the types of TEAEs related to SCD is provided in Table 10. For SCD-related TEAEs, treatment with voxelotor and placebo showed similar results for any grade TEAEs (78.4% and 80.2% respectively), Grade ≥3 TEAEs (56.7% and 57.1% respectively), serious TEAEs (52.3% and 52.7% respectively), drug-related TEAEs (5.7% and 5.5% respectively), and TEAEs leading to discontinuation (3.4% and 2.2% respectively).

Table 10 Overview of SCD-related TEAEs in the HOPE trial: safety population

SCD-related TEAE type	Placebo (n=91)	Voxelotor 1500mg (n=88)
Any grade TEAE, n (%)	73 (80.2)	69 (78.4)
Grade ≥3 TEAE, n (%)	52 (57.1)	50 (56.7)
Serious TEAE, n (%)	48 (52.7)	46 (52.3)
Drug-related TEAE, n (%)	5 (5.5)	5 (5.7)
TEAE leading to discontinuation, n (%)	2 (2.2)	3 (3.4)

CS=company submission; SCD=sickle cell disease; TEAE=treatment-emergent adverse event
Source: CS, Table 19

Most common SCD-related TEAEs

A summary of the SCD-related TEAEs experienced by patients included in the safety analysis set of the HOPE trial is presented in Table 11. The most common SCD-related TEAE reported in patients receiving voxelotor or placebo was sickle cell anaemia crisis (76.1% and 79.1% respectively). All SCD-related TEAEs showed similar rates between the voxelotor and placebo arms, except for priapism which occurred more frequently in patients treated with the trial drug.

Table 11 Summary of HOPE trial SCD-related TEAEs in ≥10% of any treatment arm: safety population

SCD-related TEAE type	Placebo, n (%) (n=91)	Voxelotor 1500mg, n (%) (n=88)
Sickle cell anaemia crises	72 (79.1)	67 (76.1)
Priapism (male patients only)	1/42 (2.4)	4/31 (12.9)
Osteonecrosis	1 (1.1%)	0%
ACS or pneumonia	13 (14.3)	16 (18.2)

ACS=acute chest syndrome; CS=company submission; SCD=sickle cell disease; TEAE=treatment-emergent adverse event
Source: CS, Table 20

4.5.3 Non SCD-related adverse events

Overview of non SCD-related TEAEs

A summary of the types of TEAEs not related to SCD is provided in Table 12. For non SCD-related TEAEs, treatment with voxelotor compared to placebo had a higher incidence rate (≥5% difference) of any grade TEAEs (96.6% and 90.1% respectively) and drug-related TEAEs (39.8% and 26.4% respectively). Similar results were found for voxelotor treatment and placebo for Grade ≥3 TEAEs (32.9% and 37.4% respectively), serious TEAEs (28.4% and 25.3%), and TEAEs leading to discontinuation (10.2% and 6.6% respectively).

Table 12 Overview of HOPE trial non-SCD-related TEAEs: safety population

Non-SCD-related TEAE type	Placebo, n (%) (n=91)	Voxelotor 1500mg, n (%) (n=88)
Any grade TEAE, n (%)	82 (90.1)	85 (96.6)
Grade ≥3 TEAE, n (%)	34 (37.4)	29 (32.9)
Serious TEAE, n (%)	23 (25.3)	25 (28.4)
Drug-related TEAE, n (%)	24 (26.4)	35 (39.8)
TEAE leading to discontinuation, n (%)	6 (6.6)	9 (10.2)

CS=company submission; SCD=sickle cell disease; TEAE=treatment-emergent adverse event
Source: CS, Table 17

Most common non SCD-related TEAEs

A summary of the non SCD-related TEAEs identified in ≥10% of patients in any treatment arm of the HOPE trial are summarised in Table 13. The most common (≥10% of patients) non-SCD-related TEAEs in patients receiving voxelotor were headache (31.8%), diarrhoea

(22.7%) and arthralgia (21.6%), and for those receiving placebo were headache (25.3%), pain in the extremities (20.9%) and pain (19.8%). The EAG highlights the following:

- treatment with voxelotor showed a lower rate (≤5% difference) than placebo only for pain in the extremities
- similar rates of TEAEs were found between voxelotor and placebo for most (11/17) types of non SCD-related TEAEs reported in ≥10% of patients
- a higher rate (≥5% difference) of TEAEs was found in the voxelotor arm than placebo for headache, diarrhoea, arthralgia, nausea and pyrexia.

Table 13 Summary of HOPE trial non-SCD-related TEAEs in ≥10% of any treatment arm: safety population

Non-SCD-related TEAE	Placebo, n (%) (n=91)	Voxelotor 1500mg, n (%) (n=88)
Headache	23 (25.3)	28 (31.8)
Diarrhoea	10 (11)	20 (22.7)
Arthralgia	13 (14.3)	19 (21.6)
Nausea	9 (9.9)	17 (19.3)
Back pain	12 (13.2)	15 (17.0)
Pain	18 (19.8)	15 (17.0)
Abdominal pain	10 (11.0)	13 (14.8)
Pyrexia	7 (7.7)	13 (14.8)
Rash	10 (11.0)	13 (14.8)
Upper respiratory tract infection	14 (15.4)	13 (14.8)
Fatigue	12 (13.2)	13 (13.6)
Pain in extremity	19 (20.9)	12 (13.6)
Vomiting	15 (16.5)	12 (13.6)
Non-cardiac chest pain	10 (11.0)	10 (11.4)
Urinary tract infection	13 (14.3)	9 (10.2)
Abdominal pain upper	6 (6.6)	8 (9.1)
Cough	10 (11.0)	8 (9.1)

CS=company submission; SCD=sickle cell disease; TEAE=treatment-emergent adverse event
Source: CS, Table 18

Mortality

The rates of fatal adverse events in the HOPE are not reported in the CS, therefore the EAG has extracted these data from the trial publication.[31] At 72 weeks, two patients in both the voxelotor arm and the placebo arm had fatal adverse events; all events were determined to be unrelated to the trial drug by investigator assessment.

4.5.4 EAG interpretation of the safety results from the HOPE trial

The EAG highlights that while some differences were observable between the voxelotor and placebo arms of the HOPE trial, the rates of SCD-related TEAEs and non-SCD-related TEAEs were broadly similar. Clinical advice to the EAG is that, based on available evidence and experience, treatment with voxelotor raises no safety concerns.

4.6 Other evidence: HOPE open-label extension study and real world data

4.6.1 The HOPE OLE study

The HOPE OLE[32] study (NCT0357882) recruited patients (n=178) from the HOPE trial who had completed treatment up to Week 72. In the HOPE OLE[32] study, all patients received treatment with 1500mg voxelotor. Treatment with voxelotor continued while patients received clinical benefit and/or were able to receive access to voxelotor through commercialisation or a managed access program.[32] The key outcomes of the HOPE OLE[32] study were change from baseline in Hb level, change from baseline in haemolysis markers, and AEs.[32]

Patient characteristics

The company presented a summary of the characteristics of patients recruited to the HOPE OLE[32] study (CS, Table 14), summarised here in Table 14. The patients recruited to the HOPE OLE[32] study had previously received either voxelotor (1500mg or 900mg) or placebo during the HOPE trial (CS, p61). The population in the HOPE OLE[32] study consisted of similar proportions of patients previously treated with voxelotor 1500mg, voxelotor 900mg or placebo (58%, 58% and 62% respectively) who were of similar ages (median age range: 24 to 27 years) and who had similar exposures to the trial drug (median: 67.9 to 72.9 weeks).

Table 14 Summary of the characteristics of patients recruited to the HOPE OLE study

	Prior treatment group, n (%)			OLE, n (%)
	Placebo (n=62)	**Voxelotor 900mg (n=58)**	**Voxelotor 1500mg (n=58)**	**Voxelotor 1500mg (n=178)**
Age, median years	27	24	25	25
Adolescent (12 to 17 years), n (%)	11 (17.7)	6 (10.3)	11 (19.0)	28 (15.7)
Adult (≥18 years), n (%)	51 (82.3)	52 (89.7)	47 (81.0)	150 (84.3)
Duration of exposure, weeks				
Median	68.6	67.9	72.9	69.9
Range (min, max)	4.6 to 102.0	1.9 to 98.3	12.1 to 100.6	1.9 to 102.0
≥72 weeks, n (%)	26 (41.9)	21 (36.2)	31 (53.4)	78 (43.8)

CS=company submission; OLE=open-label extension
Source: CS, Table 14

Efficacy results

Efficacy results from the HOPE OLE study were estimated using data from an interim data cut (31 December 2020).[32] A summary of the efficacy results from the HOPE OLE[32] study are presented in Table 15.

In the HOPE OLE[32,47] study patients who had received placebo in the previous phase 3 trial showed an improvement in Hb (mean 1.3 [SD 1.51]), and improvements in haemolysis markers (indirect bilirubin levels: -39.5%, reticulocytes: -28.6%). Patients who had previously received voxelotor showed stable Hb levels, indirect bilirubin levels and reticulocyte count. The annualised incidence rate of VOCs was lower in patients who had previously received voxelotor (1.0 to 1.1 events/year) compared to those who had previously received placebo (1.7 events/year).

Table 15 Summary of results from the HOPE OLE study from baseline to Week 48

Outcome	**Placebo → Vox 1500mg (n=62)**	**Vox 900mg → Vox 1500mg (n=58)**	**Vox 1500mg → Vox 1500mg (n=58)**
Change in Hb g/dL, mean (SD)	1.3 (1.51)	0.7 (1.48)	0.2 (1.15)
Change in indirect bilirubin levels, %	-39.5	-2.0	1.1
Change in reticulocyte count, %	-28.6	-14.6	-21.0
Annualised IR of VOCs, events/year	1.7	1.0	1.1

CS=company submission; Hb=haemoglobin; IR=incidence rate; OLE=open-label extension; SD=standard deviation; VOC=vaso-occlusive crises; Vox=voxelotor
Source: CS, Section B.2.6.8 and Achebe 2021[47]

Safety results

A summary of HOPE OLE[32] study non-SCD-related AEs reported in ≥10% of patients is presented in Table 16. Non-SCD-related AEs were reported in 83.7% of patients in the HOPE OLE[32] study (CS, Table 21). The most common non SCD-related AEs in the OLE population were arthralgia (15.2%), headache (12.9%) and pain (11.8%). There were 11 (6.2%) patients who experienced an AE that led to discontinuation of treatment, of which 4 (2.2%) were considered drug related. There were 4 deaths, none being related to voxelotor.[32]

Table 16 Non-SCD-related AEs in ≥10% of patients in the OLE study

	Prior treatment group, n (%)			OLE, n (%)
	Placebo (n=62)	Voxelotor 900mg (n=58)	Voxelotor 1500mg (n=58)	Voxelotor 1500mg (n=178)
Arthralgia	15 (24.2)	7 (12.1)	5 (8.6)	27 (15.2)
Headache	12 (19.4)	6 (10.3)	5 (8.6)	23 (12.9)
Pain	11 (17.7)	5 (8.6)	5 (8.6)	21 (11.8)
Nausea	13 (21.0)	5 (8.6)	2 (3.4)	20 (11.2)
Pain in extremity	7 (11.3)	6 (10.3)	7 (12.1)	20 (11.2)
Diarrhoea	10 (16.1)	6 (10.3)	2 (3.4)	18 (10.1)
Upper respiratory tract infection	7 (11.3)	2 (3.4)	9 (15.5)	18 (10.1)

AE=adverse event; CS=company submission; SCD=sickle cell disease; OLE=open-label extension study
Source: CS, Table 21

4.6.2 Real world evidence

The company has provided published results from analyses of real world evidence (Symphony database) to show the impact of the introduction of voxelotor on patient outcomes (Shah 2022).[48] The EAG considers that these results are of secondary importance due to data for the population of interest being available from a high quality RCT (HOPE trial). Further, the EAG considers the Shah 2022[48] results are of limited use to decision makers as these results have been generated from simple before and after comparisons, which are subject to confounding.

4.7 Conclusions of the clinical effectiveness section

Voxelotor is the only treatment licensed in Europe for patients with haemolytic anaemia associated with SCD. Voxelotor is a first-in-class Hb oxygen-affinity modulator. The HOPE trial is of good methodological quality; however, many patients with SCD were excluded from the trial, including those receiving RTT (to prevent the confounding effect of transfusions on Hb-related endpoints), those who had had >10 VOCs during the previous year that required hospital, emergency room or clinical visit, and those who had had no VOCs during the previous 12 months. Results from the HOPE trial show that, compared with placebo, statistically

significantly more patients treated with voxelotor had an Hb response (defined as a >1g/dL increase in Hb) at Week 24. However, there is no evidence to demonstrate that the HOPE trial improvements in Hb level experienced by patients treated with voxelotor are clinically meaningful or if they reduce SCD complications over a patient lifetime. There were some differences between the voxelotor and placebo arms in terms of AEs; however, rates of SCD-related TEAEs and non-SCD-related TEAEs were broadly similar.

The company's proposed positioning of voxelotor is as a treatment for patients requiring second-line treatment after HC, i.e., adults and paediatric patients aged 12 years or older with SCD who are ineligible for, intolerant of or unwilling to take HC, or for whom HC alone is insufficiently effective (CS, p12). The MHRA EAMS[20] voxelotor licence is for "the treatment of haemolytic anaemia due to SCD in adults and paediatric patients 12 years of age and older as monotherapy or in combination with HC and does not limit the use of voxelotor to after treatment with HC.

Clinical advice to the EAG is that HC and voxelotor deliver different benefits and it is therefore not appropriate to only position voxelotor after HC. The EAG considers that the company does not have robust clinical efficacy evidence to support positioning of voxelotor as 'second-line treatment after HC'.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of the use of voxelotor as an option for treating haemolytic anaemia in people with SCD. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.1 Published cost effectiveness evidence

5.1.1 Objective of the company's literature searches

The company undertook a systematic review to identify published SCD cost effectiveness models that could potentially be used to inform the development of the company's economic model. Databases were searched between database inception and April 2022. The company SLR was reported according to PRISMA[49] standards.

The search identified ten studies[37,50-58] that met the company inclusion criteria; however, none of these studies evaluated the cost effectiveness of different treatments for SCD patients with haemolytic anaemia from a UK health care system perspective.

5.1.2 EAG critique of the company's literature review

A summary of the EAG's critique of the company's literature review methods (CS, Appendix G) is provided in Table 17.

Table 17 EAG appraisal of systematic review methods (cost effectiveness)

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Were data extracted by two or more reviewers independently?	Data extracted by a single analyst and checked by a second reviewer
Were appropriate criteria used to assess the quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Undertaken by one reviewer and checked by a second reviewer
Were any relevant studies identified?	10 relevant studies[37,50-58] were identified

EAG=External Assessment Group

5.2 EAG conclusions

The EAG has no concerns about the methods used by the company to identify cost effectiveness studies. No models exploring the cost effectiveness of interventions to treat haemolytic anaemia in patients with SCD were identified by the review.

5.3 Summary of the company's submitted economic evaluation

5.3.1 NICE Reference Case checklist

Table 18 NICE Reference Case checklist completed by EAG

Element of health technology assessment	Reference case	EAG comment on company submission
Defining the decision problem	The scope developed by NICE	The model was designed around a population of patients with SCD who had haemolytic anaemia
Comparator(s)	As listed in the scope developed by NICE	SoC was the most appropriate comparator
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis Cost comparison analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	The main sources of evidence were the HOPE trial, an analysis of Symphony database data and a Delphi panel
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients or carers, or both	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

EAG=External Assessment Group; EQ-5D=EuroQol-5 Dimension; PSS=Personal Social Services; QALY=quality adjusted life year; SCD=sickle cell disease; SoC=standard of care
Source: NICE Reference Case[59]

Table 19 Drummond and Jefferson critical appraisal checklist completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partial	The effect of voxelotor on Hb was demonstrated by HOPE trial results. However, the EAG considers that the company TTE analyses are uncertain and should be interpreted with caution
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	No	The company relies heavily on assumptions that are not evidence based
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Partial	The company did not fully discuss the uncertainty around the cost effectiveness results in light of the assumptions used to populate the model

EAG=External Assessment Group; Hb=haemoglobin; TTE=time-to-event
Source: Drummond and Jefferson 1996[60] and EAG comment

5.3.2 Company model structure

The company developed a discrete event simulation (DES) model. A simplified schematic of the DES algorithm is provided in Figure 3. The model simulated time to event (TTE), for each individual patient, for all possible modelled events. The events modelled by the company were SCD-related complications and death, treatment discontinuations, HC and RTT. Treatment waning was not applied.

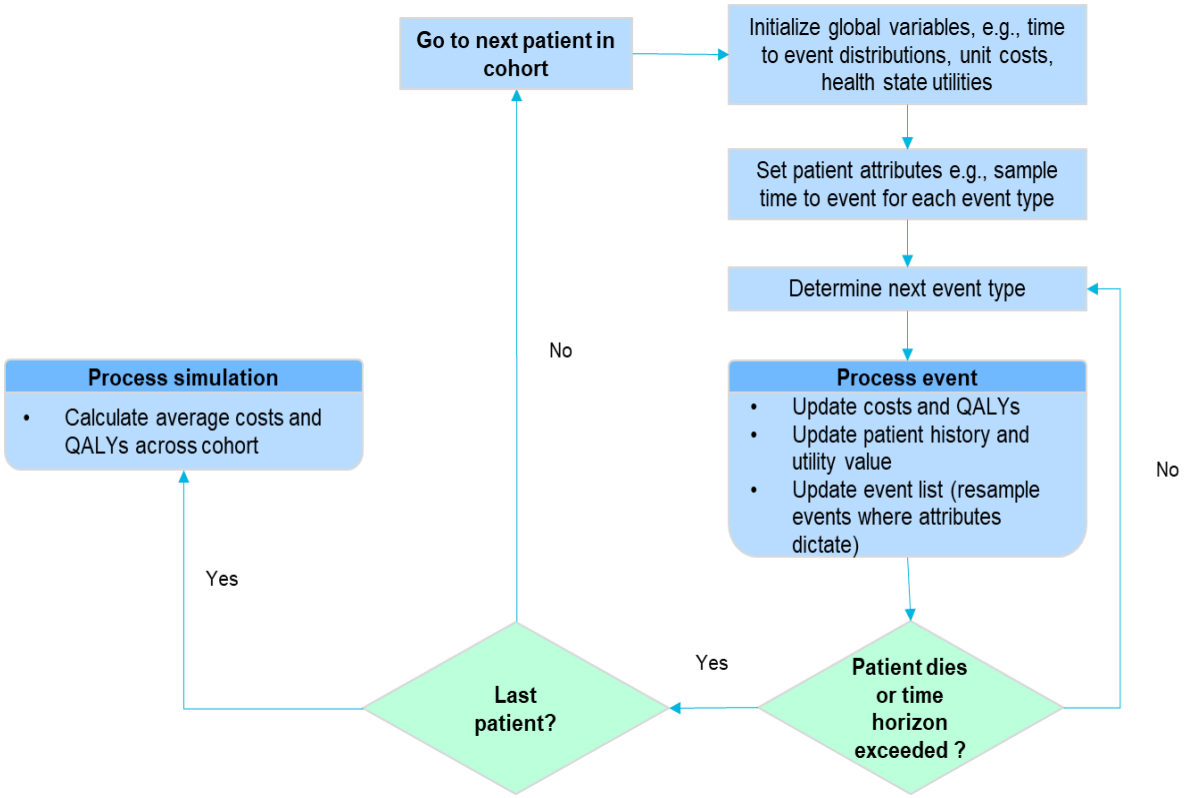


Figure 3 Company simplified discrete event simulation algorithm

CS=company submission; QALY=quality adjusted life year
Source: CS, Figure 21

5.3.3 Population

The company analysis focused on the use of voxelotor as a second-line treatment (L2+) for patients who are intolerant, ineligible or have an inadequate response to HC, or are unwilling to receive HC.

The baseline characteristics (reproduced in Table 20) of the modelled population reflect the patients recruited to the HOPE trial.

The company states that the baseline characteristics of the modelled population reflect a L2+ subset of the HES-CPRD dataset, for which Hb measurements were available. The sex distribution and starting age used to calculate the QALY shortfall are presented in Table 20.

Table 20 Baseline characteristics of the modelled populations

Characteristic	Value
Sex distribution	32 years
Proportions male/female	38%/62%

Source: CS, Table 47

5.3.4 Interventions and comparators

The intervention is voxelotor (plus SoC). The recommended dose is 1500mg daily as monotherapy or in combination with HC.[61]

The comparator is SoC, which comprises:

- HC+symptomatic care
- RTT (defined as ≥6 transfusions per year)+symptomatic care
- HC+RTT+symptomatic care
- Symptomatic care only.

Intervention and comparator treatment mixes, weighted using the Delphi panel assumption that [redacted] of patients are willing to take HC, are provided in Table 21.

Table 21 Intervention and comparator treatments

	SoC	Voxelotor
HC	[redacted]	[redacted]
RTT	[redacted]	[redacted]
RTT & HC	[redacted]	[redacted]
Neither RTT nor HC	[redacted]	[redacted]

CS=company submission; HC=hydroxycarbamide; RTT=regular transfusion therapy; SoC=standard of care
Source: CS, Table 25

5.3.5 Perspective, time horizon and discounting

The model perspective was reported to be that of the NHS and Personal Social Services. The time horizon was 100 years, and costs and outcomes were discounted at a rate of 3.5% per annum.

5.3.6 Treatment effectiveness

Treatment effectiveness was measured by change in Hb from baseline (24 weeks). The company stratified Hb response by HC usage status.

Patients receiving RTT were excluded from the HOPE trial; the company carried out SLRs to try to identify the effect of RTT on Hb levels. However, the SLRs did not yield any useful information and therefore, in the base case analysis, the company assumed that RTT had no effect on a patient's Hb level (the company tested this assumption in scenario 2). However,

RTT was included as a covariate in the company TTE analysis and therefore influences the incidences of complications in the company model.

5.3.7 Treatment discontinuation

The approaches used by the company to model treatment discontinuation are shown in Table 22.

Table 22 Approaches used by the company to model treatment discontinuation

Treatment	Model approach	Company comment
Voxelotor	TTD K-M probabilities for responders and non-responders were converted to annualised rates and used to populate exponential models	
RTT	Assumption: 5% of patients receiving RTT discontinue annually	Highly uncertain; published rates vary from 0% to 76% (CS, Table 29)
HC	Assumption: a yearly discontinuation rate of 5%	No published evidence and therefore highly uncertain

CS=company submission; HC=hydroxycarbamide; K-M=Kaplan-Meier; RTT=regular transfusion therapy; TTD=time to treatment discontinuation
Source: CS, Section B.3.3.2

5.3.8 Regular transfusion therapy

Alloimmunisation may result in discontinuation of RTT. The company identified six studies[62-67] that reported rates of alloimmunisation; in five of these studies[63-67] reported rates were less than 7.5% but the remaining study[62] reported a rate of 76% (CS, Table 29). The company has assumed that 5% of patients who receive RTT discontinue annually.

5.3.9 HC

The company identified that there was a lack of published data on HC discontinuation rates and, in the base case, has assumed an annual discontinuation rate of 5%.

5.3.10 Linking clinical events to Hb level

Links between Hb levels and long-term outcomes were made by analysing Symphony database data. Symphony database patient characteristics were weighted to reflect the characteristics of patients included in the Clinical Practice Research Database/Hospital Episode Statistics (CPRD/HES) using matching-adjusted indirect comparison (MAIC) methods. Outcomes were selected based on outcomes reported in the literature and expert opinion. Survival distributions generated by accelerated failure time (AFT) regression models (exponential) were compared with K-M data. The company determined that it was appropriate to use exponential models to generate TTE for each outcome.

The company's analyses showed that the incidence of all complications, except end-stage renal disease (ESRD), were statistically significantly linked to Hb level, varying between -

[redacted] (pulmonary hypertension [PH]) and -[redacted] (stroke). Results from the analyses showed that baseline Hb level had the largest impact on PH, leg ulcer, chronic kidney disease (CKD) and cardiomegaly.

5.3.11 Mortality

Using from CPRD/HES data, the company identified excess mortality rates associated with specific conditions (stroke had an additional one-off case fatality rate applied). The excess mortality rates used in the company model are presented in Table 23.

Table 23 Excess mortality rates due to SCD complications used in the company model

Parameter	Excess mortality input	Source
Case fatality (% of acute event)		
Stroke	13%	Strouse[68]
Standardised mortality ratio		
ARF	7.828	CPRD/HES database[69]
CKD	7.523	
ESRD	5.687	
Pulmonary hypertension	5.619	
Sepsis	4.763	
Stroke	4.818	
VOC	2.216	

ARF=acute renal failure; CKD=chronic kidney disease; CPRD-HES=Clinical Practice Research Database-Hospital Episode Statistics; CS=company submission; ESRD=end stage renal disease; SCD=sickle cell disease; VOC=vaso-occlusive crises
Source: CS, Table 35

5.3.12 Health-related quality of life

The company adjusted UK HRQoL population norms[70] to match (for age and sex) the HOPE trial population. This approach generated an overall HOPE trial population baseline utility value of [redacted] (standard error [SE]=[redacted]). A range of utility decrements were then applied.

Utility decrement due to SCD

The company then mapped HOPE trial EQ-5D-5L data to EQ-5D-3L data using UK tariffs. This generated a HOPE trial baseline population mean utility value of 0.831 and led the company to estimate that the utility decrement due to SCD was [redacted] (SE=[redacted]). This utility decrement was removed in the company revised model (provided as part of the company clarification response)

Utility decrement due to treatments

HOPE trial data showed that voxelotor had no demonstrable effect on EQ-5D-5L utility values at Week 24 or Week 72 (CS, Table 13). The company states that data (on file[71]) also showed

that treatment with HC did not affect utility. Based on published information,[52] the company modelled a utility decrement associated with RTT (0.03).

Utility decrement due to complications

Utility values stratified by Hb level were needed to populate the company model. The company literature review did not identify any relevant studies. The company analysed data from the Patient Journey Survey (n=253) (CS, Appendix T) and estimated, using a linear model, that the utility increment per 1g/dL increase in Hb level was 0.047.

The utility decrements associated with complications were sourced from the literature (Table 24). Disutilities associated with acute complications were applied once; disutilities associated with chronic complications were applied following diagnosis and then on an annual basis.

Caregiver disutilities associated with complications were included in the company base case as a one-off utility decrement upon event.

Table 24 Utility decrements associated with complications

Complication	Patient disutility		Caregiver disutility
	Disutility	Duration (days)	
Acute complications			
Acute renal failure	0.27	182.63	0.03
Arrythmia	0.07	30.44	0.03
Cardiomegaly	0.07	365.25	0.03
Gallstones	0.12	42.15	0.03
Leg ulcer	0.15	135.89	0.03
Osteomyelitis	0.466	651.36	0.03
Osteonecrosis	0.13	121.75	0.03
Pneumonia	0.688	60.88	
Priapism	0	---	0.00
Sepsis	0.223	365.25	0.03
Vaso-occlusive crises	0.033	365.25	0.001
Chronic complications			
Chronic kidney disease	0.053	Chronic	0.06
End stage renal disease	0.083	Chronic	0.05
Heart failure	0.306	Chronic	0.03
Pulmonary hypertension	0.21	Chronic	0.03
Stroke, months 1-6	0.546	Chronic	0.14
Stroke, months 7-12	0.546	Chronic	0.14
Stroke, months 13+	0.36	Chronic	0.08

CS=company submission
Source: CS, Table 36 and Table 38

5.3.13 Treatment costs

Modelled treatment costs are displayed in Table 25.

Table 25 Treatment costs

Treatment	Cost	Assumptions
Voxelotor (per day)		
Voxelotor 1500mg/day	[redacted]	[redacted] treatment adherence
Voxelotor adjusted dose for patients with ESRD (1000mg/day)	[redacted]	
Regular transfusion therapy (per transfusion)		
Patients receiving voxelotor	[redacted]	Weighted average of simple (5%) and automated exchange transfusion costs (95%) Chelation therapy Voxelotor: 18.3% of adults and 44.2% of adolescents SoC: 19.2% of adults and 44.3% of adolescents
Patients receiving SoC	[redacted]	
Chelation therapy		
Voxelotor	[redacted]	Assuming 10% of patients are adolescents Annual costs (based on patient weight and type of chelation therapy agents used in the NHS [CS, Table 39]) Adults: £12,864.95 Adolescents: £9,880.09
SoC	[redacted]	
Other costs		
Automated exchange transfusion	[redacted]	Calculated using NICE TA743[37] assumptions: [redacted] per transfusion
Simple transfusion	£608.38	NHS Reference Costs 2019/20[72] Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over: £587 Single Plasma Exchange or Other Intravenous Blood Transfusion, 18 years and under: £785
HC (daily cost)	£0.39	An adherence rate of 49.7% is subsequently applied (weighted average of two published rates)
Annual dispensary cost	£15.36	Six dispensaries per year (@ £2.56 per prescription)[73]

CS=company submission; ESRD=end stage renal disease; HC=hydroxycarbamide; SoC=standard of care
Source: CS, Table 40

5.3.14 Symptomatic management costs

Opioid costs

Expert advice to the company was that 43% of adults and 13% of adolescents use opioids. Switching from transfusions to voxelotor is expected to reduce opioid use by [redacted]% and [redacted]% for adults and adolescents respectively, leading to estimates of [redacted]% and [redacted]% of adults and adolescents using opioids.

The annual cost of opioid use was estimated using a weighted average of the proportions, based on expert opinion, of patients taking different types of opioids and British National Formulary[74] costs. The company estimated the annual cost of opioid use was £472.32 for adults and £472.20 for adolescents (CS, Table 41).

Erythropoietin stimulating agent

Expert advice to the company was that 5% of adults and 2% of adolescents take erythropoietin stimulating agents (ESA) and that on switching to voxelotor these proportions would fall, resulting in 1.7% of adults and 0.9% of adolescents being prescribed ESA. The company has estimated that the weighted average costs of ESA for patients in the voxelotor and SoC arms are £111.97 and £328.87 respectively (CS, p148).

5.3.15 Monitoring costs

The company has used the monitoring frequency and cost assumptions used in the model developed to inform TA743[37] (Table 26).

Table 26 Monitoring frequency and cost assumptions

Parameter	Cost	Source	Frequency per year	Source
Haematological (full blood cell count including reticulocyte count)	£2.56	NHS Reference Costs[72]	6	NICE TA743[37]
Renal (urea and electrolytes)	£1.20		4	
Hepatic (liver function test)	£1.20		4	
Lactate dehydrogenase test	£1.20		4	
Foetal haemoglobin	£1.20		4	

CS=company submission
Source: CS, Table 43

5.3.16 Costs of acute and chronic complications

The company estimated costs using Health Care Resource Group prices (NHS Reference Costs 2019/2020),[72] information used to inform a previous NICE appraisal (TA743[37]), and a published study.[75] Unit costs are presented in the CS (Table 44). Costs of acute events ranged from £174 (cardiomegaly) to £8,381.59 (leg ulcers) per event. Annual costs of chronic events ranged from £462.57 (chronic kidney disease) to £18,852.12 (ESRD).

The company model also includes the costs of AEs related to regular transfusions, namely £24.60 per year, and the costs associated with alloimmunisation (£4.53 per transfusion) (CS, Table 45).

Incidence data for Grade ≥3 AEs not related to SCD that are experienced by patients receiving voxelotor and HC were sourced from HOPE trial Week 72 follow-up data (frequencies in at least 2% of patients in either arm). Costs were estimated using NHS Reference Costs 2019/20 and ranged from £210.09 (fatigue) to £1051.94 (pain) (CS, Table 46).

5.4 Updated severity modifier

Updated results from the company QALY shortfall calculations are presented in Table 27.

Table 27 Updated company QALY shortfall calculation results

Outcome	Total QALYs	Shortfall	
		Absolute	Proportional
Expected total for the general population	[redacted]		
Disease specific	[redacted]	[redacted]	[redacted]
QALY multiplier		[redacted]	[redacted]
WTP threshold		[redacted]	

CS=company submission; QALY=quality adjusted life year; WTP=willingness to pay threshold
Source: Updated CS, Table 48

5.5 Updated company cost effectiveness results

During the clarification period, the company updated the TTE equations for linking Hb and SCD complications, removed the SCD utility decrement from the analyses, applied the multiplicative method to multi-comorbidities and fixed minor bugs in the model.

The company provided a revised model and updated cost effectiveness results; these were generated using the confidential price for voxelotor and list prices for the comparator. The updated company base case and scenario cost effectiveness results are presented in Table 28 and Table 29 respectively.

Table 28 Updated company deterministic base case cost effectiveness results

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Voxelotor	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CS=company submission; ICER=incremental cost effectiveness ration; QALY=quality-adjusted life year; SoC=standard of care
Source: Clarification response, Appendix 1, Table 2

5.5.1 Probabilistic sensitivity analyses

The company carried out probabilistic sensitivity analyses PSA. In total, 500 simulations of 1,000 patients were performed. In all simulations, treatment with voxelotor resulted in improved clinical benefit. In most cases, this benefit was associated with an increased cost; however, in about [redacted]% of the simulations, voxelotor was dominant (less costly and more effective). Results from the company analysis showed that, at a willingness to pay (WTP) threshold of [redacted], the probability of voxelotor being cost effective was approximately [redacted]%.

5.5.2 Deterministic sensitivity analyses

The company carried out a range of deterministic sensitivity analyses. Results from these analyses showed that the key cost effectiveness drivers were voxelotor costs, proportion of chronic transfusers, RTT costs, incremental utility per 1 g/dL Hb and discontinuation rates (Clarification response, Appendix 1, Figure 4).

5.5.3 Scenario analyses

Company scenario analysis result are presented in Table 29. The company considers that results from scenario 2 are biased against voxelotor as:

- RTT is a covariate in the TTE analysis and therefore influences the incidences of complications even in the base case when the effect of RTT on Hb is not explicitly modelled; therefore, adding an efficacy value introduces an element of double-counting
- waning of Hb levels between transfusions is not modelled.

Table 29 Company deterministic scenario analyses

Scenario	Scenario number	Values assumed for the scenario analysis	ICER per QALY gained
Base case			[redacted]
Discount rate	1a	Costs discounted at 1.5%	[redacted]
	1b	No discount for costs or benefits	[redacted]
	1c	Costs and benefits discounted at 1.5%	[redacted]
RTT benefit	2	Assume 0.8 g/dL increase in Hb among patients on RTT	[redacted]
Discontinuations	3a	Higher (25%) for both	[redacted]
	3b	Lower (1%) for both	[redacted]
	3c	RTT higher (25%) HC same as base case (5%)	[redacted]
	3d	RTT same as base case (5%) HC higher (25%)	[redacted]
Persistence	4	Assume responders do not discontinue	[redacted]
Time point of Hb evaluation	5a	At 72 weeks	[redacted]
	5b	Up to 72 weeks	[redacted]
Reimbursement population	6a	All patients treated with RTT; no benefit on Hb for those treated with RTT	[redacted]
	6b	All patients treated with RTT and assume 0.8 g/dL increase in Hb	[redacted]
Waning effect	7	Assume treatment waning of annual reduction in Hb level of 5%	[redacted]
Utility combination method	8	Additive	[redacted]

CS=company submission; g/dL=grams per decilitre; Hb=haemoglobin; HC=hydroxycarbamide ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; RTT=regular transfusion therapy
Source: Clarification response, Appendix 1, Table 6

5.6 Validation of the cost effectiveness analyses

The company reported that quality control was carried out by the model developers and by external modelling groups. In addition, the company compared model output with the data underpinning the model and with published data.

6 EAG CRITIQUE OF COMPANY COST EFFECTIVENESS MODEL

6.1 Introduction

The company economic model is flawed due to the following important issues:

- the analyses used to generate TTE equations for linking Hb and SCD-related outcomes (complications) has limitations
- the model is populated with efficacy data from the HOPE trial; the HOPE trial is limited to demonstrating that, compared with SoC, treatment with voxelotor increases Hb level (patients who were receiving RTT were excluded from the HOPE trial)
- HOPE trial data do not demonstrate that, compared with SoC, patients treated with voxelotor experience improved HRQoL
- there is no evidence from the HOPE trial to demonstrate that treatment with voxelotor reduces the requirement for RTT or reduces SCD-related complications
- for reasons that the EAG is unable to determine, the company model generates clinically implausible individual patient simulations (and, therefore, the company severity modifier estimates are not reliable).

In addition, if treatment with voxelotor leads to lower complication rates than SoC then any impact is likely to be limited.

Due to the seriousness of these issues, the EAG has not fully checked all the model algorithms (which were implemented using VBA code) and has not cross-checked the sources of all 800 model parameters with quoted sources.

For reasons that the EAG has not been able to determine, the company updated model (provided as part of the company clarification response) does not allow patients to be treated with voxelotor for more than 5 years; the company base case model does not include a stopping rule. The EAG was, therefore, unable to replicate the company base case results and was also unable to produce results using confidential Commercial Medicines Unit prices for other treatments.

Even if the company model results were reliable, the EAG considers that the company base case ICER per QALY gained would be a significant underestimate of the true value because:

- the company should not have applied a relative dose intensity (RDI) multiplier for life when estimating the cost of treatment with voxelotor (an RDI multiplier calculated based on 72 weeks of data is unlikely to reflect lifetime RDI). Reducing the length of time an RDI is applied (or the magnitude of the RDI) would increase the cost of voxelotor and therefore increase the ICER per QALY gained
- as suggested by the company Delphi panel, patients receiving RTT should benefit from having an improved Hb level (company scenario 2; [redacted] per QALY gained)
- the voxelotor discontinuation rate is likely to fall over time (company scenario 4; [redacted] per QALY gained).

The EAG have not explored these issues further given the inability to generate meaningful ICERs per QALY gained.

6.2 Summary of EAG critique of company AFT regression analyses

The company carried out AFT regression analyses to link patient Hb levels with SCD complications over the model time horizon. The EAG's summary of the company methods and full critique are provided in Appendix 2. During clarification, the company addressed several of the issues raised by the EAG, however, the EAG considers that some of the same issues remain. In summary, the EAG considers that:

- there are still several discrepancies between the baseline characteristics and regression coefficients presented in the main body of the CS and those presented in Appendix P and Appendix Q. The EAG also considers that there are some transcription errors in Appendix Q, Table 11. These errors mean that it has not been possible for the EAG to confirm the reliability of the company analyses
- the process used by the company to match patients in the Symphony database to those in the CPRD-HES dataset may not have accounted for all confounding factors, therefore, residual confounding may be present which may affect the robustness of the results
- the company should have carried out further sensitivity analyses to explore the effect of uncertainty around AFT regression results.

Based on the information available in the CS and provided by the company during clarification, the EAG considers that the reliability of the company results is unknown and therefore these results should be interpreted with caution.

6.3 Voxelotor benefit: company model assumptions and HOPE trial evidence

6.3.1 HOPE trial: voxelotor improvement in Hb level

Results from the HOPE trial showed that voxelotor was only statistically significantly better than SoC for a change in Hb level and haemolysis markers (indirect bilirubin, change in % reticulocytes) between baseline and Week 24. There were numerical differences between the trial arms for other outcomes, some of which favoured treatment with voxelotor (e.g., VOCs and leg ulcers) and some of which favoured SoC (e.g., ACS rates and annual transfusion rates). The trial was not powered to detect these outcomes. However, if numerical advantages are modelled as benefits, then numerical disadvantages should be modelled as detriments. The EAG considers that the statistical analysis performed by the company to generate the TTE rate equations used in the model is not robust and that any claim that treatment with voxelotor delivers more benefit than an increase in Hb level compared with SoC should be viewed as highly uncertain.

6.3.2 Impact of voxelotor on health-related quality of life

The company has assumed that the increase in Hb level experienced by patients in the HOPE trial who received voxelotor can be translated into an increase in utility. However, the EQ-5D data collected during the HOPE trial showed no statistically significant difference between patients in the voxelotor and SoC arms in terms of the improvement between baseline and Week 72 (at Week 72, patients in the SoC arm had experienced a numerically larger improvement in utility than patients in the voxelotor arm). The EAG considers this finding can be interpreted four ways:

- voxelotor does not improve Hb levels enough to influence utility as measured by the EQ-5D questionnaire
- the EQ-5D questionnaire is not a useful tool for capturing changes in HRQoL in patients with changing Hb levels
- patients experience a HRQoL benefit from raised Hb levels, but this is outweighed by any AEs linked to treatment with voxelotor
- Other issues, not relating to Hb.

The EAG does not know which of these four interpretations is the most likely explanation; however, it is important to distinguish (i) evidence the company has presented for the link between higher Hb levels and utility values and (ii) evidence from the HOPE trial for the link between higher Hb levels (whilst receiving voxelotor) and utility values. Having no evidence from the HOPE trial to demonstrate that the raised Hb levels experienced by patients in the voxelotor arm resulted in increased patient utility casts doubt on whether the company should have included such a benefit in their model.

6.3.3 Regular transfusion therapy

In the company model, based on feedback from a Delphi panel of clinicians, the company has assumed that [redacted]% of patients treated with voxelotor and [redacted]% of patients treated with SoC require RTT at baseline. No patients start RTT at any other point over the model time horizon although patients can discontinue RTT. Receipt of RTT accounts for [redacted]% of the total SCD treatment costs for patients treated with SoC. The EAG highlights that the Delphi panel considered that [redacted]%, not [redacted]%, of patients receiving SoC would receive RTT. Using a value of [redacted]% rather than [redacted]% decreases the cost of SoC and so increases the ICER per QALY gained for the comparison of voxelotor+SoC versus SoC.

Patients treated with RTT were excluded from the HOPE trial. There is, therefore, no evidence from the HOPE trial that can inform modelling assumptions about RTT. The only transfusion-related evidence from the HOPE trial showed that there was no statistically significant difference between the voxelotor and placebo arms in terms of the annualised acute

transfusion rate over 72 weeks. The EAG therefore considers it was inappropriate for the company base case to include baseline differences in RTT rates and that the company should have assumed the same RTT rate in both arms or, preferably, modelled the risk of having RTT. Removing RTT from the start of the model or assuming the same RTT rate would increase the company base case ICER per QALY gained.

6.3.4 Impact of treatment with voxelotor on complication rates is limited

Even if the statistical approach to estimating TTE probabilities was robust, the company model generates very modest reductions in complications for patients treated with voxelotor compared with patients treated with SoC. For the comparison of treatment with voxelotor versus SoC, over a mean model life expectancy of approximately 30 years, the discounted QALY gain per patient due to a reduction in complications is [redacted] QALYs (although patients treated with voxelotor also accrue an additional [redacted] discounted QALYs related to increased life expectancy). The impact of treatment with voxelotor on costs is similarly small, with discounted cost savings from reduced complications being [redacted] of the baseline difference in treatment costs ([redacted]) between arms.

The EAG considers that the short period of time that patients are treated with voxelotor means that even if Hb levels are linked to complications in the way proposed by the company, any impact on complication rates for patients treated with voxelotor compared with those treated with SoC over an average patient lifetime is limited.

Voxelotor discontinuation rates used in the company model ([redacted] per annum for responders and [redacted] per annum for non-responders) results in most patients no longer receiving voxelotor by the end of Year 3 and, by the end of Year 10, only [redacted] of patients are still being treated with voxelotor (Table 30).

Table 30 Percentage of model patients receiving voxelotor over time

Year	Percentage of patients still receiving voxelotor at end of year
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
10	[redacted]
15	[redacted]
20	[redacted]

Source: Company model

The annual probabilities of events in the model that have a long-term significant impact on utility and costs are relatively low; the event with the highest probability is stroke (approximately [redacted] per annum). Even if the increase in Hb level that occurs as a result of treatment with voxelotor reduces the likelihood of SCD complications occurring, the probabilities of these events are low and as most patients are only treated with voxelotor for a small proportion of the model time horizon; this means that treatment with voxelotor can only ever have a small impact on QALYs. The EAG therefore considers it unlikely that more accurate modelling of SCD-related complications would result in a significant increase in QALYs for patients treated with voxelotor.

6.3.5 The company model does not generate ICERs per QALY gained that are suitable for decision making

On receipt of the original CS, the EAG undertook face validity checks of the model outputs and identified that the mean utility values for patients receiving voxelotor and SoC appeared implausibly low (just over [redacted]). The EAG raised this concern via an early telephone conference with the company and NICE and also as a clarification question (B3).

In their response to clarification, the company stated that errors had been identified in the model (although it did not state whether these affected utility values or QALYs), a disutility from simply having SCD was removed, and SCD-complication disutilities were calculated using a multiplicative rather than an additive approach. These model changes resulted in a new average utility value of [redacted] for patients in the SoC arm. The company considered that this value was acceptable as it was in line with other published research in this disease area (0.648). The EAG does not consider that a value of [redacted] is in line with 0.648 and highlights that the value considered acceptable in CG143[24] to represent 'steady state SCD' was 0.732 (estimated based on a pooled analysis of four studies all with similar mean values).

The company model was constructed in MS Excel and uses a combination of formulas in worksheets and VBA code to generate results. Algorithm checking in this type of model is complex and so making anything other than simple alterations to model parameter values is challenging. Therefore, during clarification, the EAG asked the company to provide the output for the individual 50,000 patient simulations that were used to provide the cost effectiveness estimates (clarification question B3). Examination of the experiences of a random sample of 100 patients showed that the individual runs generated patient experiences that were often clinically implausible. The EAG has presented two examples to illustrate the seriousness of the issue.

Patient 1: [redacted]

Patient 2: [redacted]

Whilst there are patients in the sample examined by the EAG that had more plausible outcomes, the EAG also identified:

[redacted]

Whilst the EAG commends the company for attempting to model a complex condition that results in multiple co-morbidities, these examples show that the model is generating patient experiences that are not clinically plausible; this means that the overall model results have no face validity. Whilst there may be rare patients who do suffer from many different serious conditions due to SCD, the frequency that the model generates such patient outputs suggests that there is a problem with either the TTE probabilities or with the application of mortality rates following events.

The model includes over 800 parameters and, as the algorithms are 'hard wired' using VBA code, it is not possible for the EAG to identify the source of the problem. The EAG considers that the modelled TTE event probabilities may not be properly accounting for the risk of subsequent events (including mortality) following a first or second event. The EAG considers that the low mean utility values generated by the company model reflect the implausible patient simulations.

Given the lack of face validity of the individual patient simulations, the EAG considers that the company model results should not be used to inform decision making. The EAG has not made any amendments to model parameters as it is not clear whether changing parameters would result in more or less accurate cost effectiveness results.

6.4 EAG cost effectiveness discussion

The EAG has not been able to generate any reliable ICERs per QALY gained. However, the evidence provided by the company only demonstrates that treatment with voxelotor leads to an increase in Hb level. Effect on HRQoL, reduced complications or the need for RTT has not been demonstrated. The EAG therefore considers that treatment with voxelotor may be dominated by SoC, i.e., costing more than SoC but not delivering any additional QALYs. Even if the improvement in Hb level arising from treatment with voxelotor did result in improved HRQoL, the size of this improvement is likely to be small and therefore the ICER per QALY gained would be significantly higher than the company base case ICER per QALY gained ([redacted]).

6.5 EAG cost effectiveness conclusions

The evidence provided by the company does not robustly support any benefit from treatment with voxelotor other than an increase in Hb level for patients whilst they are being treated with voxelotor. The EAG has identified three key areas where evidence is absent:

- the EQ-5D data collected during the HOPE trial showed no statistically significant difference between patients in the voxelotor and SoC arms in terms of the improvement between baseline and Week 72. At Week 72, patients in the SoC arm had experienced a numerically larger improvement in utility than patients in the voxelotor arm, therefore, the EAG considers that there is no direct evidence that treatment with voxelotor improves HRQoL compared with SoC

- there is no evidence that treatment with voxelotor reduces the need for RTT; the HOPE trial explicitly excluded patients who were regularly receiving RTT or who had received a red blood cell transfusion for any reason within 60 days of signing the informed consent form (CS, Table 5); the EAG therefore considers that, at baseline, the SoC arm of the company model should not include RTT as a treatment

- the EAG does not have any confidence in the reliability of the analyses that generated the complication rates; however, even if they were reliable, company model output

shows only small differences in complications rates between patients treated with voxelotor and those treated with SoC.

Even if the company model had been populated with robust evidence, as it generates implausible individual patient simulations, it lacks face validity and therefore model results should not be used to inform decision making.

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8 APPENDICES

8.1 Appendix 1: EAG assessment of the statistical approaches used in the HOPE trial

Table 31 EAG assessment of the statistical approaches used in the HOPE trial

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	The analysis populations of the HOPE trial are clearly defined in Section B.2.4.1 of the CS and pre-specified in the TSAP (p29). Analyses of Hb response, CFB in Hb, change in haemolysis measures and time to first RBC transfusion (exploratory outcome) were carried out in the ITT population (defined as all randomised patients). Analysis of the VOC rate and time to first ACS or pneumonia (exploratory outcome) were carried out in the mITT population (defined as all patients who were randomised to treatment and received at least one dose of the study drug). Safety analyses were carried out in the safety analysis set (all patients who received at least one dose of the study drug). The EAG is satisfied that these populations were pre-specified and clearly defined
Was an appropriate sample size calculation pre-specified?	Yes	The study sample size calculation for the HOPE trial is outlined in Table 7 of the CS and in the TSAP (p18); the EAG is satisfied that the sample size calculation was appropriate
Were all protocol amendments made prior to analysis?	Yes	The original protocol of the HOPE trial (dated 19 October 2016) was amended 4 times. A summary of the key amendments made prior to the most recent version of the HOPE trial protocol are provided in the CSR (Section 9.8.1.1). The EAG considers that all protocol amendments are appropriate and notes that all were made prior to the latest database lock (22 November 2019)
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	In the CS, results are presented from the HOPE trial for the primary outcome of Hb response, and secondary outcomes of CFB in Hb, CFB in haemolysis measures and VOC incidence rates (Section B.2.6.1 to Section B.2.6.4). Additional exploratory outcomes are described in the CS (Table 7). The definitions and analysis approaches for primary, secondary and additional outcomes are described in the CS (Table 7); the EAG is satisfied that these outcomes and the analytic approaches used were clearly defined and pre-specified (TSAP, Section 8.2)
Was the analysis approach for PROs appropriate and pre-specified?	Yes	Exploratory endpoints of the HOPE trial included the assessment of CFB in HRQoL as measured by the CGIC, SCDSM and EQ5D-5L. Results for PROs were summarised descriptively in the CS (Section B.2.6.6); the EAG considers that this approach was appropriate, however notes a lack of clarity over which analysis populations are used in the PRO analyses

Item	EAG assessment	Statistical approach with EAG comments
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Safety data relating to exposure and AEs in the HOPE trial are presented in the CS (p75-81) and Appendix F (empty appendix). AEs were assessed and graded using the NCI-CTCAE version 4.03 classification system (CSR, p40) and coded using MedDRA® version 22.0; for AEs not adequately assessed in NCI-CTCAE version 4.03, grading criteria are specified in the CSR (p40). The safety population was defined as patients randomised to treatment who received at least one dose of the study drug. The presented safety analyses were descriptive only and no formal statistical analyses of AEs was conducted. The EAG is satisfied that the analysis approach for AEs was appropriate and pre-specified (TSAP, Section 8.3)
Was a suitable approach employed for handling missing data?	Yes	The company's approach for handling missing data in the HOPE trial is described in the CS (Table 7). For the primary outcome of Hb response, the non-missing value was used in the event that one value was missing for either of the two timepoints (Week 20 or Week 24), with non-responder imputation being used if both values were missing. For secondary outcomes, missing data for CFB in Hb level and CFB in haemolysis measures as a result of patient dropout, VOC or VOC hospitalisation was assumed to be missing at random and not imputed in the primary analysis; no adjustments were made for missing data related to the outcome of rate of VOC. Sensitivity analysis explored the imputation rule for missing data by assigning haemolysis measures from the last assessment. The EAG is satisfied that the approaches used to handle missing data were appropriate.
Were all subgroup and sensitivity analyses pre-specified?	Yes	Subgroup analyses were conducted for the primary outcome (Hb response) and secondary outcome for Hb (CFB in Hb) at Week 24 and up to Week 72 for demographic variables (age, sex, race, geographic region, baseline HC use [yes/no], baseline VOC history [1 or >1], and baseline Hb [5.5 to <7g/dL or ≥7g/dL]). The rate of VOC was also analysed by subgroup based on VOC history at baseline (1 or >1). Results of these pre-specified subgroup analyses are presented in the CS (Section B.2.7) and Appendix E. The EAG is satisfied that all of the subgroup analyses were appropriate, and notes that all subgroups (with the exception of sex and race) were pre-specified (TSAP, Section 8.45).

ACS=acute chest syndrome; AE=adverse event; CFB=change from baseline; CGIC=Clinical Global Impression of Change scale; CS=company submission; CSR=clinical study report; EAG=External Assessment Group; EQ5D-5L=EuroQol Health Questionnaire-5 Dimension; Hb=haemoglobin; HRQoL=health-related quality of life; ITT=intent-to-treat; mITT=modified intent-to-treat; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRO=patient reported outcome; RBC=red blood cell; SCDSM=Sickle Cell Disease Severity Measure; TSAP=trial statistical analysis plan; VOC=vaso-occlusive crises
Source: CS, CSR,[42] trial protocol[31] and trial statistical analysis plan[31]

8.2 Appendix 2: EAG summary and critique of company AFT regression

The chronic complications resulting from organ damage caused by the pathology of SCD evolve over time and get worse as patients get older. The HOPE trial was not designed to show an effect on chronic complications, which require a longer time scale for evaluation. The company therefore performed an analysis to explore associations between Hb levels and longer-term outcomes (based on outcomes derived from the Symphony database). The company stated that to maximise applicability to the UK, Symphony database patients were weighted to patient characteristics derived from a UK database using MAIC methods.

8.2.1 Summary of company's approach

The company has presented results from an analysis exploring the link between Hb levels and SCD-related outcomes, as it is suggested in the literature[76,77] that modest reductions in Hb are correlated with SCD-related morbidity and mortality. To inform the economic model, the company has performed a TTE analysis using evidence from two data sources to determine the impact of Hb levels on clinical events.

The company identified and selected study outcomes (i.e., events) to be evaluated using a regression modelling approach by exploring the literature and seeking clinical expert opinion. The company stated (CS, p118) that analyses of chronic conditions including CKD, heart failure, PH were limited to patients without a history of the condition at the index date. Analyses of ESRD data were limited to patients with a history of CKD and analyses of priapism were limited to males only (CS, p118). A list of SCD-related outcomes selected by the company for analysis is presented in Table 32.

Table 32 Symphony database SCD-related outcomes included in the company model

Event	Included in the model
Acute renal failure	Yes
Arrythmias	Yes
Cardiomegaly	Yes
Chronic kidney disease	Yes
End-stage renal disease	Yes - patients must be diagnosed with chronic kidney disease prior to having end-stage renal disease
Gallstones	Yes
Heart failure	Yes
Leg ulcer	Yes
Osteomyelitis	Yes
Osteonecrosis	Yes
Pulmonary hypertension	Yes
Pneumonia	See vaso-occlusive crisis
Priapism	Yes

Sepsis	Yes
Stroke	Yes
Vaso-occlusive crisis	Yes - joint endpoint which includes vaso-occlusive crises complicating to acute chest syndrome (ACS) or not. In HOPE, ACS and pneumonia are deemed indistinguishable and therefore considered the same. When looking in databases, there is no code for ACS and pneumonia is therefore used as proxy for ACS.

ACS=acute chest syndrome; CS=company submission; SCD=sickle cell disease
Source: adapted from CS, Table 30

The company identified two sources of data to use to determine the impact of Hb levels on clinical events; one dataset assessed patients in the Symphony database and the other assessed patients in the CPRD-HES Database; CPRD contains primary care data and HES provides secondary care data.

The company considered that the UK CPRD-HES dataset was more relevant to the population of interest than the Symphony dataset; however, the CPRD-HES database L2+ population only included 2,106 patients. The company therefore used data from the Symphony database, and justified the use of these data as being a more suitable source of evidence due to the "large data available in Symphony" (CS, Section B.3.3.3, p116).

The company presented results from two sets of TTE analyses (CS, Appendix Q); the 'primary analysis' was an unweighted analysis that was carried out using Symphony database data to estimate the link between the incidence of SCD-related outcomes and the baseline characteristics of the Symphony population. To account for differences in populations between the Symphony data and the HES-CRPD data, the company also conducted a 'secondary analysis' which involved performing a "matching-adjusted indirect comparison" analysis, using Symphony database individual patient data (IPD) and aggregate data (AgD) from the CPRD-HES database. The company has presented a short summary of the TTE analyses approach (CS, Section B.3.3.3) with further information in accompanying Appendices (Appendices P, Q and R). In response to clarification questions, the company also provided revised Appendices P, Q and R which superseded the original versions shared by the company.

8.2.2 Summary of company methods

Primary analyses

The company performed a TTE analysis. The first occurrence of each event was assessed during the "follow-up period", defined as the period beginning with the index date and ending with the last activity date. AFT regression equations were fitted, with the index Hb value, age, number of VOCs during the 12-months pre-index, and the interaction between Hb and number of VOCs during the 12-months pre-index as explanatory variables. The company stated that the regression was performed with "all patient characteristics included in the model" and these

were subsequently eliminated iteratively, "starting with the covariate with the highest p-value, until all variables had p-values less than or equal to 0.05." (Appendix Q, Section 2.5, p4).

For each event, estimated regression equations were used to generate predicted survival distributions "by generating a predicted survival distribution for each patient and averaging the survival probabilities at each timepoint across all patients" (Appendix Q, Section 2.5, p4). These were then compared with K-M data. The company selected exponential distributions as they considered that "there was no reason to believe there would be any temporal association between the hazard and time since the Hb assessment". The company's further justification for using exponential distributions was that a visual inspection of the hazard functions showed that the hazards were generally constant.

Weighted (secondary) analyses

The company described the populations and the approach adopted to match patients in the Symphony database to the target CPRD-HES population. The company explained that "patients in the Symphony database were weighted using matching-adjusted indirect comparison methods" (CS, Section B.3.3.3, p116) and that they "were weighted so that their aggregate baseline characteristics matched those reported by HealthIQ in their analyses … using … MAIC methods" (Appendix Q, Section 2.6, p4). Limited details were provided about the MAIC approach in the CS; however, as part of the company response to clarification question A2, the company provided further information about the approach used in the 'secondary analysis' to match patients in the Symphony database to those in the CPRD-HES database and stated that procedures described by Signorovitch et al. 2010[78] were used. Specifically, Symphony database IPD were weighted by the inverse variance of their propensity score to balance the covariate distribution with that of the target AgD population. A "method of moments" approach was used to estimate the corresponding weights. The EAG considers the company use of "MAIC" terminology is potentially misleading as no indirect comparison was actually performed but, instead, weights were estimated for patients in the Symphony database to align them with the UK (CPRD-HES) population, with the objective being to retain a large sample size of Symphony data which 'matched' the UK target population.

Characteristics of a sample of L2+ patients (N=2,106) in the CPRD-HES data were used to inform the matching process; specifically, this included patients aged ≥12 years with no evidence of SCD or bone marrow transplant during the study period who met the inclusion criteria (i.e., those who had ≥3 SCD confirmed secondary care interactions within a year prior to the index date (first recorded Hb level), with ≥1 Hb measurement recorded. Patients in the Symphony database were matched to this cohort of 2,106 patients in the CPRD-HES

database using 21 factors – in response to clarification question A2, the company confirmed that these factors included mean age at baseline, gender, baseline Hb levels, number of VOCs during the 12 months prior to the index date, prior treatment with HC, prior treatment with chronic transfusion, as well as history of: acute renal failure, arrhythmia, cardiomegaly, CKD, ESRD, any kidney failure, gallstones, heart failure, leg ulcer, osteomyelitis, osteonecrosis, PH, priapism, sepsis and stroke. The company also confirmed in a response to clarification question A2 that the process adopted to identify which factors to include in the matching process was based on the factors that were "hypothesised as being potentially prognostic for the events of interest, and were in line with subgroups analysed in the HOPE trial, with some additional clinically relevant covariates". The company did not describe whether any data issues were encountered when conducting the matching (i.e., the approach used to handle any missing covariate data, issues of convergence, or whether low proportions of patients were included across a number of categorical factors used in the matching).

8.2.3 Results of the company's analyses

Patients in the Symphony database were weighted to 'match' the CPRD-HES population. A comparison of Symphony database baseline characteristics and the CPRD-HES database is presented in Table 33. The data show the average population characteristics for the CPRD-HES data, as well as the unweighted and weighted characteristics of the Symphony database population. Post-weighting, baseline characteristic values from the Symphony database were consistent with the aggregate values in the CPRD-HES data, with minimal or no differences observed.

Table 33 Baseline characteristics for Symphony patients MAIC weighted to match patients in CPRD-HES

	CPRD-HES (N=2,106)	Symphony Data		Difference Weighted vs. CPRD-HES
		Unweighted All Patients (N= 14,971)	MAIC Weighted All Patients (N=14,971)	
Age, Years - Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Number with HB reading	[redacted]	[redacted]	[redacted]	[redacted]
Index Hb Value, mg/dL - Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
VOCs - no. (%)	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]
1-2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5 or more	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxyurea treatment - no. (%)	[redacted]	[redacted]	[redacted]	[redacted]
Chronic transfusion therapy - no. (%)	[redacted]	[redacted]	[redacted]	[redacted]
History of complications - no. (%)	[redacted]	[redacted]	[redacted]	[redacted]
ARF	[redacted]	[redacted]	[redacted]	[redacted]
Arrhythmias	[redacted]	[redacted]	[redacted]	[redacted]
Cardiomegaly	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]
CKD	[redacted]	[redacted]	[redacted]	[redacted]

	CPRD-HES (N=2,106)	Symphony Data		Difference Weighted vs. CPRD-HES
		Unweighted All Patients (N= 14,971)	MAIC Weighted All Patients (N=14,971)	
ESRD	[redacted]	[redacted]	[redacted]	[redacted]
Any kidney failure	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]
Gallstones	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Hyposplenism	[redacted]	[redacted]	[redacted]	[redacted]
Leg ulcer	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial injury	[redacted]	[redacted]	[redacted]	[redacted]
Opioid dependence	[redacted]	[redacted]	[redacted]	[redacted]
Osteomyelitis	[redacted]	[redacted]	[redacted]	[redacted]
Osteonecrosis	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Priapism - male gender only	[redacted]	[redacted]	[redacted]	[redacted]
Retinopathy	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]

AFR=acute renal failure; CKD=chronic kidney disease; CPRD-HES= Clinical Practice Research Databases and Hospital Episode Statistics Database; ESRD=end-stage renal disease; Hb=haemoglobin; MAIC=matching-adjusted indirect comparison; N=total number of patients; SD=standard deviation; VOC=vaso-occlusive crises
Source: Revised Appendix Q, Table 9

The company also presented a comparison of Symphony and CPRD-HES database baseline characteristics alongside HOPE trial baseline characteristics (CS, Table 31, p116-17). Whilst not stated explicitly in the CS, the EAG believes that the values presented by the company for Symphony patients in Table 31 (CS, p116-17) are unweighted, however, the EAG has identified some discrepancies between the values presented in the CS (Table 31, Section B.3.3.3, p116-17) and those presented in the revised version of Appendix Q (Table 9, p56-7). Specifically, the proportions of patients in the Symphony database with a history of VOCs (0, 1-2, 3, 4 and 5 or more) in the last 12 months prior to the index date, history of CKD complications and a history of any kidney failure in Table 31 (CS, Section B.3.3.3, p116-17) do not match the values presented in Table 9 (revised Appendix Q, p56-7), however, the reason for these differences is unclear to the EAG.

The EAG sought clarification in regard to the patient characteristics values presented for the CPRD-HES data, including the proportion of patients who have received either current or prior HC treatment. The EAG identified discrepancies between values in Table 4 (Appendix P, p11) and Table 8 (Appendix Q [original version], p56). The company confirmed in their response to clarification question A5 that the figures in both documents (Appendix P and Q) were in fact, incorrect. In regard to the proportion of patients with a history of ESRD and the proportion of patients who have a history of any kidney failure, the company stated that the figures in Table 4 (Appendix P, p11) were correct and have been updated accordingly in Table 9 (revised Appendix Q, p56-7). Further, the company performed additional corrections “prior to re-running the MAIC”, including: adjusting the codes in the Symphony database related to the

definition of chronic transfusions to match the codes in the CPRD-HES database. The company also identified an error related to two prognostic factors (treatment history with HC treatment and chronic transfusion therapy) which were initially considered to occur at any timepoint; a correction was made by the company to consider these factors only up until baseline.

As part of the 'secondary analysis', the company estimated weights which were then applied to patients in the Symphony data to align with the CPRD-HES population. As part of clarification question A2, the company provided details in regard to how the weights were both calculated and incorporated into the AFT regression analyses. The company stated that weights were calculated using statistical software, R, which were standardised by dividing unstandardised weights by the mean value of the unstandardised weights. In the Symphony database, each observation's contribution to the log likelihood was multiplied by its corresponding weight and observations with small weights (<0.0001) were dropped from the regressions "to ensure that valid solutions could be obtained", however the company also stated that this rule was in fact, not required in the absence of any weights being less than 0.0001. A summary and an assessment of the weights has been presented by the company as a response to clarification question A2 (revised Appendix Q, Table 10 and Figure 16). The results from the company's 'secondary analysis' based on weighted Symphony data are presented in Table 34 (reproduced from Table 11, revised Appendix Q, p59-60). The company concluded as part of a response to clarification question A2 that the 'secondary analyses' (using weights applied to patients in the Symphony database) provided similar estimates to those using the unweighted sample; the coefficient signs were identical in both weighted and unweighted analyses and the coefficient for baseline Hb levels was "generally similar" for the weighted and unweighted samples. The company interpreted the findings of the TTE regression analyses as providing evidence that "the incidence of almost all complications (with the exception of ESRD) are statistically linked to Hb level. The impact of Hb level on complication incidence varies between [redacted] for stroke and [redacted] for PH" (CS, Section B.3.3.3, p123) and suggested that baseline Hb level was estimated to have the largest impact on reducing the incidence of PH, leg ulcer, CKD and cardiomegaly (CS, Section B.3.3.3, p123). However, the EAG is unclear for the reason why the regression coefficients in Table 11 (revised Appendix Q, p59-60) remain identical to those originally presented in Table 32 (CS, Section B.3.3.3, p120-22), despite the company updating the MAIC in light of the issues identified by both the EAG and company. Further, there appears to be a shift in the placement of the regression coefficient values presented in Table 32 (CS, Section B.3.3.3, p120-22), suggesting there are potential inaccuracies or transcribing errors

Table 34 AFT Regressions, patients MAIC weighted to match patients in CPRD-HES (reproduced from Table 11 in revised Appendix Q, p59-60)

	ARF	Arrhythmias	Cardio-megaly	CKD	ESRD	Gallstones	Heart Failure	Leg ulcer	Osteo-myelitis
N	[redacted]								
Effective Sample Size									
Median Follow-up, Years									
No. of events									
Rate (Months)									
Covariates									
Age, Years									
Female (vs male)									
Index Hb Value (mg/dL)									
VOC Count									
Hb x VOC									
Hydroxyurea treatment									
Chronic transfusion therapy									
History of complications (vs. no)									
ARF									
Arrhythmias									
Cardiomegaly									
CKD									
ESRD									
Gallstones									
Heart failure									
Leg ulcer									
Osteomyelitis									
Osteonecrosis									
Pulmonary hypertension									
Priapism									
Sepsis									
Stroke									
Probability of event at 12 months									
Kaplan-Meier									
Regression-predicted									

(Table 34 continued) AFT Regressions, patients MAIC weighted to match patients in CPRD-HES (reproduced from Table 11 in revised Appendix Q, p59-60)

	Osteo-necrosis	Pulmonary Hypertension	VOC	Priapism	Sepsis	Stroke
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Effective Sample Size	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median Follow-up, Years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate (Months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Covariates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, Years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female (vs male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Index Hb Value (mg/dL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VOC Count	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb x VOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxyurea treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic transfusion therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of complications (vs. no)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arrhythmias	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiomegaly	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESRD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gallstones	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leg ulcer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteomyelitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteonecrosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Priapism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probability of event at 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regression-predicted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: *P-value<.05; †P-value<.01 ‡ P-value<.001; § P-value<.0001
AFR=acute renal failure; CKD=chronic kidney disease; CPRD-HES=Clinical Practice Research Database-Hospital Episode Statistics; ESRD=end-stage renal disease; Hb=haemoglobin; MAIC=matching-adjusted indirect comparison; N=total number of patients; VOC=vaso-occlusive crises
Source: Table 11, revised Appendix Q

8.2.4 Critique of company's analyses

The company stated in response to clarification question A2 that "the variables included were considered sufficient to effectively match the patients in Symphony to those in CPRD-HES on the key prognostic characteristics available in the two datasets". However, the company also stated that other factors under consideration for inclusion in the matching process were ethnicity, indices of multiple deprivation status and opioid dependence; however, these variables were not reported in both the Symphony database or the CPRD-HES database, and that the history of events including cellulitis, depression and retinopathy were not included "due to noncredible coefficient estimates". The EAG believes that despite the company utilising matching methods to overcome observed differences in patient populations of the Symphony and CPRD-HES databases, there is the potential for remaining residual confounding to be present due to other observed or unobserved differences between the two populations which may affect the robustness of the results.

For the AFT regression analyses, the company fitted a selective model to the Symphony data (both weighted and unweighted) which utilised elimination methods to identify which covariates were considered to statistically significantly impact outcomes (p-value <0.05). The company justified the use of fitting a selective model due to the lack of convergence of the saturated model (i.e. a model fitted by including all covariates of interest). The company also presented results from the saturated regression model in their response to clarification question A3. The company stated that saturated models only converged for four outcomes (cardiomegaly, gallstones, osteonecrosis and sepsis), and results from these models yielded "similar results to the regression models with covariate selection"; the company stated that "the signs of the coefficients were the same for all the models, except for the covariate for VOC count for gallstones, which was negative for the saturated model and positive for the model with covariate selection. The coefficient for the covariate for baseline Hb levels was similar (+/-5% relative difference) for all outcomes except osteonecrosis, for which the coefficient was 63% greater with covariate selection than without". The EAG considers a selective regression modelling approach to be appropriate.

Despite the company describing the 'secondary analysis' as a "matching-adjusted indirect comparison", the weights obtained from the matching process were not, in fact, used to inform any treatment comparison. Instead, patients in the Symphony database were assigned a greater weight if they were considered 'similar' to the UK CPRD-HES database. An assessment of the weights was provided as a response to clarification question A4. A histogram showing the distribution of the weights is presented by the company (revised Appendix Q, Figure 16, p58); the EAG is satisfied that an assessment of the weights has been

adequately performed, however, the EAG also notes that there is at least one observation in the Symphony database associated with a large weight, the reasons for this observation were not specified by the company. The effective sample size (ESS) was also estimated alongside the AFT regression analyses, which showed a reduction in the original sample size (N=14,971) after attempting to match patient populations. However, in a response to clarification question A6, the company confirmed that the ESS was in fact incorrect in for some outcomes. Despite the company presenting updated results in the revised Appendix Q, the EAG believes that there remain some transcription errors for a number of ESS values in Table 11 (revised Appendix Q, p59-60), where the ESS is presented as equal to the total sample size used in the analysis, meaning that is difficult for the EAG to assess the reliability of the matching process that has been undertaken by the company.

The EAG believes that the company could have performed additional analyses to explore the uncertainty around the AFT regression results; for example, the set of prognostic factors selected to include in the matching process to estimate the weights of Symphony patients could have been altered to explore the sensitivity of the weights based on different sets of factors selected for matching. Additionally, despite the company stating its justification for the use of Symphony data, the EAG believes that further sensitivity analyses could have been explored to investigate the use of UK CPRD-HES database directly in the AFT regression to determine the impact on findings, instead of relying upon weighted analyses applied to a different study population.

The EAG has a number of concerns regarding the company's TTE regression modelling. Specifically, the EAG has identified discrepancies in regard to the summary baseline characteristics tables presented in the CS compared to those presented in Appendices P and Q (original and revised versions). Furthermore, the EAG has identified in the TTE regression results; those presented in Table 32 in the CS do not match the results presented in Table 9 (Appendix Q [original version]) and regression coefficient values appear unchanged for any of the outcomes in Table 11 (revised Appendix Q), despite the company having corrected a number of errors prior to re-performing the analysis.

Further, the EAG has identified a number of discrepancies between the regression coefficients obtained from the TTE regression analyses presented in Table 9 (Appendix Q [original version], p56-7) and Table 11 (revised Appendix Q, p59-60) compared with those presented in the CS (Table 32, p120-122). The EAG believes that Table 32 in the CS contains implausible values and therefore erroneous results (for example: the probabilities of observing each event at 12 months are not correct; the EAG considers these values to have been transcribed incorrectly). However, the EAG is also not able to validate the results presented in Table 11

(revised Appendix Q, p59-60) to determine if this updated table also contains erroneous results. The EAG therefore has concerns in regard to the accuracy of the results obtained from the company's TTE regression analyses conducted to explore the link between Hb levels and SCD-related outcomes due to the number of inconsistencies and errors identified.

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 7 September 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Positioning of voxelotor as a 'second-line treatment' [Report sections 3.2.1 and 4.7]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table A Issue 1, and elsewhere The EAG states that "The company's positioning of voxelotor as a 'second-line treatment' is problematic".	This issue should be removed.	Hydroxycarbamide (HC) is recommended by the British Society for Haematology (BSH) for all sickle cell disease (SCD) patients, so can be regarded as first-line treatment. The second-line positioning was chosen after consultation with nine UK clinicians, via a Delphi panel (submitted as Appendix U of the company submission [CS]). It focuses on patients with the highest unmet need, i.e. those for whom treatment with the first-line option (HC) is either not feasible, or who remain inadequately treated despite taking HC. This is the population in which voxelotor is most likely to be used in clinical practice in the NHS, according to clinicians consulted for the Delphi panel. Furthermore, there is some confusion in the EAG report over what constitutes 'second-line'. The company's stated position is "adults and paediatric patients aged 12 years or older with SCD who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective." (CS, B1.1). These patients are considered to be second-line, because the first-line treatment (HC) is not appropriate or not	In the CS, the company uses the phrase 'second-line treatment after hydroxycarbamide'. The EAG considers that the use of the phrase 'after hydroxycarbamide' implies that patients have already received HC. However, the company considers that this term also describes the following patients: "those who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective." (CS, B1.1). The EAG also considers that 'after hydroxycarbamide' suggests that patients are no longer receiving hydroxycarbamide. However, in the HOPE trial, the main source of evidence supporting this submission, 64% of patients were receiving hydroxycarbamide at baseline and therefore did not receive voxelotor after hydroxycarbamide.

		adequate. It is not necessary for patients to be taking voxelotor *after* HC to fit this definition. The fact that patients are designated ineligible or unwilling for HC means that use of HC must have been considered in order for these designations to be made. Thus, HC is still the first line of consideration, but because it is not suitable for whatever reason, patients must move to the next (i.e. second) line option. As noted in CS B1.1 (p. 10-11), for patients in HOPE on concomitant HC, investigators and patients chose to participate in a trial of an investigational product in addition to continuing HC. It is reasonable to assume that this decision was based on the premise that HC was delivering inadequate efficacy. Again, this means that voxelotor constitutes a second-line treatment. Finally, the EAG states that the HOPE trial does not provide robust evidence on the efficacy of voxelotor in second-line patients. The Company disagrees with this statement. As stated in the CS and above, the Company does not accept the EAG's assertion that voxelotor constituted first-line treatment for some patients in HOPE. As described in the CS, based on the availability of HC in all participating countries and the global consensus that all SCD patients should receive HC it is reasonable to assume that monotherapy patients have previously been	The EAG highlights that the MHRA EAMS indication for voxelotor is for the treatment of haemolytic anaemia due to sickle cell disease in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide. The EAG considers that the HOPE trial population, which includes all the patients described in the MHRA EAMS indication. It is, therefore, appropriate to use HOPE trial data as the main source of evidence for this appraisal. No changes have been made to the EAG report.

		considered for treatment with HC and are either had an inadequate response to HC or were intolerant, ineligible, or unwilling to take it Furthermore, there is no reason to believe that patients' response to voxelotor would vary depending on whether or not they had previously taken HC, and as shown in the subgroup results in Section 4.3.7 of the EAG report, voxelotor showed benefit regardless of whether patients were taking concomitant HC. The company therefore believes that the evidence from HOPE is generalisable to all eligible patients with haemolytic anaemia and SCD – as reflected in the licensed indication. In summary, the Company maintains that the second-line positioning for voxelotor is appropriate and consistent with NICE recommendations that assessments reflect clinical practice. The positioning is validated by clinical opinion and BSH recommendations. Furthermore, the evidence from HOPE is generalisable to this population.	

Issue 2 Clinical meaning of an increase in Hb of >1g/dL in SCD patients with haemolytic anaemia [Report sections 4.3.2 and 4.7]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
1.4 The cost effectiveness evidence: summary of the EAG's key issues, p. 11 The EAG states that: "It is unclear if an increase in Hb of >1g/dL is clinically meaningful for SCD patients with haemolytic anaemia" **4.3.2 Hb outcomes, p. 35** The EAG states that: "Clinical advice to the EAG is that it is not known whether an increase of 1g/dL is clinically meaningful, although occasionally in clinical practice they would infuse one unit of blood if a patient is symptomatic."	This issue should be removed, as the statement is inaccurate.	Voxelotor has been approved for haemolytic anaemia (HA) in SCD by the EMA and MHRA on the basis of the proportion of patients achieving an increase in Hb of >1g/dL with voxelotor. The EMA states that: "Treatment with voxelotor has resulted in a beneficial effect in terms of reduction in haemolysis and an increase in Hb, which are considered of clinical relevance to the patients."[1] There is good evidence for the relationship between higher haemoglobin (Hb) and improved outcomes in SCD, as presented in the CS p. 123-124. As noted in the CS: "In summary, the relationship between higher Hb levels and reduced risk of SCD-related events and complications is biologically plausible and supported by extensive observational evidence, including a meta-analysis of mainly observational data. In addition, there is some evidence from the HOPE randomised controlled trial (RCT) to support the association. Taken together, this constitutes strong evidence for the surrogacy relationship." Conversely, low Hb	This is not a factual inaccuracy. However, the EAG report has been updated by deleting the following text: "although occasionally in clinical practice they would infuse one unit of blood if a patient is symptomatic." And adding: "however, the European Medicines Agency considers that treatment with voxelotor has resulted in a beneficial effect in terms of reduction in haemolysis and an increase in Hb, which are considered of clinical relevance to patients."

		has been shown to be associated with SCD with cerebrovascular disease (0.6 g/dL) albuminuria (0.6g/dL) and death (0.6 g/dL) and a modelled increase of 1 g/dL reduced the risk of negative clinical outcomes of 41%-64%.[2] In addition, a published analysis of voxelotor-treated patients in Symphony experienced statistically significant and clinically meaningful reductions in annualised rates of hospitalisations, transfusions and vaso-occlusive (VOC) events, and reduced use of iron chelation and opioids.[3] According to the NICE manual and real-world evidence (RWE) framework, RWE should be considered to reduce uncertainties and resolve gaps in evidence. The use of RWE where unvalidated surrogate outcomes are used is specifically stated in the RWE framework. Considering the regulator's decision, the evidence showing that higher Hb is associated with better outcomes in SCD and the evidence of real-world patient-relevant benefits with voxelotor, it is incorrect to state that "it is not known whether an increase of 1g/dL is clinically meaningful".	

Issue 3 Impact of voxelotor on long-term complications [Report section 4.7]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
1.4 The cost effectiveness evidence: summary of the EAG's key issues, p. 11 The EAG states that: "The impact of voxelotor on long-term complications is unknown."	The following additional text should be added to the EAG report: "However, the Company presented evidence in the CS (Table 34, p.124) that the relationship between higher Hb levels and reduced risk of SCD-related events and complications is biologically plausible and supported by extensive observational evidence, including a meta-analysis of mainly observational data. The CS also notes that there is some evidence from the HOPE RCT to support the association: patients treated with voxelotor had a clinical benefit for patients with leg ulcers[4] (CS Table 34). In addition, the CS presents published analyses showing that voxelotor-treated patients in the Symphony database had significant reductions in annualised rates of hospitalisations, transfusions and VOC events, and reduced use of iron chelation and opioids (CS Section B.2.6.9)."	The Company acknowledges that a small RCT in a chronic rare disease alone will not conclusively prove the impact of voxelotor on long-term complications. However, the Company believes that the EAG report should acknowledge that all supplemental data from the OLE and RWE support the, biologically plausible, hypothesis that by inhibiting polymerisation, the reduction of anaemia and haemolysis will improve long-term outcomes. There is evidence that increased Hb is both biologically plausible and associated with improved outcomes, as set out in the response to Issue 2 above and in the CS. In addition, a published analysis of voxelotor-treated patients in Symphony experienced statistically significant and clinically meaningful reductions in annualised rates of hospitalisations, transfusions and	The EAG report heading text has been updated by replacing 'unknown' with 'uncertain'. In addition, the text in the box has been changed to: "The company has provided clinical effectiveness data from the HOPE/OLE trial for a maximum of 144 weeks. The available trial data do not provide evidence for the long-term impact of treatment with voxelotor on the development of SCD complications (for example, stroke, ESRD and heart failure) over a patient lifetime."

		VOC events, and reduced use of iron chelation and opioids.[3] Additionally, it is important to consider that voxelotor is indicated to treat HA in SCD; therefore, only long-term complications associated with HA can be expected to have improvements.	

Issue 4 Methods used for TTE probabilities [Report section 6.2 and appendix 8.2]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
1.4 The cost effectiveness evidence: summary of the EAG's key issues, p.12 The EAG states that "the process used by the company to match patients in the Symphony database to those in the CPRD-HES dataset may not have accounted for all confounding factors"	This sentence should be amended to read: "the process used by the company to match patients in the Symphony database to those in the CPRD-HES dataset (matching the most important factors for which data was available in both datasets) may not have accounted for all confounding factors. IT is however not possible to account for all confounding factors in the patient matching process"	It Is not possible to account for all confounding factors in the patient matching process. The Company attempted to match to the most important factors for which the data was available in both datasets.	This is not a factual inaccuracy. However, the EAG report has been updated as follows: "the process used by the company to match patients in the Symphony database to those in the CPRD-HES dataset (matching the most important factors for which data were available in both sets) may not have accounted for all confounding factors. It is however, not possible to account for all factors in

			the patient matching process”
1.4 The cost effectiveness evidence: summary of the EAG’s key issues, p. 12 The EAG states that “the company should have carried out further sensitivity analyses to explore the effect of uncertainty around AFT regression results”	The bullet should be amended to reflect the comparison of direct HES-CPRD and Symphony datasets contained within the validation section of the CS. The section should read: “acknowledging that the company compared the regression results on the matched Symphony dataset and directly on the HES-CPRD dataset, further sensitivity analyses to explore the uncertainly effect around AFT regression results could have been considered”	Work was completed to compare what the results of regression on the matched Symphony dataset and directly on the HES-CPRD dataset in the validation section which should be acknowledged.	This is not a factual inaccuracy. However, the EAG report has been updated as follows: “acknowledging that the company compared the regression results on the matched Symphony dataset and directly on the HES-CPRD dataset, further sensitivity analyses to explore the effect of uncertainty around AFT regression results could have been considered.”

Issue 5 Modelled impact of voxelotor on HRQoL not supported by trial evidence [Report section 6.3.2]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
1.4 The cost effectiveness evidence: summary of the EAG’s key issues, p. 12 The EAG state “therefore, the EAG considers that there is no	This statement should be change to: “Therefore, the EAG considers that there is no direct RCT evidence that treatment with voxelotor improves utility, when	As shown in Table 13 Summary of health-related quality of life (HRQoL) and sickle cell disease severity measure (SCDSM) of CS p.59 using the HRQoL measure Clinical Global Impression of Change (CGIC), a significantly greater proportion of patients in the voxelotor 1500 mg group (74% [p = 0.0057]) were rated as “very	The EAG report has been updated as follows: “…therefore, the EAG considers that there is no direct evidence that treatment with voxelotor improves HRQoL compared with SoC, when

direct evidence that treatment with voxelotor improves HRQoL compared with SoC”	measured by EQ-5D-5L mapped to utility using the NICE reference case, compared with SoC.”	much improved” or “moderately improved” compared with the placebo group (47%) at week 72. Also, it is worth noting that at baseline only 62 of the 92 and 60 of the 90 patients in the placebo and voxelotor arms, respectively, completed the EQ-5D-5L questionnaire and that by week 72 only 29 and 28, less than one third of participants, answered the questionnaire. Moreover, limitations related to using generic instruments with short recall period to assess utility in in SCD have been discussed in NICE TA 743[5] and its inadequacy accepted with real-world data used instead As such, it is not correct to say that there is no evidence of improvement in HRQoL from HOPE	measured using the EQ-5D-5L questionnaire.”

Issue 6 Inappropriate regular transfusion therapy rates [Report section 6.3.3]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 6 title p.13 Inappropriate regular transfusion therapy rates	Uncertainty around the proportion of patients on regular transfusion therapy (RTT)	The estimates for RTT rates were generated during a modified Delphi panel of nine clinical experts. Which is described in the CS and provided as an appendix.	In line with the company suggestion, this heading in the EAG report has been changed to:

		While this type of evidence may be associated with uncertainty, it is the best alternative option and acknowledged in the NICE manual in the absence of other available evidence. Moreover, the issue being discussed refers to the proportion of patients on RTT in each arm, and not to the rates of RTT.	"Uncertainty around the proportions of patients receiving regular transfusion therapy."
1.4 The cost effectiveness evidence: summary of the EAG's key issues, p. 13 The EAG state "the HOPE trial explicitly excluded patients who were regularly receiving RTT or who had received a RBC transfusion for any reason within 60 days of signing the informed consent form (CS, Table 5)"	This statement should begin with the following clarifying point: "Because of the confounding effect of transfusions on Hb endpoints, …."	It is important to clarify why patients on RTT had to be excluded from HOPE. This might not be obvious to a reader less informed about the disease.	This is not a factual inaccuracy, however, for clarity, the EAG report has been updated as follows: "There is no evidence from the HOPE trial that treatment with voxelotor reduces the need for RTT. To prohibit the confounding effects of transfusions on Hb endpoints, the HOPE trial explicitly excluded patients who were regularly receiving RTT or who had received a RBC transfusion for any reason within 60 days of signing the informed consent form (CS, Table 5);"
1.4 The cost effectiveness evidence: summary of the EAG's key issues, p. 13 The EAG state "There is no evidence that treatment	This statement should be removed as it is inaccurate	Evidence regarding the impact of voxelotor on RTT has been presented in the CS. Firstly, results from a modified Delphi panel involving nine UK experts in treating SCD patients indicate that current	This is not a factual error, however, for clarity, the EAG report has been amended to: "There is no evidence from the HOPE trial that treatment with

with voxelotor reduces the need for RTT”		standard of care (SoC) for patients who would be treated with voxelotor, if available, includes RTT.[6] As such, if voxelotor were available those patients would be taking voxelotor and not RTT. Secondly, real-world evidence shows that voxelotor is associated with a reduction in the need for transfusions[7]. According to the NICE manual and RWE framework, RWE should be considered to where there are uncertainties and to resolve gaps in evidence. Also worth noting, in the latest assessment by NICE of a medicine for SCD [TA743][5] a similar scenario was considered and was deemed acceptable. More specifically, RTT was an exclusion criterion in the SUSTAIN trial[8], but RTT was included in the SoC arm (and not in the treatment arm) of the economic analysis. Therefore, it is incorrect to state that there is no evidence that treatment with voxelotor reduces the need for RTT.	voxelotor reduces the need for RTT.”

Issue 7 Model generates clinically implausible individual patient simulations [Report section 6.3.5]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 7 title p.13 The company model generates clinically implausible individual patient simulations	This statement should be removed as it is misleading	Haemolytic anaemia in patients with SCD is a complex multi system disease which has a significant impact on patients and causes complications throughout the human body and may result in end organ damage A complex multi-system disease requires an appropriate economic model. This point was raised in the ERG assessment of crizanlizumab as detailed below "with the available data, a time-to-event approach seems more logical since it does not require a definition of health state, transition probabilities and re-distribution of patients after each cycle. It can also accommodate complications as "events" in the model simulation and these can be linked directly to death (ERG assessment of company model, crizanlizumab submission)[5] The company conducted a systematic literature review (SLR) (CS Section B.3.1 and Appendix G) to identify relevant cost-effective models. As detailed in the CS and outlined in the EAG report page 48. The search identified ten studies that met the company inclusion criteria; however, none of these studies evaluated the cost-	This is not a factual inaccuracy. The EAG report includes two examples of implausible individual patient simulations. No changes have been made to the EAG report.

		effectiveness of different treatments for SCD patients with haemolytic anaemia from a UK health care system perspective. Patient level simulations are a standard modelling technique and have been employed in a number of disease areas, such as diabetes for several years. The company model is stochastic and as such is subject to random variation but importantly the model averages outcomes across the entire patient cohort. Extensive validation work has been conducted on these averages which indicates model predictions are in line with, or close to published data and/or data obtained from HES. The company is undertaking further analysis of the cost economic model. The company does not recognise that the model is unfit for decision making.	

Other factual accuracy items, by EAG report section

Section 1 Executive summary

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
1.6 Summary of preferred assumptions, p. 14 The EAG states that "Even if the improvement in Hb level	This should be amended to "If the improvement in Hb level arising from treatment with voxelotor did	There is uncertainty over the effect of voxelotor on complication rates over a patient's lifetime. Complications are associated with significant detriment	For clarity, the EAG has been updated as follows: "The EAG further considers that even if the improvement in Hb

arising from treatment with voxelotor did result in improved HRQoL, the size of this improvement is likely to be small”	result in improved utility, the size of any improvement is uncertain.”	to utility, therefore there is the potential for significant gains in utility if the beneficial effect of voxelotor on complications were to be confirmed. It is difficult to quantify the change in utility using the current available RCT data, and the data does not allow the EAG to conclude that the improvement is likely to be small.	level arising from treatment with voxelotor did result in improved HRQoL, the size of the improvement is likely to be small…”

Section 2 Introduction and background

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
2 Introduction and background, p. 15 The EAG states that “In this EAG report, the term ‘company submission’ (CS) refers to the company’s document B, which is the company’s full evidence submission.”	Please amend to “In this EAG report, the term ‘company submission’ (CS) refers to the company’s document B, which is the company’s full evidence submission, and to the addendum to document B supplied at Clarifications stage.”	Readers of the report should be aware of the addendum.	This is not a factual inaccuracy, however, for clarity, the EAG report has been amended to: “In this EAG report, the term ‘company submission’ (CS) refers to the company’s document B, which is the company’s full evidence submission. Documents provided by the company as part of the clarification process are referenced separately.”

2.1 Sickle cell disease, p. 15 The EAG states that "The most common complication of SCD is severe acute episodes of pain known as vaso-occlusive crises (VOCs)".	This should be amended to: "The well-known and obvious complication of SCD is severe acute episodes of pain known as vaso-occlusive crises (VOCs). However, their frequency varies between individuals, and many patients will not experience a VOC in any given year [ref Shah 2019[9] and Vora 2022[10]]	For a significant proportion of SCD patients, VOCs are infrequent and are not the primary manifestation of SCD. As described in the CS p. 28, in two cohorts of patients from specialist SCD centres in the UK over 1-year periods, 47.5% and 73.9% of patients had no recorded VOCs that were hospital-treated or required prescribed analgesia. As described below SCD is associated with a number of other complications to various organs, of which VOCs are just one. Chronic organ complications is the main cause of mortality.[11] It is important to note voxelotor is not indicated for the anti-adhesion of occlusions.	The EAG has amended the text to: "The most well-known and obvious complication of SCD is severe acute episodes of pain known as vaso-occlusive crises (VOCs).[9] VOCs occur when sickled red blood cells block blood flow to the point that tissues become deprived of oxygen.[10] The frequency of VOCs varies between individuals, and many patients will not experience a VOC in any given year.[11,12]"
2.1 Sickle cell disease, p. 15-16 The EAG states that "Over time, reduced blood flow and repeated blockages damage blood vessels, leading to chronic complications. Chronic complications of SCD increase with age, and include lung damage, pulmonary hypertension, kidney	The placement of this information in the paragraph on VOCs is misleading. Furthermore, the first sentence is an over-simplification of the SCD disease process and is inaccurate because it omits important information on that process. The information should be placed in a new paragraph and should be amended as follows: "Over time, patients with SCD develop chronic	These processes, and the subsequent chronic complications, are caused by sickling and haemolysis, and occur regardless of whether the patient experiences VOCs. It is important that readers of the report understand these aspects of SCD pathophysiology, as they relate directly to the mechanism of action of voxelotor and its potential benefits.	The EAG has included a paragraph detailing the information on chronic complications related to SCD as suggested. The text has been amended to: "Over time, the sickling and subsequent breakdown (haemolysis) of red blood cells leads to haemolytic anaemia, blood vessel damage and vaso-occlusion (including

dysfunction, retinopathy and leg ulcers."	complications caused by the sickling and subsequent breakdown (haemolysis) of red blood cells. Sickling and haemolysis lead to haemolytic anaemia, blood vessel damage and vaso-occlusion (including VOCs). This results in reduced oxygen delivery to the tissues, and chronic inflammation caused by free cell contents in the blood.[ref Kato 2017[12] and Rother 2005[13]]. Together, these pathologies cause a range of acute and chronic severe complications. Chronic complications of HA in SCD increase with age, and include lung damage, pulmonary hypertension, kidney dysfunction, retinopathy and leg ulcers."	The proposed amendment is based on CS Section B.1.3.1.1 (p. 19-20).	VOCs). This can result in reduced oxygen delivery to the tissues, and inflammation, which contribute to a range of acute and severe complications. Chronic complications of SCD increase with age, and include lung damage, pulmonary hypertension, kidney dysfunction, retinopathy and leg ulcers."
2.1.1 Haemolytic anaemia in sickle cell disease, p. 16 The EAG states that: "Red blood cells are broken down through the process of haemolysis. Sickle cells are broken down more easily than normal red blood cells."	This should be modified to: "The breakdown of red blood cells is termed haemolysis. Repeated sickling leads to abnormally high levels of haemolysis including excessive haemolysis in blood vessels."	The EAG statement implies that haemolysis as it occurs in SCD is an active process carried out by the body, and that the haemolysis of sickled cells takes place in the same way as the normal breakdown of old or damaged red blood cells in the spleen. This is misleading. Haemolysis of sickled cells is a process of mechanical rupture and takes place in the blood vessels	The EAG report has been amended as follows: "The breakdown of red blood cells is termed haemolysis. Repeated sickling leads to abnormally high levels of haemolysis including excessive haemolysis in blood vessels."

		(intravascular haemolysis). Unlike haemolysis in the spleen (extravascular haemolysis), this deposits free Hb and other cell contents into the blood, where they cause inflammation and vessel damage.[12,14] It is important that readers of the report are aware of all the consequences of haemolysis in SCD.	
2.2 Voxelotor, p. 16 The EAG states that: "Voxelotor is a HbS polymerisation inhibitor (CS, Table 2). Inhibiting polymerisation increases the ability of Hb to retain oxygen, maintain red blood cells in their normal shape and helps to prevent haemolysis and associated anaemia."	There is a typographical error: it should read "maintains red blood cells in their normal shape". In addition, the following sentence should be added: "Polymerisation of HbS is the underlying molecular event that causes sickling, haemolysis and the resulting cascade of pathology [ref Piel 2017[15]]"	The EAG statement is referenced to the NICE final scope and does not fully reflect the mechanism of action of voxelotor. It is important for readers of the report to understand that voxelotor acts on the underlying molecular basis of SCD (as described on CS p. 174).	A change has been made to correct the typographical error and the EAG has added additional text to the report as suggested, namely: "Polymerisation of HbS is the underlying molecular event that causes sickling, haemolysis and the resulting cascade of pathology [ref Piel 2017[15]]"
2.2 Voxelotor, p. 16 The EAG states that: "Healthcare records for patients with haemolytic anaemia due to SCD and who are treated with voxelotor are available from the Symphony Health Solutions Integrated	This should be rephrased as: "Healthcare records for patients with haemolytic anaemia due to SCD, including 3,128 patients who are treated with voxelotor, are available from the Symphony Health Solutions Integrated	While Symphony does contain data on over 100,000 patients with SCD aged 12+, the analyses in the submission were conducted in 3,128 SCD patients aged 12+ who were treated with voxelotor with evidence of SCD based on ≥3 claims and at	The EAG report has been updated as follows: "Healthcare records for patients with haemolytic anaemia due to SCD, including 3,128 patients who are treated with voxelotor are

Dataverse Database (known as the 'Symphony database').[20]	Dataverse Database (known as the 'Symphony database').[20]	least 1 Hb value recorded; treatment with voxelotor was not required for inclusion in the TTE analysis (Appendix Q p. 2). CS also presents a published analysis on voxelotor-treated patients in Symphony.[3]	available from the Symphony Health Solutions Integrated Dataverse Database (known as the 'Symphony database')."
2.3.1 Available treatments for SCD, p. 17 The EAG states that: "The company lists the available treatments for SCD as best supportive care (BSC), HC, blood transfusions, crizanlizumab and allogenic stem transplant; the EAG considers that SoC comprises these treatment options."	This should be modified by deleting the final phrase, to: "The company lists the available treatments for SCD as best supportive care (BSC), HC, blood transfusions, crizanlizumab and allogenic stem transplant. The SoC for HA in SCD is BSC, HC and blood transfusions.	Voxelotor is licenced for the treatment of HA in SCD; therefore, should only be compared against SoC of HA in SCD and not the SoC for the broader disease of SCD. The company disagrees that crizanlizumab and allogeneic stem cell transplant are part of SoC for patients with SCD and haemolytic anaemia. Crizanlizumab is indicated only for the subset of patients who require medication for prevention of recurrent VOCs. In adults, NHS England restricts Allo-SCT to patients with a matched sibling donor, and who have severe SCD that is associated with reduced survival, chronic morbidity, or where current treatments are not effective.[16] It is not part of routine practice.	The EAG report has been updated as follows: "The company lists the available treatments for SCD as best supportive care (BSC), HC, blood transfusions, crizanlizumab and allogenic stem transplant. Current SoC for the treatment of haemolytic anaemia in SCD is BSC, HC and blood transfusions. The company highlights (CS, Section B.1.3.2.2) that voxelotor is the only therapy specifically indicated for the treatment of haemolytic anaemia due to SCD."
2.3.1 Available treatments for SCD, p. 18 The EAG states that: "BSC for patients with SCD is lifestyle advice, vaccinations,	This should be modified to: "BSC for patients with SCD is lifestyle advice, vaccinations, prophylactic antibiotics, pain medicines, blood	The current wording does not reflect the CS (p. 32) as stated. The CS states "Some patients also receive blood transfusions as part of	The EAG report has been updated as follows: "BSC for patients with SCD is lifestyle advice, vaccinations,

prophylactic antibiotics, pain medicines, blood transfusions (occasional) and management of co-morbidities (CS, p31)".	transfusions (occasional or regular) and management of co-morbidities (CS, p32)."	supportive care, either occasionally or on a regular schedule."	prophylactic antibiotics, pain medicines, blood transfusions and management of co-morbidities (CS, p31)."
2.3.2 Number of patients eligible for voxelotor, p 19 The EAG states that: "The company estimates (CS, Document A, Table 12) that voxelotor would be a suitable treatment for [redacted] patients in Year 1, rising to [redacted] patients in Year 5."	This should be modified to: "The company estimates (CS, Document A, Table 12) that voxelotor would be used to treat [redacted] patients in Year 1, rising to [redacted] patients in Year 5."	The numbers in the budget impact table are only partially based on suitability. The number of suitable patients is multiplied by the estimated uptake (as a proportion of suitable patients) each year to obtain the estimated number treated.	This is not a factual inaccuracy. No changes have been made to the EAG report.

Section 3 Critique of company's definition of the decision problem

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 2, Decision problem, Population, p.21 The EAG states that: "In the HOPE trial, 64% of patients in the voxelotor arm and 63% of patients in the placebo arm were taking HC at baseline. Therefore, the HOPE population is not patients who are receiving voxelotor as a	The second sentence should be deleted.	The company's stated position is "adults and paediatric patients aged 12 years or older with SCD who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective." (CS, B1.1). These patients are considered to be second-line, because the first-line treatment (HC) is not appropriate or not adequate. It is	Please see the EAG response to Issue 1. No changes have been made to the EAG report.

second-line treatment after HC.”		not necessary for patients to be taking voxelotor *after* HC to fit this definition. As noted in CS B1.1 (p. 10-11), for patients in HOPE on concomitant HC, investigators and patients chose to participate in a trial of an investigational product in addition to continuing HC. It is reasonable to assume that this decision was based on the premise that HC was delivering inadequate efficacy. Furthermore, because 64% and 63% in the voxelotor and placebo arms, respectively, were taking HC at baseline does not allow the EAG to state that the population is not second-line.	
3.2 Population, p. 26 The EAG states that: “The population described in the final scope issued by NICE is people with SCD. However, the indication for voxelotor is referred to in the title of the final scope as ‘voxelotor for treating haemolytic anaemia in people with sickle cell disease’”.	This should be amended to: “The population described in the final scope issued by NICE is people with SCD. However, the indication for voxelotor is referred to in the title of the final scope as ‘voxelotor for treating haemolytic anaemia in people with sickle cell disease’, in line with the licensed indication”.	The licensed indication (EMA, MHRA and EAMS) for voxelotor is “for the treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide”. [17] The definition in the title of the final scope is the correct one as it reflects the licensed indication. EAG repeatedly and casually interchanges SCD and HA in SCD in its analysis. This is particularly important in making the wrong determination on SoC which	This is not a factual inaccuracy; however, the EAG report has been updated as follows: “The population described in the final scope issued by NICE is people with SCD. However, the indication for voxelotor is referred to in the title of the final scope as ‘voxelotor for treating haemolytic anaemia in people with sickle cell disease’, in line with the licensed indication.”

		must be for the indication in question, namely HA in SCD and not SCD writ large. This mistake undermines multiple elements of the EAG analysis and conclusions.	
3.2.1 Positioning of voxelotor, p.26-27 The EAG considers that the company's positioning of voxelotor as a [redacted] is not appropriate.	This statement should be removed it is not based on fact	The company have undertaken a modified Delphi panel with nine clinical experts to determine where voxelotor would be used in clinical practice. This positioning is also supported by BSH guidelines on the use of HC. All patients should and are considered for HC as it is SOC. Voxelotor would be offered if patients are intolerant to HC, have an insufficient response (combined with HC), contraindication (monotherapy) or are unwilling to take HC due to previous exposure or otherwise. It is possible to debate the semantics of whether a drug has to have been used or simply considered for use to make it first line. Describing Voxelotor as second line reflects practice (including the company's experience in early access in the UK) and clinical guidelines and is easier for treating physicians to understand.	Please see the EAG response to Issue 1. No changes have been made to the EAG report.
3.2.1 Positioning of voxelotor, p.26	This sentence should be deleted.	The Company agrees that HC and voxelotor offer different benefits, but does not accept that this makes	Please see the EAG response to Issue 1. No changes have been made to the EAG report.

The EAG states that: “Clinical advice to the EAG is that, as the two drugs deliver different benefits, it is not appropriate to only position voxelotor after HC.”		second-line positioning inappropriate. The reasons for this are elaborated in the response to Issue 1. Clinical practice and BSH guidelines plus the lower age range that HC is used for all presume use or at least consideration of HC prior to use of Vox	
3.2.1 Positioning of voxelotor, p.26 The EAG states that: “The company has assumed that patients who were not receiving HC at baseline (approximately 36% of patients) had previously been offered treatment with HC and had either stopped treatment, declined treatment, or were ineligible for treatment with HC; therefore, some of these patients would have been receiving second-line treatment with voxelotor after HC whilst others would have been receiving voxelotor as a first-line treatment.”	The second half of this should be deleted. It should be amended to read: ““The company has assumed that patients who were not receiving HC at baseline (approximately 36% of patients) had previously been treated with or considered for treatment with HC and had either stopped treatment, declined treatment, or were ineligible for treatment with HC.”	The statement that voxelotor represents a first-line treatment in patients who had declined HC or were ineligible for HC is not accurate. While terminology around lines of treatment can vary, it is legitimate to describe voxelotor as second-line in these patients. It is reasonable to assume that they are only being offered an investigational treatment (voxelotor) because HC has been used or considered but is not a suitable treatment for whatever reason. Voxelotor is not a first-line treatment in these patients because it is only offered after HC or because HC cannot be used.	Please see the EAG response to Issue 1. No changes have been made to the EAG report.
3.2.2. Generalisability of HOPE trial results, p 28 “There is therefore no evidence for the clinical	This statement should be amended to: “There is no evidence for the clinical effectiveness of	There is evidence as described in the CS but that does not reside in the HOPE 24 week trial. The EAG is failing in its responsibility to consider all	This is not a factual inaccuracy. As indicated in the heading of Section 3.2.2, the text refers only to the HOPE trial. However, for clarity

effectiveness of voxelotor for patient in any of these groups."	voxelotor in these patients groups within the HOPE RCT."	evidence as required by the NICE manual and RWE Framework	the EAG report has been updated as follows: "There is therefore no evidence from the HOPE trial for the clinical effectiveness of voxelotor for patient in any of these groups."

Section 4 Clinical effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
4.2.2, Table 4, p. 33 The table states that the primary outcome was "CFB in number of patients with an increase in Hb (>1g/dL) at Week 24."	This should be changed to: "Number of patients with an increase in Hb >1 g/dL from baseline to week 24."	Current statement is not accurate; correct information is in CS Table 5, p. 45.	The EAG report has been updated as follows: "Number of patients with an increase in Hb >1 g/dL from baseline to week 24."
4.4 Patient-reported outcomes, p. 26 Clinical advice to the EAG is that SoC used in the HOPE trial was in line with SoC provided in the NHS, except that NHS patients may now also be treated with crizanlizumab to prevent	Clinical advice to the EAG is that SoC used in the HOPE trial was in line with SoC provided in the NHS.[34] For the avoidance of doubt, Crizanlizumab, which was not available at the time of the HOPE trial, is not a comparator as per the NICE scope (ref).	The wording is misleading and may infer the company had a decision to not involve crizanlizumab in the HOPE trials. Crizanlizumab has no effect on HA in SCD	This is not a factual inaccuracy. The statement is taken from Section 3.4 of the EAG report. The first sentence in Section 3.4 is: "The comparators listed in the final scope[19] issued by NICE are HC, blood transfusions (exchange and

recurrent VOCs if aged 16 years or over.[34]			top-ups) and best supportive care." No changes have been made to the EAG report.
4.3.2 Hb outcomes, p. 35 The report refers to the primary endpoint as being "the change in Hb response rate (RR) from baseline to Week 24."	Change description to: "number of patients with an increase in Hb >1 g/dL from baseline to week 24." (as per CS Table 5, p. 45.)	This terminology is incorrect. Patients cannot have a response at baseline, therefore the response cannot 'change from baseline'.	The EAG report has been updated as follows: "The primary outcome of the HOPE trial was the number of patients with an increase in Hb >1g/dL from baseline to Week 24."
4.3.2 Hb outcomes, p. 35 The EAG states that: "Clinical advice to the EAG is that it is not known whether an increase of 1g/dL is clinically meaningful, although occasionally in clinical practice they would infuse one unit of blood if a patient is symptomatic."	This statement should be removed as it is inaccurate.	See response to Issue 2	The EAG has removed the following text: "although occasionally in clinical practice they would infuse one unit of blood if a patient is symptomatic." And has included the following text: "however, the European Medicines Agency (EMA) considers that treatment with voxelotor has resulted in a beneficial effect in terms of reduction in haemolysis and an increase in Hb, which are

			considered of clinical relevance to patients.”
4.3.2 Hb outcomes, p. 35 In the ITT population, a statistically significantly higher proportion of patients treated with voxelotor compared to placebo experienced a change in Hb levels at Week 24 (least squares [LS] mean: 1.13 versus -0.10 respectively).	Change to: “Patients in the voxelotor 1500 mg group had an adjusted (least square [LS]) mean change in Hb from baseline to 24 weeks of 1.13 g/dL, compared with -0.10 g/dL in the placebo group (P< 0.001).” [as per CS Table 9]	This is inaccurate. The endpoint is not the proportion of patients who experience a change in Hb levels, it is the magnitude of that change.	The EAG report has been updated as follows: “In the ITT population, patients in the voxelotor arm had an adjusted (least square [LS] mean change in Hb from baseline to 24 weeks of 1.13g/dL compared with -0.10g/dL in the placebo arm (p<0.001).
4.3.3 Haemolysis markers, p 36 In the ITT population, patients who received voxelotor showed a statistically significant reduction against placebo for indirect bilirubin levels (-29.1 versus -3.2 respectively) and percentage of reticulocytes (-19.9 versus 4.5 respectively) at Week 24. At Week 72, a statistically significant reduction was maintained in patients receiving voxelotor in indirect bilirubin levels (p<0.001) and	In the ITT population, patients who received voxelotor showed a statistically significant reduction against placebo for indirect bilirubin levels (-29.1 versus -3.2 respectively) and percentage of reticulocytes (-19.9 versus 4.5 respectively) at Week 24. At Week 72, a statistically significant reduction was maintained in patients receiving voxelotor in indirect bilirubin levels (p<0.001) and percentage of reticulocytes (p<0.05). These are biological markers for haemolytic anaemia that are reviewed by treating clinicians when making treatment decisions.	The detailed biological markers have importance for clinicians when reviewing patients and making treatment decisions. These markers are not modelled in the submitted cost economic model but their importance in evaluating patient’s health and to clinicians making treatment decisions	This is not a factual inaccuracy, however, the EAG report has been updated to the following: “In the ITT population, patients who received voxelotor showed a statistically significant reduction against placebo for indirect bilirubin levels (-29.1 versus -3.2 respectively) and percentage of reticulocytes (-19.9 versus 4.5 respectively) at Week 24. At Week 72, a statistically significant reduction was maintained in patients receiving voxelotor in

percentage of reticulocytes ($p<0.05$)		should not be ignored.	indirect bilirubin levels ($p<0.001$) and percentage of reticulocytes ($p<0.05$). These are biological markers for haemolytic anaemia that are reviewed by treating clinicians when making treatment decisions. Patients who received voxelotor showed an improvement compared to placebo for absolute reticulocyte count and lactate dehydrogenase levels, but these differences were not statistically significant at any timepoint.”
4.3.5 Other exploratory outcomes, p 38 The EAG states that: “The EAG highlights that that the trial population on which these results are based consisted of patients who did not receive RTT or who had a transfusion in the 60 days prior to the start of the trial.”	Change to: “The EAG highlights that that the trial population on which these results are based consisted of patients who did not receive RTT or had not received a transfusion in the 60 days prior to the start of the trial because of the confounding effect of transfusions on Hb endpoints.”	Patients were not eligible if they had received a transfusion in the 60 days prior to the start of the trial.	This is a transcription error. The EAG report has been updated to the following: “The EAG highlights that the trial population on which these results are based consisted of patients who did not receive RTT or had not received a transfusion in the 60 days prior to the start of the trial because of the confounding effect of transfusions on Hb endpoints.”

4.3.5 Time to first transfusion, p 38 The EAG states that: "The EAG highlights that that the trial population on which these results are based consisted of patients who did not receive RTT or who had a transfusion in the 60 days prior to the start of the trial."	There is a typographical error. The sentence should read: "….did not receive RTT and did not have a transfusion in the 60 days prior to the start of the trial."	Typographical error	This is a transcription error. The EAG report has been updated to the following: "The EAG highlights that the trial population on which these results are based consisted of patients who did not receive RTT or had not received a transfusion in the 60 days prior to the start of the trial because of the confounding effect of transfusions on Hb endpoints."
4.3.6 Post hoc analyses, p. 38 Incidence of severe anaemic episodes is discussed as a post hoc analysis.	This section should be moved to the Section that covers Secondary and exploratory endpoints, as per CS p. 54. The post-hoc analysis described in the final sentence can remain in its current position.	Incidence of severe anaemic episodes was a pre-specified analysis. An additional analysis, which was post hoc, was also presented.	The EAG report has been updated as suggested.
4.3.7 Subgroup analyses Rates of post-baseline opioid use were similar between voxelotor and placebo for patients with and without prior opioid history (CS, Appendix E).	Additional clarification point should be added "Rates of post-baseline opioid use were similar between voxelotor and placebo for patients with and without prior opioid history. Further data seen in the symphony data analysis has demonstrated a significant reduction in OPIOD usage for voxelotor patients."	The full data subset has not been considered by the EAG as per NICE guidelines on considering RWE (need to demonstrate RWE is	This is not a factual inaccuracy. No changes have been made to the EAG report.

<table>
<tr><td></td><td></td><td>claims data, has been presented and major conferences and published in peer review journals</td><td></td></tr>
<tr><td>4.4 Patient-reported outcomes, p. 41
The EAG states that the Company highlights that: “SCDSM results showed no difference in reported disease severity between the voxelotor and placebo arms at Week 24.”</td><td>Please add the following to this bullet point: “The company highlights that SCDSM data are difficult to interpret due to low baseline scores and high variability in symptom scores.” [as per CS p. 59</td><td>This addition gives a more accurate picture of what the company highlighted on SCDSM.</td><td>This is not a factual inaccuracy, however the EAG has added the text as requested:
“SCDSM results showed no difference in reported disease severity between the voxelotor and placebo arms at Week 24. The company highlights that SCDSM data are difficult to interpret due to low baseline scores and high variability in symptom scores.”</td></tr>
<tr><td>4.6 HOPE open-label extension study, p45
Table 14</td><td>Please correct Table 14 to the updated table below:<table><tr><td></td><td colspan="3">Prior treatment group, n (%)</td><td>OLE, n (%)</td></tr><tr><td></td><td>Placebo (n=62)</td><td>Voxelotor 900 mg (n=58)</td><td>Voxelotor 1500 mg (n=58)</td><td>Voxelotor 1500 mg (n=178)</td></tr></table></td><td>The patient characteristics table omits data from patients recruited to HOPE OLE from the voxelotor 900 mg arm from the HOPE trial. The “OLE” column is a combined population of all three treatment</td><td>The EAG report has been updated as suggested.</td></tr>
</table>

<table>
<tr>
<td></td>
<td>
<table>
<tr><td>Age, median, years</td><td>27</td><td>24</td><td>25</td><td>25</td></tr>
<tr><td>Adolescent, 12-17 years</td><td>11 (17.7)</td><td>6 (10.3)</td><td>11 (19.0)</td><td>28 (15.7)</td></tr>
<tr><td>Adult, ≥18 years</td><td>51 (82.3)</td><td>52 (89.7)</td><td>47 (81.0)</td><td>150 (84.3)</td></tr>
<tr><td colspan="5">Duration of exposure, weeks</td></tr>
<tr><td>Median</td><td>68.6</td><td>67.9</td><td>72.9</td><td>69.9</td></tr>
<tr><td>Range (min, max)</td><td>4.6 to 102.0</td><td>1.9 to 98.3</td><td>12.1 to 100.6</td><td>1.9 to 102.0</td></tr>
<tr><td>≥72 weeks, n (%)</td><td>26 (41.9)</td><td>21 (36.2)</td><td>31 (53.4)</td><td>78 (43.8)</td></tr>
</table>
</td>
<td>arms in the “Prior treatment group” column. Without all the subgroups the data in the “OLE” column does not appear consistent.</td>
<td></td>
</tr>
<tr>
<td>4.6 HOPE open-label extension study, p45

The EAG states that “The population in the HOPE OLE study consisted of similar proportions of patients previously treated with voxelotor or placebo (58% and 62% respectively) …”</td>
<td>This paragraph should be corrected as follows

“The population in the HOPE OLE study consisted of a similar number of patients previously treated with voxelotor 1500 mg, voxelotor 900 mg and placebo (58%, 58% and 62%, respectively) …”</td>
<td>The EAG report the number of patients enrolled from the HOPE trial treatment arms as proportions. This should be corrected and the voxelotor 900 mg arm also included.</td>
<td>The EAG report has been updated as suggested.</td>
</tr>
</table>

<table>
<tr>
<td>4.6 HOPE open-label extension study, p45
“In the HOPE OLE study patients who had received placebo in the previous phase 3 trial showed an improvement in Hb (mean 1.3 [SD 1.1])”</td>
<td>This should be corrected to:
“In the HOPE OLE study patients who had received placebo in the previous phase 3 trial showed an improvement in Hb (mean 1.3 [SD 1.5])”</td>
<td>The SD as reported in the reference is 1.51</td>
<td>The EAG report has been updated as follows:
“In the HOPE OLE[32,47] study patients who had received placebo in the previous phase 3 trial showed an improvement in Hb (mean 1.3 [SD 1.51])…”
Reference to the abstract Achebe 2021 has also been added.</td>
</tr>
<tr>
<td>4.6 HOPE open-label extension study, p45
Table 16</td>
<td>Please correct Table 16 to the updated table below:
<table>
<tr><td></td><td colspan="3">Prior treatment group, n (%)</td><td>OLE, n (%)</td></tr>
<tr><td></td><td>Placebo
N = 62
n (%)</td><td>Voxelotor 900 mg
N = 58
n (%)</td><td>Voxelotor 1500 mg
N = 58
n (%)</td><td>Voxelotor 1500 mg
N = 178
n (%)</td></tr>
<tr><td>Arthralgia</td><td>15 (24.2)</td><td>7 (12.1)</td><td>5 (8.6)</td><td>27 (15.2)</td></tr>
<tr><td>Headache</td><td>12 (19.4)</td><td>6 (10.3)</td><td>5 (8.6)</td><td>23 (12.9</td></tr>
<tr><td>Pain</td><td>11 (17.7)</td><td>5 (8.6)</td><td>5 (8.6)</td><td>21 (11.8)</td></tr>
</table>
</td>
<td>The AEs table omits data from patients recruited to HOPE OLE from the voxelotor 900 mg arm from the HOPE trial. The “OLE” column is a combined population of all three treatment arms in the “Prior treatment group” column. Without all the subgroups the data in the “OLE” column does not appear consistent.</td>
<td>The EAG report has been updated as suggested.</td>
</tr>
</table>

	Nausea	13 (21.0)	5 (8.6)	2 (3.4)	20 (11.2)		
	Pain in extremity	7 (11.3)	6 (10.3)	7 (12.1)	20 (11.2)		
	Diarrhoea	10 (16.1)	6 (10.3)	2 (3.4)	18 (10.1)		
	Upper respiratory tract infection	7 (11.3)	2 (3.4)	9 (15.5)	18 (10.1)		
4.7 Conclusions of the clinical effectiveness section, p. 48 The EAG states that: "The HOPE trial is of good methodological quality; however, many patients with SCD were excluded from the trial, including those receiving RTT, those who had had >10 VOCs during the previous year that required hospital, emergency room or clinical visit, and those who had had no VOCs during the previous 12 months."	Please add the following sentence: "Patients receiving RTT were not eligible for HOPE because of the confounding effect of transfusions on Hb-related endpoints."					The list of exclusions is correct. However, it is important to point out that the exclusion of patients receiving RTT was necessary to avoid confounding.	This is not a factual inaccuracy, however, the EAG report has been updated as follows: "The HOPE trial is of good methodological quality; however, many patients with SCD were excluded from the trial, including those receiving RTT (to prevent the confounding effect of transfusions on Hb-related endpoints), those who had had >10 VOCs during the previous year that required hospital, emergency room or clinical visit, and those who

			had had no VOCs during the previous 12 months.”
4.7 Conclusions of the clinical effectiveness section, p. 48 The EAG states that: “Clinical advice to the EAG is that HC and voxelotor deliver different benefits and it is therefore not appropriate to only position voxelotor after HC. The EAG considers that the company does not have robust clinical efficacy evidence to support positioning of voxelotor as ‘second-line treatment after HC’”	This paragraph should be deleted.	The Company agrees that HC and voxelotor have different benefits, but disagrees that positioning voxelotor as second-line to HC is inappropriate. The reasons for this are elaborated in the response to Issue 1. The Company also disagrees that the HOPE trial does not provide robust clinical efficacy evidence as second-line treatment to HC. As stated in the CS and in the response to Section 3.2.1 above, the Company does not accept the EAG’s assertion that voxelotor constituted first-line treatment for some patients in HOPE. Furthermore, there is no reason to	Please see EAG response to Issue 1.

		believe that patients' response to voxelotor would vary depending on whether or not they had previously taken HC, and as shown in the subgroup results in Section 4.3.7 of the EAG report, voxelotor showed benefit regardless of whether patients were taking concomitant HC. The company therefore believes that the evidence from HOPE is generalisable to all eligible patients with haemolytic anaemia and SCD – as reflected in the licensed indication. Generalisability in substantiated in RWE, which the EAG has ignored, not following NICE guidance and the RWE framework	

4.7 Conclusions of the clinical effectiveness section p. 49 Clinical advice to the EAG is that HC and voxelotor deliver different benefits and it is therefore not appropriate to only position voxelotor after HC. The EAG considers that the company does not have robust clinical efficacy evidence to support positioning of voxelotor as 'second-line treatment after HC'	Clinical advice to the EAG is that HC and voxelotor deliver different benefits and it is therefore not appropriate to only position voxelotor after HC. The company conducted a modified Delphi accepted evidence as per the DSU guidelines where nine clinical experts in England advised where voxelotor would be used in clinical practice. Second-line in the CS means: concomitant use with patients on, and continuing to take HC; use in monotherapy for patients previously on HC; and use in patients who have been considered for HC but who are ineligible or unwilling to take it.	A modified Delphi panel was conducted, including nine clinical experts, to determine the most appropriate positioning of voxelotor, as per DSU guidance. This evidence should be made clear to the reader	Please see EAG response to Issue 1.
4.7 Conclusions of the clinical effectiveness section p. 48 there is no evidence to demonstrate that the HOPE trial improvements in Hb level experienced by patients treated with voxelotor are clinically meaningful or if they reduce SCD complications over a patient lifetime	Replace with argument that there is evidence that >1g d/l is clinically meaningful and has a positive outcome for patients	There is evidence in existence directly from voxelotor patients and the literature on the impact and clinical meaningfulness of increasing Hb 1g/dl>. The HOPE trial does demonstrate clinically meaningful benefits, as confirmed by EMA (and approved by MHRA).	Please see EAG response to Issue 2.

		Furthermore, post-HOPE RWE, which the EAG is required to consider per the NICE Manual, guidance and the RWE Framework confirms the impact on complications of HA in SCD	
4.7 Conclusions of the clinical effectiveness section p. 48 The MHRA EAMS[17] voxelotor licence is for "the treatment of haemolytic anaemia due to SCD in adults and paediatric patients 12 years of age and older as monotherapy or in combination with HC and does not limit the use of voxelotor to after treatment with HC.	The positive scientific opinion granted for an EAMS by the MHRA detailed that eligibility criteria which includes for voxelotor monotherapy and in combination with HC. This is broadly reflective of the MHRA licence. Furthermore, the proposed second line position allows to voxelotor as a monotherapy and in combination therapy. Clinical advice received states some patients have a insufficient (partial response) to HC and would benefit from being prescribed voxelotor as a second-line treatment. Second-line in the CS means: concomitant use with patients on, and continuing to take HC; use in monotherapy for patients previously on HC; and use in patients who have been considered for HC but who are ineligible or unwilling to take it.	The statement is factually incorrect and could cause misunderstanding	Please see EAG response to Issue 1.
4.7 Conclusions of the clinical effectiveness section p. 48	Clinical advice to the EAG is that HC and voxelotor deliver different benefits and it is therefore not appropriate to only position voxelotor after HC. The company conducted a modified Delphi accepted evidence as per the DSU guidelines which nine	A modified Delphi panel was conducted, including nine clinical experts, to determine the	Please see EAG response to Issue 1.

Clinical advice to the EAG is that HC and voxelotor deliver different benefits and it is therefore not appropriate to only position voxelotor after HC. The EAG considers that the company does not have robust clinical efficacy evidence to support positioning of voxelotor as 'second-line treatment after HC'	leading clinical experts in England advised where voxelotor would be used in clinical practice.	most appropriate positioning of voxelotor, as per DSU guidance. This evidence should be made clear to the reader	
5.7 Conclusions of the clinical effectiveness section p. 48 Voxelotor is the only treatment licensed in Europe for patients with haemolytic anaemia associated with SCD	Voxelotor is the only treatment licensed in Europe by the EMA and Great Britain by the MHRA for patients with haemolytic anaemia associated with SCD. Siklos made an application for a HA license, but this was rejected by the EMA due to lack of data.	The statement is not factually complete the additional information is relevant to the GB license.	This is not a factual inaccuracy. No changes have been made to the EAG report.
Real-world evidence The company presented published evidence showing improved outcomes in voxelotor-treated patients in the Symphony database (CS B.2.6.9), but this is not acknowledged in the EAG report.	Please add the following (as a minimum description of the RWE): "The company presented a published analysis of voxelotor-treated patients in the Symphony database experienced statistically significant and clinically meaningful reductions in annualised rates of hospitalisations, transfusions and VOC events, and reduced use of iron chelation and opioids."	This published real-world evidence presented in the CS should be mentioned in the EAG report in order to give a full picture of the evidence submitted, as required by the NICE manual, Guidelines and the RWE framework	An additional section has been added to the EAG report: **4.6.2 Real world evidence** The company has provided published results from analyses of real world evidence (Symphony database) to show the impact of the introduction of voxelotor on patient outcomes (Shah 2022). The

			EAG considers that these results are of secondary importance due to data for the population of interest being available from a high quality RCT (HOPE trial). Further, the EAG considers the Shah 2022 results are of limited use to decision makers as these results have been generated from simple before and after comparisons, which are subject to confounding."

Section 5 Cost-effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
5.3.3 Population, p. 52 The EAG states that "The baseline characteristics (reproduced in Table 20) of the modelled population reflect the patients recruited to the HOPE trial"	Sentence should read "The baseline characteristics of the modelled population reflect a L2+ subset of the HES-CPRD dataset, for which Hb measurements were available" The table 20 should also be deleted.	The sentence and following table are inaccurate, because they present the modelled population as being representative of HOPE, while in fact it is representative of a UK L2+ population.	Thank you for clarifying. The EAG report has been updated using the text suggested by the company. The sex distribution and starting age (used to calculate the QALY shortfall) are now presented in Table 20. These are the only specific

			population details provided in the CS.
5.3.6 Treatment effectiveness, p. 53 The EAG states that "The company assumed that the effectiveness of voxelotor was not affected by HC use"	Sentence should read "The company stratified Hb response by HC usage status"	The sentence doesn't reflect the data entering the model.	As stated by the company in the CS (Table 1), "HOPE trial results show that there was a consistent treatment benefit in patients with and without stable HC use at baseline…. However, the patient population from HOPE has been stratified by HC use for the purpose of modelling" (CS, Table 1). For clarity, the EAG report has been updated as suggested by the company to: "The company stratified Hb response by HC usage status."
5.3.7 Treatment discontinuation, p. 53 Table 22 the line "Assumption: 5% of patients receiving RTT discontinue annually (due to	The line should be replaced with "Assumption: 5% of patients receiving RTT discontinue annually"	Alloimmunisation including other adverse events results in discontinuation. Patients with risk of alloimmunisation are provided with matched blood donation. The rate of alloimmunisation is highly	Thank you for clarifying the meaning of the text in the CS. The EAG report has been updated as suggested.

alloimmunisation)" is not correct.		uncertain with published rates vary from 0% to 76% (CS, Table 29). There is lack of information of discontinuation rate from the literature. Thus, the assumption is made to use 5% as the discontinuation rate.	
5.3.11 Mortality, p. 55 The EAG states that "Using from CPRD/HES data, the company identified excess mortality rates associated with specific conditions (except stroke)."	Sentence should read "Using from CPRD/HES data, the company identified excess mortality rates associated with specific conditions (stroke had an additional one-off case fatality rate applied)"	The sentence is misleading in current form. Stroke has an excess ongoing mortality applied in the model, and a one-off case fatality.	Thank you for clarifying the meaning of the text in the CS. The EAG report has been updated as suggested.
5.3.12 Health-related quality of life, p. 55 The EAG states that "The company then mapped HOPE trial EQ-5D-5L data to EQ-5D-3L data using UK tariffs. This generated a HOPE trial baseline population mean utility value of 0.831 and led the company to estimate that the utility decrement due to SCD was 0.096 (SE=0.015)."	Additional sentence should be added to make clear that this was removed in the company's revised model.	Sentence not true for the company's revised model.	In line with the company suggestion, the following text has been added to the EAG report: "This utility decrement was removed in the company revised model (provided as part of the company clarification response)."

5.3.12 Health-related quality of life, p. 57 In Table 25 of the EAG report the treatment adherence for Voxelotor is incorrectly reported as [redacted].	This value should be corrected to [redacted]	The reported data is inaccurate; correct value is given in CS Table 40.	This is a transcription error. The EAG report has been updated.
5.3.12 Health-related quality of life, p. 57 In Table 25 of the EAG report the costs of regular transfusion therapy (per transfusions) are incorrectly reported; costs for 'patients receiving voxelotor' are incorrectly reported as costs for 'patients receiving SoC', and vice versa.	Values should be amended as follows. Patients receiving voxelotor: [redacted] Patients receiving SoC: [redacted]	The reported data is inaccurate; correct value is given in CS Table 40.	This is a transcription error. The EAG report has been updated.
Section 5.3.12 Health-related quality of life, p. 57 In Table 25 of the EAG report the costs of chelation therapy are incorrectly reported; costs for 'patients receiving voxelotor' are incorrectly reported as costs for 'patients receiving SoC', and vice versa.	Values should be amended as follows. Patients receiving voxelotor: [redacted] Patients receiving SoC: [redacted]	The reported data is inaccurate; correct value is given in CS Table 40.	This is a transcription error. The EAG report has been updated.

Section 5.3.12 Health-related quality of life, p. 57 In Table 25 of the EAG report the treatment annual cost of chelation therapy in adolescents is incorrectly reported as £9,880.89	This value should be corrected to £9,880.09	The reported data is inaccurate; correct value is given in CS Table 39.	This is a transcription error. The EAG report has been updated.
Section 5.4 Updated severity modifier, p. 59 In Table 27 of the EAG report the disease specific QALY shortfall values are incorrect.	The disease specific values should be amended as follows. Total QALYs: [redacted] Absolute Shortfall: [redacted] Proportional shortfall: [redacted]	The reported data is inaccurate; correct values are given in Clarification response, Appendix 1, Table 27.	The EAG report has been updated using the values suggested by the company.

Section 6 EAG critique of company cost-effectiveness model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
6.1 Introduction, p.62 The EAG states that "The company economic model is flawed due to the following important issues:" followed by this issue "If treatment with voxelotor leads to lower complication	This should be deleted.	This isn't a model flaw; it is an outcome of the analysis. It is driven by high discontinuation rates on Voxelotor (an assumption that can be modified and is tested in scenario analysis), and the impact of Hb level increase on complication rates.	The EAG accepts that this is not a model flaw. The bullet has been deleted and the following text has been added below the list of bullet points: "In addition, if treatment with voxelotor leads to

rates than SoC then any impact is likely to be limited”			lower complication rates than SoC then any impact is likely to be limited.”
6.1 introduction p.64 For reasons that the EAG has not been able to determine, the company updated model (provided as part of the company clarification response) does not allow patients to be treated with voxelotor for more than 5 years; the company base case model does not include a stopping rule. The EAG was, therefore, unable to replicate the company base case results and was also unable to produce results using confidential Commercial Medicines Unit prices for other treatments.	Sentence should be deleted.	This isn’t true and is directly contradicted by the Table 30 in the EAG report, p.65	The data presented in the EAG report, Table 30 were calculated from the voxelotor discontinuation rates provide in the CS. It was not necessary to run the model to obtain these numbers. No changes have been made to the EAG report.
6.1 Introduction, p.62 The EAG states “the company should not have applied a relative dose intensity (RDI) multiplier for life when	Justification for assertion should be added.	It is not clear why the relative dose intensity (adherence) collected in HOPE would improve in a real-world setting. There is no evidence to suggest relative dose intensity would increase over time.	This is a matter of opinion, not a factual inaccuracy. However, for clarity, additional text has been added to the EAG report as follows:

estimating the cost of treatment with voxelotor”			“the company should not have applied a relative dose intensity (RDI) multiplier for life when estimating the cost of treatment with voxelotor (an RDI multiplier calculated based on 72 weeks of data is unlikely to reflect lifetime RDI). Reducing the length of time an RDI is applied (or the magnitude of the RDI) would increase the cost of voxelotor and therefore increase the ICER per QALY gained.”

6.3.1 HOPE trial: voxelotor improvement in Hb level, p 63 Results from the HOPE trial showed that voxelotor was only statistically significantly better than SoC for a change in Hb level between baseline and Week 24. There were numerical differences between the trial arms for other outcomes, some of which favoured treatment with voxelotor (e.g., VOCs and leg ulcers) and some of which favoured SoC (e.g., ACS rates and annual transfusion rates). If numerical advantages are modelled as benefits, then numerical disadvantages should be modelled as detriments. The EAG considers that the statistical analysis performed by the company to generate the TTE probabilities used in the model is not robust and that any claim that treatment with voxelotor delivers more benefit than an increase in Hb level compared	Results from the HOPE trial showed that voxelotor was statistically significantly better than SoC for a change in Hb level and haemolysis markers (indirect bilirubin, change in % reticulocytes) between baseline and Week 24. There were numerical differences between the trial arms for other outcomes, some of which favoured treatment with voxelotor (e.g., VOCs and leg ulcers) and some of which favoured SoC (e.g., ACS rates and annual transfusion rates); However, the trial was not powered to detect these outcomes.		The EAG report has been updated in line with the company suggestions. "Results from the HOPE trial showed that voxelotor was statistically significantly better than SoC for a change in Hb level and haemolysis markers (indirect bilirubin, change in % reticulocytes) between baseline and Week 24. There were numerical differences between the trial arms for other outcomes, some of which favoured treatment with voxelotor (e.g., VOCs and leg ulcers) and some of which favoured SoC (e.g., ACS rates and annual transfusion rates). The trial was not powered to detect these outcomes. However, if numerical advantages are modelled as benefits, then numerical disadvantages should be modelled as detriments. The EAG considers that

with SoC should be viewed as highly uncertain.			the statistical analysis performed by the company to generate the TTE probabilities used in the model is not robust and that any claim that treatment with voxelotor delivers more benefit than an increase in Hb level compared with SoC should be viewed as highly uncertain."
6.3.1 HOPE trial: voxelotor improvement in Hb level, p 63 The EAG refers to "TTE probabilities"	Sentence should be amended to "TTE rate equations"	The equations predict an event rate not a probability	The EAG report has been updated as suggested by changing "probabilities" to "rate equations".
6.3.2 Impact of voxelotor on health-related quality of life, p 64 The EAG states that "The EAG considers this finding can be interpreted four ways" The last of the interpretations provided is "patients experience a HRQoL benefit from raised Hb levels, but this is outweighed by any	Interpretation 4 should be removed.	Presenting interpretation 4 as equally likely as the others ignores evidence from HOPE that AE rates were low and comparable between trial arms.	This is not a factual inaccuracy. The EAG explains in the text following these bullets that it is not clear which is the most likely explanation. The ordering of the EAG bullets has now changed in response to issues raised by the company (see below); interpretation 4 is

AEs linked to treatment with voxelotor”			now interpretation 3 (and has not been removed).
6.3.2, Impact of voxelotor on health-related quality of life, p 64 The EAG considers this finding can be interpreted four ways**:**	Add: • Other, unrelated to Hb, such as short recall period which creates high variability in a chronic disease with significant, severe, and frequent acute manifestations	May simply be related to a short recall period which creates high variability in a chronic disease with significant and frequent but short-term acute manifestations. Of note despite a 45% reduction in annualised VOC rate and a more than double proportion of patients with zero VOCs, no statistically significant difference in utility was achieved in the SUSTAIN phase II trial either (NICE TA 743)	The following additional bullet point has been added to the EAG report: • Other issues, not relating to Hb
6.3.2, Impact of voxelotor on health-related quality of life, p 64 • Hb levels do not influence HRQoL	Delete or replace with • Hb levels do not influence utility in SCD despite available evidence across diseases	Evidence from HOPE shows a statistically significant difference in HRQoL as measured by Clinical Global Impression of Change (CGIC) in the voxelotor arm compared to placebo at 72 weeks (and an improvement in Hb was observed in the voxelotor arm) (CS document B, Table 13). Other sources suggest an association between EQ-5D and HRQoL[18], data generated by the	The EAG has deleted this bullet point.

		company suggests the same association and numerous publications link anaemia (low Hb) to fatigue and reduced HRQoL[19,20]	
6.3.3 Regular transfusion therapy p 64 One of the values for proportion of patients receiving SoC requiring RTT is incorrectly reported as [redacted]: "Using a value of [redacted] rather than [redacted] decreases the cost…"	This value should be corrected to [redacted]	The reported data is inaccurate; correct value is given in CS Table 25.	This is a transcription error. The EAG report has been updated.
6.3.3 Regular transfusion therapy p 64 The EAG highlights that the Delphi panel considered that [redacted]%, not [redacted]%, of patients receiving SoC would receive RTT	Please correct, the [redacted] reflects expert´s input collected at the modified Delphi panel	During the modified Delphi panel, participants were asked to focus on the set of patients eligible to voxelotor to whom the nine experts would prescribe voxelotor if available because that set of patients would be the one benefiting the most from the drug. Of note, that "set of patients" need not be the same for all experts, there was no predefinition of the characteristics of those patients, each expert was free to "design his set".	Thank you for adding the extra detail about the origin of the [redacted]. value – all the information required to calculate this number were not provided in the CS (and addenda). However, the Delphi panel report (Table 6) appears to indicate that the value of [redacted]% is accurate. No changes have been made to the EAG report.

		Experts had been asked, in a previous question, what was the proportion of patients unwilling to take HC. For patients unwilling to take HC, the only option available is RTT (or nothing). Results from the modified Delphi panel indicate that [redacted] of patients willing to take HC are treated with RTT in the absence of voxelotor, and [redacted] of those unwilling to take HC are treated with RTT in the absence of voxelotor. Given that [redacted] of patients are unwilling to take HC, the weighted average of patients on RTT is [redacted] which is what was assumed in the model.	
6.3.3 Regular transfusion therapy p 64,65 The only transfusion-related evidence from the HOPE trial showed that there was no statistically significant difference between the voxelotor and placebo arms in	The only transfusion-related evidence from the HOPE trial is related to acute transfusion needs, therefore unrelated to RTT, and showed that there was no statistically significant difference between the voxelotor and placebo arms in terms of the annualised incidence transfusion rate over 72 weeks.	This refers to top-up transfusions used to treat acute events. This is not the topic being discussed in this section (RTT).	This is a transcription error. The EAG report has been amended as follows: "The only transfusion-related evidence from the HOPE trial showed that there was no statistically significant difference

terms of the annualised incidence transfusion rate over 72 weeks.			between the voxelotor and placebo arms in terms of the annualised acute transfusion rate over 72 weeks.”
6.3.3 Regular transfusion therapy p 65 The EAG stated “The EAG therefore considers it was inappropriate for the company base case to include baseline differences in RTT rates and that the company should have assumed the same RTT rate in both arms“	An additional statement should be added after listing the evidence in HOPE and before stating the EAG´s opinion. According to expert opinion gathered, namely, during the modified Delphi panel only in very special situations will a patient be treated with voxelotor and RTT. As RTT is intended to increase Hb levels and reduce the percentage of sickled cells. Pre-clinical and HOPE trial data demonstrate a similar effect of decreased sickling and increased Hb with voxelotor treatment, therefore, RTT and voxelotor are not used in combination. It is therefore not clinically plausible that the [redacted]% of voxelotor eligible patients currently being treated with RTT due to absence of voxelotor would keep the RTT therapy and add voxelotor on top of it once available.	Since voxelotor and RTT will not be prescribed simultaneously in the vast majority ([redacted]%) cases, and given the fact that [redacted]% of patients who would benefit from voxelotor if available according to nine UK experts are currently treated with RTT, the company sees it as implausible that both arms should have the same proportion of patients on RTT	This is a matter of opinion, not a factual inaccuracy. No changes have been made to the EAG report.
6.3.4 Impact of treatment with voxelotor on complication rates is limited, p.65	Suggest amending to “Percentage of patients entering the model still receiving voxelotor over time”	Clarifies that the denominator of the proportion is patients starting the model, not those	For clarity, the EAG has changed the title to “Percentage of model

The EAG states in the caption of Table 30 “Percentage of patients still receiving voxelotor over time”		surviving, i.e., dead patients are not receiving voxelotor	patients receiving voxelotor over time.”
6.3.5 The company model does not generate ICERs per QALY gained that are suitable for decision making, p.66 The EAG states that “These model changes resulted in a new average utility value of [redacted] for patients in the SoC arm. The company considered that this value was acceptable as it was in line with other published research in this disease area (0.648) .”	Suggest amending to “…The company considers that this value was acceptable because it is only slightly lower than the value derived from a utility analysis by age that was generated based on 220 SCD UK patients. There are two key reasons that support the company position: 1. Severity of disease – in the modelled population the Company expects a lower mean utility than that of the general population because the Company is modelling a more severely affected sub-group of SCD 2. Age – the published steady state values are taken from studies where the mean age is generally far lower than that of the mean age over the model lifetime. Given this, the company considers slightly lower average utility value acceptable”	Don’t believe EAG has accurately represented the company position.	This is not a factual inaccuracy. No changes have been made to the EAG report.

6.3.5 The company model does not generate ICERs per QALY gained that are suitable for decision making, p.67 The EAG states “a patient had ESRD without CKD (which should not happen in the model)”	This bullet point should be deleted	This patient had no simulated CKD event, but it is possible to have CKD on entry to the model and this would have correctly not manifested as an event in the patient history.	Thank you for the clarification. This detail was not provided in the model output shared with the EAG. This statement has been removed from the EAG report.

Incorrect AIC/CIC marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
3.2.1 Positioning of voxelotor, p.26 The EAG states that: “Clinical advice to the EAG is that, as the two drugs deliver different benefits, it is not appropriate to only position voxelotor after HC.”	The positioning of voxelotor should be marked CIC, as elsewhere in the report.	Clinical advice to the EAG is that, as the two drugs deliver different benefits, it is not appropriate to only position voxelotor after HC.	Thank you for pointing this out. The EAG report has been amended to reflect the CIC status of the text.

(Please add further lines to the table as necessary)

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR in section 1.1.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Friday 14th October 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Global Blood Therapeutics UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nothing to disclose**

Executive Summary

Thank you for the opportunity to respond to the technical considerations and areas of uncertainty as identified through the External Assessment Group (EAG) report. We have carefully considered the issues highlighted by the EAG and have developed a comprehensive and robust response which addresses these uncertainties. In addition, we have provided further evidence and materials which support voxelotor as a clinically and cost-effective treatment of haemolytic anaemia in patients with sickle cell disease (SCD). In summary our response includes and addresses the following:

1. Further clarification and argumentation is provided in relation to the clinical benefit of voxelotor. This includes further discussion of the relevance of the Company's [redacted] positioning, as well as further contextualisation of the relevance of an improvement in haemoglobin and the impact of voxelotor on future complications. In addition, further clarification and evidence is provided to support the positive impact of voxelotor on quality of life for patients and why it is appropriate to capture this improvement in the economic model.

2. An updated and revised economic model has been presented which addresses the EAGs concerns regarding robustness and is suitable for health technology assessment (HTA) decision making. The economic model also includes alternative base case model assumptions which further strengthen the robustness of the economic case.

3. [redacted]. The impact of the PAS and the post-technical engagement ICER are presented below within this Executive Summary. A full set of updated economic results are presented in the supporting Appendix 1: technical engagement analysis addendum.

4. Updated supporting documentation such as Appendices P and Q – derivation of HES and Symphony time to event (TTE) analyses respectively, are provided which present updated equations and correct any typographical errors. In addition, an

updated Appendix U – Delphi panel report, is available which contains further clarification regarding the derivation of the proportion of patients on regular transfusion therapy (RTT).

Updated agreed PAS discount for voxelotor

The agreed PAS discount for voxelotor has been updated from [redacted] to [redacted]. The updated PAS has been applied within this response and for reference, the base case from the Clarification stage of the process is presented in Table 1, alongside the company's preferred base case post-technical engagement. Please note that the preferred base case post technical engagement includes the adoption of additional base case assumptions which are presented in full in the supporting Appendix 1: technical engagement analysis addendum.

Table 1: Cost-effectiveness results

	Post-clarification base case	Post-technical engagement base case
ICER versus SOC	[redacted]	[redacted]
ICER: incremental cost-effectiveness ratio; SOC, standard of care		

HTA context and health inequalities

Health inequalities are unfair and avoidable differences exist in health across the population, and between different groups within society.[1] In the recent appraisal for crizanlizumab (TA743)[2] it was acknowledged that there is an unmet need for effective treatments for people with SCD. People with SCD face health inequalities because the condition is not well understood, results in disability, and is more common in people of African or African-Caribbean family origin, who tend to have poorer health outcomes and experience higher levels of social deprivation than other ethnicities in the UK.

Tackling health inequalities forms parts of the NHS long term plan. The COVID-19 pandemic, with its disproportionate impact on those already disadvantaged in society, has brought the issue of health and wider inequalities into sharp focus. The NICE 2021-2026 strategy refers to the organisation's need to enhance their offer and strengthen the role it plays in reducing health inequalities.[3]

Conclusion

As outlined in the company submission, voxelotor address an important and relevant unmet need for safe and effective treatments for patients with haemolytic anaemia due to SCD. The company's [redacted] positioning is appropriate and reflects where voxelotor will be used in clinical practice following robust consultation with clinicians. The inclusion of an [redacted] and revised model assumptions address the uncertainties as reported by the EAG and the updated base case ICER is within a threshold considered cost-effective by NICE, for medicines for severe diseases in neglected patient populations. Therefore, we believe that voxelotor represents a clinically and cost-effective treatment option in a disease area with a high unmet need and significant patient inequity and should be made available for patients within the National Health Service (NHS).

Key issues for engagement

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: The company's positioning of voxelotor is problematic	No	The company has used the term [redacted] to describe the positioning of voxelotor in the submission, following consultation with clinical experts (see Delphi panel report, CS appendix U). The company recognises that terminology around lines of treatment is not exact and is open to different interpretations. The detailed rationale for the choice of this population, and for its designation as [redacted] is set out below. This population corresponds well to that in the HOPE study; the rationale for this is also given below. **Definition of [redacted]** Hydroxycarbamide (HC) is an established treatment that is recommended by the British Society of Haematology for all SCD patients.[4] HC can thus be regarded as 'first line treatment', insofar as HC will be considered for every patient ***prior to*** any other treatment. This characterisation is widely confirmed by health-care professionals, treatment guidelines and by the company. The company defined [redacted] patients as patients who are [redacted]; this is the positioning of voxelotor for the submission. These patients can be described as follows:

		[redacted] **Choice of population and position in therapy** The population for the submission is "adults and paediatric patients aged 12 years or older with SCD [redacted]" (CS, B1.1). This is the population in which voxelotor is likely to be used in clinical practice in the NHS, as confirmed by: • UK clinicians consulted for the modified Delphi panel (CS Appendix U). • The submission by the Royal College of Pathologists (RCP) (TE papers item 3e) confirms that some patients are assessed as [redacted] and require alternatives. The RCP respondent states that "There is a need for an alternative treatment that can improve haemoglobin and haemolysis in sickle cell disorder. Hydroxycarbamide has the potential to improve both to a similar level as voxelotor, but a number of people do not tolerate hydroxycarbamide or are 'non-responders'. Because of concerns about fertility and fears of using an anti-cancer drug, patients are sometimes reluctant and prefer to opt out of treatment for these reasons. Blood transfusion (exchange or top up) will also improve these parameters, but is more invasive than an oral treatment. There is a risk of iron overload in the more anaemic

		sickle cell patients. Some patients become hard to transfuse due to the development of allo-antibodies. A number of sickle cell patients are members of Jehova's Witness communities and do not wish to receive blood products. Voxelotor fulfils the need for disease-modifying treatment in these groups." This population is clearly defined, clinically appropriate and reflects the position where voxelotor is likely to be used in the NHS (consistent with NICE recommendations that assessments reflect clinical practice). **Differing interpretations of the term "[redacted]" should not be a barrier to consideration of this population by NICE. If NICE prefers, the designation "[redacted]" can be modified and the population can be referred to simply as "patients who are [redacted]"** **The trial evidence is applicable to the submission population** The inclusion criteria for the HOPE trial did not require documentation that patients were [redacted] However, as previously stated in the CS (B.1.1 and B.2.12.2) and the CQ response, it is reasonable to assume that most patients in HOPE fell into this category: • Two-thirds of patients (64% and 63% in voxelotor 1500 mg and placebo groups, respectively) were already taking HC when they and their physicians decided they should enter a trial of an investigational product. It is reasonable to assume that this decision was made because current management of their SCD was not optimal (i.e. they had inadequate efficacy from HC alone, and therefore fall within the submission population).

		○ A prespecified subgroup analysis showed that the effect of voxelotor on Hb was not significantly different between patients who were on HC and those who were not. ○ Given the different mechanisms of action of HC and voxelotor, there is no reason to assume that voxelotor would have a different treatment effect (as measured by haemoglobin (Hb) response) in patients who were documented as [redacted] for HC compared with the effect seen in the HOPE trial population. • There is an international consensus that all patients with SCD should be offered HC; this is reflected in numerous guidelines, including those from the British Society of Haematology.[4] HC is available in all the countries in which HOPE was conducted. In clinical trials it is common practice to only enrol patients who have no licenced alternatives that are suitable for that patient. It is thus unlikely that for patients in HOPE who were not taking HC, HC had not been either considered or used for them in the past. However, the reasons for patients not being on HC at baseline were not captured in the case report form. In summary, the population in HOPE is sufficiently representative of the submission population.
Issue 2: It is unclear if an increase in haemoglobin of >1g/dL is clinically meaningful for people with haemolytic anaemia in sickle cell disease	Yes. The full analysis by Telfer et al.[5] was not available at the time of the original submission. The figure from Howard 2019[6] was not presented in the original submission.	The clinical relevance of an Hb increase of >1g/dL seen with voxelotor is evidenced by several different factors, described below. **Clinical relevance has been confirmed by regulatory bodies** The European Medicines Agency (EMA) has stated that: "there is a high unmet need for medicines to treat haemolytic anaemia, which is experienced to various degrees by all SCD patients."[7] Voxelotor was approved for haemolytic anaemia in SCD by the EMA and Medicines and Healthcare products Regulatory Agency (MHRA) on the basis of

		the proportion of patients achieving an increase in Hb of >1g/dL with voxelotor. The EMA states that: "Treatment with voxelotor has resulted in a beneficial effect in terms of reduction in haemolysis and an increase in Hb, which are considered of clinical relevance to the patients."[8] **Increased Hb with voxelotor is a marker of reduced disease activity** Haemolytic anaemia in SCD results from increased rates of haemolysis (breakdown of red blood cells), caused by repeated sickling due to the polymerisation of HbS (the abnormal Hb present in SCD). As set out in the CS (B.1.3.1.1): • HbS polymerisation results in a cascade of pathological events, starting with RBC sickling and haemolysis and leading to haemolytic anaemia, blood vessel damage (vasculopathy) and vaso-occlusion (including VOCs). This results in reduced oxygen delivery to the tissues, and chronic sterile inflammation caused by the presence of free cell contents in the blood.[9,10] • Together, these pathologies cause a range of acute and chronic severe complications, including progressive organ damage and associated symptoms and comorbidities. Voxelotor acts by inhibiting HbS sickling, which reduces haemolysis and thereby both increases Hb levels and reduces the other effects of haemolysis the pathological cascade as described above. **The increase in Hb levels seen with voxelotor is therefore a marker of reduced disease activity, rather than simply an isolated occurrence.** The same is not true for transfusions, where an increase in Hb is not related to an improvement in disease activity. The effect of voxelotor on the percentage of irreversibly sickled cells is shown in Figure 1 below.

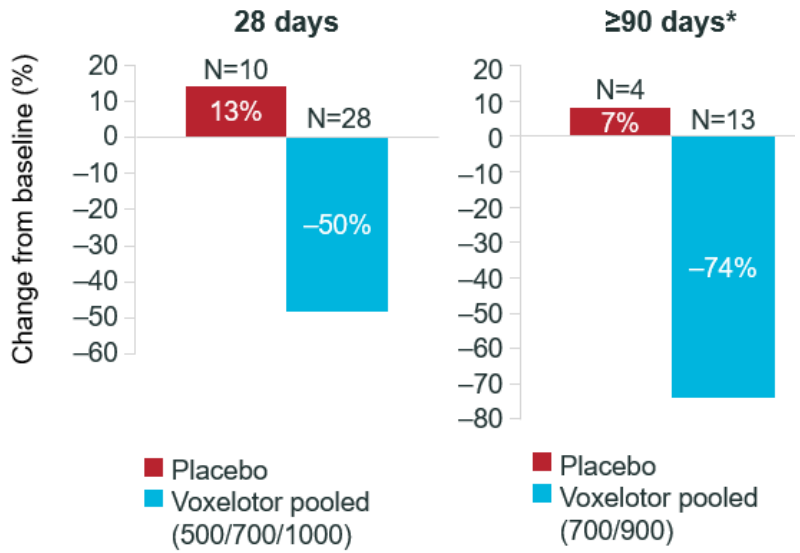

Figure 1 Percentage change in irreversibly sickled cells from baseline after treatment with voxelotor or placebo.

Data from Howard et al. 2019[6]. *90 days to 6 months of dosing (two patients had 90 days of dosing, one patient had 118 days of dosing, and four patients had 6 months of dosing).

Voxelotor's effect in reducing disease activity at the physiological level explains the association between higher Hb levels and improved outcomes, described below.

The RCP submission (TE papers item 3e, p. 3) stated that: "Voxelotor has a unique ability to keep oxygen bound to haemoglobin which results in less cell destruction and improvement of anaemia as well as rate of haemolysis. Some of the long-term morbidities in sickle cell disorder are directly related to the degree of anaemia and/or haemolysis and voxelotor has the option to target

		both. The reduced strain on bone marrow can also improve fatigue and quality of life for people with this chronic disorder." **Increased Hb is associated with improved outcomes in SCD** There is considerable evidence for the relationship between higher haemoglobin (Hb) and improved outcomes in SCD (and lower Hb and poorer outcomes), as presented in the CS p. 123-124 and summarised here: • A meta-analysis by Ataga et al. of 41 studies (mainly retrospective and prospective cohort studies) showed lower haemoglobin concentration was consistently associated with higher incidence or history of stroke, silent cerebral infarct, increased transcranial doppler (TCD) velocity, albuminuria, pulmonary hypertension and mortality, in SCD patients of all ages (see Section B.1.3.1.2).[11] • Ataga et al. also conducted a risk-reduction meta-analysis, and found that the modelled risk reduction for negative clinical outcomes decreased at all modelled levels of increased Hb concentration. An increase in Hb of ≥1 g/dL predicted risk reductions of 41% for stroke/silent cerebral infarct, 53% for albuminuria, 57% for elevated estimated pulmonary artery systolic pressure (PASP) and 64% for death.[11] The authors concluded that even modest increases in Hb may be beneficial in SCD. • An association between Hb levels and TTE for a range of outcomes was found in the Symphony health claims database see appendix P (revised version submitted at technical engagement) for details. • An association between Hb levels and TTE for a range of outcomes was also found in the HES/CPRD database see Appendix Q (revised version submitted at technical engagement) for details. • *Figure 2 demonstrates the hazard ratio per 1 g/dL increase in Hb for the risk of complications from the Symphony and HES/CPRD

databases. Across both datasets there is generally very good alignment for most complications, showing a robust link between Hb and risk of complications.

- An additional analysis of HES/CPRD by Telfer et al.[5] found that an increase in Hb of 1 g/dL was associated with a statistically significant reduction in risk for six common end organ damage outcomes and clinical complications (leg ulcer, pulmonary hypertension, chronic kidney disease, end-stage renal disease, acute chest syndrome and stroke; see Section B.1.3.1.2 for details) over a 12-year period. Evidence is also available from a number of studies published after the inclusion date for the Ataga et al. meta-analysis, as described in Section B.1.3.1.2.
- Analysis of data from approximately 4,000 SCD patients, who at enrollment ranged from birth to 66 years, from the Cooperative Study of Sickle Cell Disease (CSSCD), showed patients with the lowest Hb levels had an increased risk of death.[12] Subsequent analyses from this long-term cohort dataset were also included in the Ataga et al. meta-analysis.[11]

Figure 2 Hazard ratio for each 1 g/dl increase in Hb derived from the Symphony TTE analysis weighted to HES-CPRD vs the HES-CPRD analysis.

Evidence on non-Hb outcomes with voxelotor

Evidence on non-Hb outcomes seen with voxelotor, e.g. a reduction in leg ulcers in the HOPE trial, and reduction in hospitalisations and use of concomitant medication in the Symphony database, also support the clinical benefits arising from treatment. This is described in more detail under Issue 3.

Summary

The positive decision by the regulatory authorities, the status of Hb level with voxelotor as a marker of disease activity in SCD, the evidence showing that

		higher Hb is associated with improved outcomes in SCD, and the evidence of real-world patient-relevant benefits with voxelotor, all confirm that the Hb increase of 1g/dL seen with voxelotor is clinically meaningful. The use of real-world evidence to resolve gaps in knowledge is one of the stated aims of the NICE Real World Evidence Framework and the real-world evidence provided by the company meets NICE's standards for data quality.[13]
Issue 3: The impact of voxelotor on long-term complications is unknown	No	The chronic complications resulting from the pathology of SCD evolve over time, and worsen as patients get older. The HOPE trial was not designed to show an effect on chronic complications, as these require a longer time scale, and different population at baseline as well as potentially more patients for evaluation. The link to long-term outcomes in the modelling is therefore made using associations between Hb concentration and outcomes of interest based on TTE equations derived from the HES/CPRD databases and validated using equations derived from the Symphony database. These are all typical when modelling treatments for chronic conditions, where surrogate endpoints are frequently used. The relationship between Hb and these outcomes is robust, as discussed in relation to Issue 2, above. **Non-Hb outcomes with voxelotor** ***In HOPE*** The principal endpoints in HOPE were Hb-related and the trial was not designed or powered to study the impact on VOCs or other SCD-related complications. However, patients treated with voxelotor had numerically lower incidences of VOCs than the placebo group[14] and there was a potential clinical benefit for patients with leg ulcers;[15] although these differences did not reach statistical significance, for either outcome. Leg ulcers are a painful and often debilitating complication of SCD. A published post hoc analysis of leg ulcers in HOPE over 72 weeks showed that 5 of 5 patients with leg ulcers in the voxelotor 1500 mg group and 8 of 9 in the 900 mg group had their leg ulcers improve or resolve by week 72, compared with 5 of 8 in the placebo group.[15] During the 72-week treatment period, nine additional

		patients developed new leg ulcers: one in the voxelotor 1500 mg group (mild severity), three in the 900 mg group (two mild, one moderate), and five in the placebo group (three mild, two moderate).[15,16] This suggests that voxelotor has a potential clinical benefit on leg ulcers, [15] (See CS Section B.2.6.7). The HOPE open label extension study (OLE) is ongoing, with a currently planned end-date in Oct 2024. HOPE OLE will continue to deliver Hb and haemolysis data to demonstrate the sustainability of the treatment effect with voxelotor and report on long-term safety. However, the OLE is not designed to deliver data on other outcomes as it does not contain a comparator arm and does not allow for meaningful comparisons to baseline. In addition, the drop-out of patients over time, e.g. due to voxelotor becoming commercially available in additional countries, reduces patient numbers and introduces bias. ***Real-world evidence for voxelotor*** Voxelotor has been commercially available in the US since 2019, and the positive clinical impact of voxelotor has also been confirmed by real-world evidence from there. A published analysis of voxelotor-treated patients in the Symphony database demonstrated statistically significant and clinically meaningful reductions in annualised rates of hospitalisations, transfusions and vaso-occlusive (VOC) events, and reduced use of iron chelation and opioids[17] (presented in CS Section B.2.6.9). According to the NICE RWE framework, RWE can be used to reduce uncertainties and resolve gaps in evidence. The use of RWE in situations where trials are based on unvalidated surrogate outcomes is specifically mentioned in the RWE framework.[13] The company respects the hierarchy of evidence highlighted in the RWE Framework and is confident that real world data submitted by the company meets the standards on data quality (specifically, with regard to provenance, transparency and minimisation of bias) set out in the RWE Framework. To ensure fair and transparent implication by NICE of its own methods and

		processes, this evidence should be considered. The company will continue to analyse Symphony data and are conducting a prospective registry in the US. **Summary** Data on the effect of voxelotor on the incidence of long-term complications of SCD are not yet available. However, there is strong evidence that meets NICE's standards for acceptability, to support the link between Hb levels and outcomes in SCD, which in turn supports the expectation that voxelotor will reduce the risk of long-term complications.
Issue 4: Methods used by the company to generate time to event probabilities are not robust	Yes, Cost-effectiveness analysis has been conducted using updated TTE equations, shown in Appendix 1: technical engagement analysis addendum	To address the EAG's comments in the EAR, the company has made several changes to our approach in the base case outlined below: • Appendices P and Q, containing the reports of the TTE analyses, have been updated and supplied as part of the technical engagement response. Updated tables of the equations used in the model, have also been supplied in the revised results addendum following technical engagement. An updated appendix R was not required for the updated analysis so has not been supplied. • Following a suggestion in the EAR, the HES-CPRD dataset was used directly to derive TTE equations. This means that the model TTE equations are derived directly on the linked HES-CPRD records of a sub-set of the entire UK SCD population. Thus, there is no longer the requirement to match patients in the US Symphony database to the UK SCD population. The updated validation section (Appendix 1: technical engagement analysis addendum; Section 3, pg.23) shows very good agreement between our model simulations for event occurrence at 5 years, and Kaplan Meier estimates from the HES-CPRD analysis. • The parameterisation of the TTE equations has been adjusted as follows:

		• The number of VOCs in the prior year was changed from a continuous variable and replaced with two categorical variables (1) 1–4 VOCs and (2) ≥ 5 VOCs. • The interaction term between the number of VOC events in the prior year and the Hb level was removed. The continuous variable and interaction terms were causing some issues with model stability. For patients entering the model with a very high number of VOCs, some degree of runaway effect was observed, where the incidence rate of VOCs and then the events that depend on VOCs gets ever higher throughout the model. • Cardiomegaly and priapism as events were removed from the model. These events had very little impact in either terms of cost (cardiomegaly) or utility (priapism) and no impact on mortality (both). In the interests of simplifying the model equations and the model itself, it was felt that these events could be removed without biasing the results in either direction. • Following the prior changes, during model validation it was observed that the incidence rate of VOCs over the first 5 years was less than the mean number of VOCs in the year prior to baseline in the HES cohort. We tested other TTE equation forms and found that the log-logistic equation best fitted the 5-year event occurrence and incidence rate for VOC. With the implementation of the changes described above, along with the correction of typographical errors in appendices P and Q, the reliability of both the methods used and the TTE equations generated thereby is assured,
Issue 5: The modelled impact of treatment with voxelotor on health-related quality of life is not supported by trial evidence	Yes, additional sources of evidence supporting the association between changes in Hb and HRQoL.	The Company does not agree that modelling an Hb-related utility benefit is inappropriate. It is common for phase 3 trials, and more so in rare diseases, to show no significant difference in HRQoL scores between treatment arms, as they are powered for efficacy outcomes only.

Why was a benefit in utility in favor of voxelotor not demonstrated in the HOPE trial when a statistically significant increase in Hb was demonstrated?

Limitations of the EQ-5D data in HOPE

Several factors may explain the fact that voxelotor showed no significant effect on HRQoL as measured by EQ-5D in HOPE. Of note, HRQoL was also measured using the Clinical Global Impression of Change (CGIC) measure, and more patients in the voxelotor 1500 mg were rated as improved compared with the placebo arm. These points are elaborated below.

Missing data

The power of the HOPE trial to assess HRQoL outcomes was limited by the large amount of missing data for EQ-5D; only [redacted] of 90 patients in the placebo group and [redacted] of 90 in the voxelotor 1500 mg group had a baseline value. The number who had a change from baseline value at Week 24 was [redacted] and [redacted] respectively, falling to [redacted] in both arms at Week 72 (CSR Table 14.2.15.1, summarised in Table 1 below).

The power of between-arm comparisons at different time points is also limited by missing data: the number of patients with data was 63 and 64 for placebo and voxelotor 1500 mg respectively at Week 24, with lower numbers at the preceding assessments. At 72 weeks the number fell to [redacted] and [redacted]. The amount of missing data further reduces the statistical power to detect significant between-arm differences in scores, and reduces confidence in the robustness of the data, as values may not be missing at random

Table 1 Number of patients with EQ-5D data available at each time point, HOPE trial

	Placebo (N=92)	Voxelotor 1500mg (N=90)

Timepoint, weeks	Patients with data N (%)	Patients with CFB value N (%)	Patients with data N (%)	Patients with CFB value N (%)
0 (baseline)	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]

CFB: change from baseline
Source: CSR Table 14.2.15.1

High baseline EQ-5D levels

As noted in the CS [p. 87 and 136], the mean utilities recorded in both groups in HOPE were unexpectedly high: they were very close to population norms for the UK and higher than utilities reported in the literature for SCD patients.[18,19] This value may not reflect the considerable burden of the disease.[20] The high baseline makes it difficult to detect improvements. In addition, as noted by the EAG, EQ-5D may also be insufficiently sensitive to capture all the HRQoL effects associated with SCD.

Effect of long-term complications on HRQoL is not captured in HOPE

		HRQoL in SCD will be strongly influenced by the presence of long-term complications, which develop over a longer timescale than that covered by the HOPE trial. Complications are associated with reduced HRQoL (utility decrements), as can be seen from the literature (see CS Section B.3.4.4.2, p. 131, Table 36). Due to its mechanism of action, as described in Issues 2 and 3 above, voxelotor is expected to slow the development of these complications. This in turn is expected to slow the decline in patients' HRQoL that would occur in the absence of disease-modifying treatment. Thus, an important part of voxelotor's HRQoL benefit will be realised through prevention of HRQoL decline, and this aspect is not captured in the trial EQ-5D data as the duration is too short. ***Validity of EQ-5D in SCD*** The Office of Health Economics (OHE) report that generic measures of HRQoL like EQ-5D in certain contexts fail to capture relevant aspects of QoL. They highlight in the case of SCD there has been relatively little research testing the validity of EQ-5D in SCD, which in part may be explained by the lack of funding for research in SCD compared to other similar diseases, such as cystic fibrosis. Furthermore, fatigue, a major component of SCD, is not captured explicitly in the EQ-5D and therefore, EQ-5D may lack validity in SCD patients, as it does in multiple sclerosis.[21] This may explain, in part, why improvements in HRQoL were not detected by EQ-5D in the HOPE trial. **Evidence to support the association between Hb level and HRQoL** The NICE RWE framework outlines that in the absence of randomised controlled trial data or where randomised evidence is not sufficient, RWE should be used to fill evidence gaps. RWE has already been widely used in evaluating the effects of medical devices and procedures and is becoming more frequently used in regulatory approval of medicines.

		An analysis was performed on data from the Patient Journey survey, a study enrolling patients (n = 253) with SCD from the UK (17.19%), France (17.79%), Brazil (17.79%), Germany (13.04%), Spain (11.86%), Italy (11.86%), and Canada (9.88%). Survey data collected included demography, symptoms, current and previous treatments, Hb levels, and HRQoL, among others. HRQoL was measured in the survey using the EQ-5D-3L questionnaire. To assess the relationship between Hb levels and HRQoL, linear models of utilities as a function of Hb were adopted including patient age as a covariate (See CS Section B 3.4.4.3 and Appendix T for more details). The resulting estimated utility increment per 1g/dL increase in Hb was calculated to be 0.047 (p <0.00001**Error! Reference source not found.**). This relationship was applied in the model to all patients, irrespective of treatment arm. **Justification for modelling an Hb-related utility benefit** SCD is a systemic progressive disease associated with a range of chronic and acute events. SCD-related adverse outcomes extend far beyond the list of comorbidities explicitly modelled in the economic model. For example, as part of the National Heart Lung and Blood Institute Cure Sickle Cell Initiative, Johnson et al.[22] recently identified 26 acute and chronic events that were considered, by a wide range of stakeholders, as critically relevant and have a significant impact of HRQoL and resource use (Figure 3). The set of complications explicitly modelled in the CS was determined in part by the need for simplification inherent to any model and, on the other hand, the limitations of the data available.

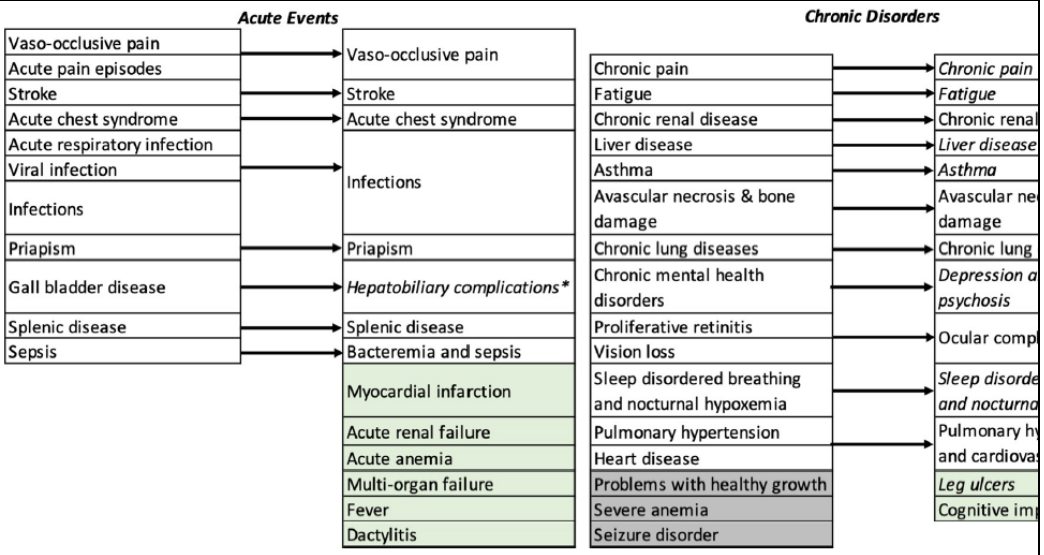

Figure 3 List of critically relevant complications identified by Johnson et al.[22]

Several complications with well-established links to lower HRQoL in non-SCD patients were not included in the CS model due to data limitations, such as fatigue, anaemia, hypoxemia, fever, cognitive impairment and retinopathy. It is reasonable to assume that these events would impact SCD patients a similar way they impact non-SCD patients.

The link between increasing Hb levels and reduced incidence of some of these excluded complications has been demonstrated (anaemia by definition, cognitive impairment,[23] nocturnal and diurnal hypoxemia[24], retinopathy[25], silent cerebral infarct[26], fat embolism syndrome[27], etc). Furthermore, the incidence of others, such as acute hepatopathy[28] result from the sickling process and are therefore expected to be, at least partially, prevented by increases in healthy red blood cells.

		While some of these adverse outcomes occur infrequently or have a limited impact on HRQoL, SCD is a chronic and progressive disease and over their lifetime the number of complications that SCD patients are at risk of causes a major impact on HRQoL. Demonstrated by patient experts consulted in the context of the NICE TA743[29] ***"(…) build-up of complications over time and resulting organ damage significantly affects their quality of life***." This applies especially in the target population being considered for voxelotor which is a subset of SCD patients with a high unmet need, where the disease *is* progressing, and end-organ damage *is* occurring despite treatment with available options. Excluding these comorbidities from the CS model would result in an underestimation of the treatment effect of voxelotor. To capture the long-term benefits of increased Hb level without adding comorbidities/events and overcomplicating an already sophisticated model, a benefit associated with increased Hb was considered. Of note, in the model, this benefit is assumed to apply to both treatment arms irrespectively. Based on expert opinion, ***such an assumption is conservative***. According to expert opinion consulted on October 10th 2022, the impact of regular red blood cell transfusions (RTT) on HRQoL is limited since patients feel a boost within the first couple of weeks post transfusion but they feel progressively worse over the course of the following weeks leading up to the next transfusion session 6-8 weeks from the previous. More than that, according to the experts consulted, the improvement in HRQoL observed in the first couple of weeks seems to occur at the early stages of the program but reduces as time on RTT increases. **Summary** Considering the evidence presented above describing the relationship between Hb levels in SCD patients and the development of complications, which adversely impact HRQoL, the company believe that the approach taken to model HRQoL benefits associated with Hb is appropriate. The response also explained why improvements in HRQoL were not able to be demonstrated in

		the pivotal clinical, and therefore, why an alternative source was required to estimate HRQoL. Furthermore, there is precedent for NICE to consider submissions where utility benefits were undetected in the pivotal trial, further reiterating the difficulty of capturing HRQoL improvements in SCD patients. Finally, it justifies attributing a benefit to voxelotor as a reasonable approach.
Issue 6: Inappropriate regular transfusion therapy rates	No, Delphi panel updated only to provide clarification	The EAG considers that "at baseline, the SoC arm of the company model should not include RTT as a treatment" and states that "The company should have assumed the same proportions of patients were receiving RTT in both arms or, preferably, modelled the risk of having RTT." [EAG Report p.13] Patients on regular transfusion therapy (RTT) were not eligible for inclusion in the HOPE trial as transfusions would have confounded the Hb-related endpoints. Nevertheless, the Company recognises that blood transfusions are an important part of second line treatment for patients with haemolytic anaemia in SCD, as set out in British society of Haematology guidelines on transfusions[30,31] and the NICE Spectra Optia guidance.[32] Because they are an important part of management for some patients, the Company believes it is appropriate and necessary to include RTT as a treatment in the SoC arm. **Source of RTT rates in the economic model** • The company consulted nine practising English clinicians who are experts in SCD in a modified Delphi panel exercise (report presented as CS Appendix U), following NICE DSU guidelines. In the absence of any other data on the proportion of patients receiving RTT, this is best available data source. • The proportion of patients receiving RTT in the model was [redacted]%. This was derived from the Delphi panel as follows: Given that "Table 6. Treatment utilisation before and after voxelotor introduction among adults with SCD", in Appendix U refers to patients

		[redacted], a follow-up question was sent to the experts asking how patients [redacted] are currently treated. • A weighted average between the [redacted] was calculated as per the following (Table 8 in Appendix U the revised Delphi panel report, shown below) [redacted] **Treatment of RTT in the crizanlizumab appraisal** The company notes in the recent crizanlizumab submission in SCD the submitting company included a proportion of regular transfusion therapy in the SoC arm, despite patients on RTT being excluded in the SUSTAIN registrational trial. Thus there is a precedent to this approach
Issue 7: The company model generates clinically implausible individual patient simulations	Yes, an updated model has been supplied see Appendix 1: technical	The EAR highlighted the EAG's concerns that the model was generating substantial numbers of clinically implausible patient simulations. The EAR suggests that one of the reasons for this was that post-event mortality for certain events was not being accurately accounted for. While the prior model was incorporating the long-term excess risk of mortality from these events it

Age 18+	Without voxelotor			With voxelotor		
Treatment options	[redacted]	[redacted]	Weighted average	[redacted]	[redacted]	Weighted average
Percent of patients (from question 4.5.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regular transfusions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Voxelotor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* It was assumed that the proportion of patients on regular transfusions + voxelotor is independent of willingness to take HC status
Abbreviations: HC = Hydroxycarbamide

	engagement analysis addendum for further details	was considered that the risk of mortality immediately after certain events wasn't being captured. Reviewing the literature, the company determined that there were several events for which the immediate risk of death wasn't included. Using sources derived from the literature the company added additional one-off mortality risk to ARF, Arrhythmias, Heart Failure, and Sepsis. After the addition of these excess one-off mortality rates, the proportion of patients with a large number of certain events was considerably reduced. In their report the EAG called into question the face validity of the model with the explanation that there were meaningful numbers of clinically implausible patient profiles generated in the base case analysis (e.g., a patient with over 100 cardiomegaly admissions). Whilst it is almost impossible to state with any degree of certainty when a clinically implausible patient profile becomes plausible, it is acknowledged that there were several modelled patients with event counts, for example in acute renal failure, where survival would not be likely. To illustrate this visually, we constructed event histograms. In the model analysis submitted at CQs, although the number of patients having large numbers of ARF events is low, there were patients who experienced over 100 events (*Figure 4). In the revised modelling submission (*Figure 5), we can see clearly that the number of patients experiencing large numbers of events has reduced, indeed the total proportion of patients in the model experiencing 100 or more, 50 or more, and 20 or more events was [redacted]%, [redacted]% and [redacted]% respectively, compared to [redacted]%, [redacted]% and [redacted]% in the previous version. This is expected model behaviour with the revised mortality parameterisation, as now each ARF event has a one-time risk of mortality of [redacted]% (Appendix 1: technical engagement analysis addendum; Section 1.1.2, pg.9). This pattern is repeated across all recurring events in the model with the exception of VOC, which is to be expected given that VOC events do recur frequently in the population used in the model.

		[redacted]Figure 4 – Event frequency distribution for ARF in the standard of care arm (as of per the prior base case model supplied in the first results addendum) **[redacted]Figure 5 Event frequency distribution for ARF in the standard of care arm (as of per the current base case model supplied in the second results addendum)** Another criticism the EAG made of the model was that the mean utility value generated in the SoC arm was lower than estimated using company data ([redacted] vs approx. [redacted] for age matched estimate from the real-world analysis of the relationship between age and EQ-5D based utility among 220 SCD patients in the UK (Appendix T). The revised model now predicts mean utility in the SoC arm of [redacted] (Appendix 1: technical engagement analysis addendum; Section 3.1, pg.23), which agrees very well with the company estimates. An additional change made to address the plausibility issue was that gallstones has been changed to non-recurring event. The cost applied in the model is for gallstones removal, therefore this should only be allowed to happen once.

Additional issues

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Is voxelotor expected to show improved clinical outcomes and health-related quality of life compared with standard care? [Issue raised by EAG]	Issues 2, 3 and 5	No	Yes, voxelotor is expected to show improved clinical outcomes and health-related quality of life compared with standard care. Voxelotor is indicated by the MHRA for the treatment of haemolytic anaemia due to sickle cell disease in adult and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide (hydroxyurea).[33] The population covered by the submission is [redacted]." SoC for these patients (which is the comparator in the economic model) consists of HC only, regular transfusion therapy (RTT), RTT + HC, or symptomatic (supportive) care only. These patients currently have no pharmacological disease-modifying options for the treatment of haemolytic anaemia; RTT results in a temporary increase in Hb that wanes between transfusions, but is not indicated for the treatment of haemolytic anaemia (as confirmed by BSH guidelines[31] and by clinicians consulted by the Company at Technical Engagement phase). On its approval of voxelotor, the EMA noted that there is a high unmet need for treatments for haemolytic anaemia.[7] The MHRA Public Assessment report states that "There is an unmet need in significant proportion of patients with sickle cell disease who do not respond adequately to currently available treatments or in whom these treatments cannot be administered due to intolerability."

			Voxelotor is the first and only medicine approved specifically for the treatment of haemolytic anaemia in SCD, and was approved on the basis of beneficial effects on haemolysis and Hb levels, which were considered as being clinically relevant for patients.[8] The MHRA states that "The observed improvement in blood haemoglobin levels after treatment with voxelotor therefore offers a significant benefit in the management of patients with sickle cell disease.[33]" The evidence confirming that the impact of voxelotor on Hb is clinically meaningful is set out in response to Issue 2, and the evidence supporting voxelotor's expected beneficial impact on long-term complications of SCD is set out in response to Issue 3. As occurs with many trials, the EQ-5D data collected in the HOPE trial do not show a significant difference in HRQoL between treatment arms. Potential reasons for this are discussed in the response to Issue 5, together with real-world evidence indicating that patients do experience improvements to their health status with voxelotor. The HRQoL benefit of voxelotor is expected to become further apparent over time due to the expected reduction in patients' risk of long term SCD-related complications, compared with standard of care. Taken together, the information presented in the TE responses clearly indicates that patients experience improved clinical outcomes and HRQoL compared with standard of care, and that the difference between voxelotor and SoC can be expected to increase over time.
Additional issue 2: How long are people expected to be treated with voxelotor for? [Issue raised by EAG]		No	No additional evidence or discussion is provided regarding this issue at this stage.

Summary of changes to the company's cost-effectiveness estimate(s)

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 4: Methods used by the company to generate time to event probabilities are not robust	• TTE equations were derived using the Symphony database, matched to the HES patient population • VOCs were considered as a continuous variable • Model included cardiomegaly and priapism events	**Change 1** • Used the HES-CPRD dataset directly to derive TTE equations • Altered the parameterisation of VOCs, to a categoric variable, in the TTE equations • Removed cardiomegaly and priapism as events in the model. • See Appendix 1: technical engagement analysis addendum; Section 1.1.1, pg.23	[redacted](+20.7% vs prior base case)
	• VOC TTE equation was exponential	**Change 2** • Changed VOC TTE equation to log-logistic	[redacted](-18.2% vs change 1)
Issue 7: The company model generates clinically implausible individual patient simulations	• Long-term excess risk of mortality was applied for ARF, arrhythmias, heart	**Change 3** • Additional one-off mortality risk to ARF, arrhythmias, heart failure, and sepsis.	[redacted](+6.9% vs change 2)

Technical engagement response form

	failure, and sepsis events	Sources derived from literature	
	• Patients could experience multiple gallstones events	**Change 4** • Gallstones has been changed to non-recurring event	[redacted](+0.5% vs change 3)
Issue 6: Inappropriate regular transfusion therapy rates	• No change in Hb levels for RTT	**Change 5** • Increase in Hb level of [redacted] g/dl for RTT	[redacted](+14.0% vs change 4)
	• Utility decrement for patients on RTT previously 0.038	**Change 6** • Utility decrement for patients on RTT changed to 0.18	[redacted](-31.3% vs change 5)
NA – Changes to address NICE resource impact assessment	• Cost per ARECT transfusion: [redacted] • Cost per simple transfusion £608.38	**Change 7** • Cost per ARECT transfusion: £3,674.37 • Cost per simple transfusion £493.28	[redacted](-8.6% vs change 6)
NA – Updated patient access scheme discount	• Annual cost of voxelotor [redacted] (assumes [redacted] discount)	**Change 8** • Annual cost of voxelotor [redacted] (assumes [redacted] discount)	[redacted])

Sensitivity analyses around revised base case

Further sensitivity analyses around the revised base case are reported in Appendix 1: technical engagement analysis addendum (Section 1.3)

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR in section 1.1. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Friday 14th October 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Treating haemolytic anaemia in people with sickle cell disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Emma Drasar
2. Name of organisation	Whittington Health
3. Job title or position	Haematology Consultant
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with haemolytic anaemia in sickle cell disease? ☒ A specialist in the clinical evidence base for haemolytic anaemia in sickle cell disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No past or present links

8. What is the main aim of treatment for haemolytic anaemia in people with sickle cell disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	There is no single aim for treatment as there are as many presentations of sickle cell disorder as there are patients. However with haemolytic anaemia specifically the aim would be to reduce the severity of haemolysis, increase baseline (steady-state) haemoglobin and potentially reduce the long term impacts on the organs of chronic haemolytic cause vasculopathy and chronic anaemia
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	This is exceedingly difficult to quantity and is one of the reasons why NICE reviews are not necessarily fit for purpose for people with life long conditions. Fundamentally patients have no concept of wellness and their baseline is going to be completely different from the general population and also not the same as other people living with sickle cell disorder. Putting a number on improvements is very convenient for funding bodies and clinicians but does not necessarily translate into positive patient impacts. What if someone feels significantly better but has only a minor improvement in their Hb for example – or the reverse? This needs to actually be taken into account in these decisions
10. In your view, is there an unmet need for patients and healthcare professionals in haemolytic anaemia in people with sickle cell disease?	100% yes. We currently have 2 licenced drugs for sickle cell one of which has no impact on haemolysis that we are aware of. There is a significant group of patients for whom haemolysis rather than pain is their most prevalent issue who would not necessarily be eligible for Crizanlizumab. However chronic anaemia has long term organ impacts. As evidenced by this weeks Amber alert blood stocks are an uncertain commodity and we know that patients with SCD have specific transfusion requirements which it is already hard to meet. If an alternative to improving Hb could be used then this could be valid and valuable option for some patients. It would also avoid the risks of iron loading in simple top up transfusions and potentially also have other benefits that will come out in long term use.
11. How is haemolytic anaemia in people with sickle cell disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	These are covered by the BSH transfusion guidelines in Sickle Cell Disease, The BSH hydroxyurea guidelines and the sickle cell standards. The evidence base isn't really there and different clinicians will have different thresholds for example to initiate transfusion depending on availability of transfusion, patient choice etc.

across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Introducing another option will only improve the treatment of patients.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This could be used in a number of groups. a) Patients on regular transfusions who want to transition onto oral therapy for certain indications (wouldn't be appropriate for primary or secondary prevention of stroke, acute chest syndrome who have failed HU) but might be useful in other pt groups b) Those pts who have chronic haemolytic anaemia but who have numerous allo-antibodies, a history of severe DHTR/hyperhaemolysis or from religious choice do not want transfusion c) As an additive or alternative treatment for those patients who are intolerant of or unwilling to take hydroxyurea This is an oral outpatient based therapy so no additional investment would be required
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	It has become clear to me in the last year that we actually have no idea how many patients are living with sickle cell disorder in the UK. The numbers between hospital appointments, GP registrations and A&E attendances are vastly discrepant. I think it would be hard to make any judgements on life expectancy in what is a significantly underprivileged group of patients who exist in a systemically racist society and system. I would hope that having an additional therapy has the potential to improve patients QOL IN ADDITION to current care
14. Is voxelotor expected to show improved clinical outcomes and health-related quality of life compared with standard care?	In my experience in using it with my patients I would expect so yes.

15. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This could be used in a number of groups. a) Patients on regular transfusions who want to transition onto oral therapy for certain indications (wouldn't be appropriate for primary or secondary prevention of stroke, acute chest syndrome who have failed HU) but might be useful in other pt groups b) Those pts who have chronic haemolytic anaemia but who have numerous allo-antibodies, a history of severe DHTR/hyperhaemolysis or from religious choice do not want transfusion c) As an additive or alternative treatment for those patients who are intolerant of or unwilling to take hydroxyurea
16. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	No additional practical implications as is Oral OP based therapy.
17. How long are people expected to be treated with voxelotor for?	Long-term until risks outweigh benefits. This is a cradle to grave disorder.
18. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No but would expect patients to be discussed at HCC MDT as per current practice on open access scheme
19. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some	As I have said frequently to NICE I feel that these instruments are not fit for purpose for people living with chronic disorders. As an oral therapy it will be easier to deliver that some more complex therapies which require hospital attendance

been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
20. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes I consider it to be an innovative approach. We need to move more towards a multimodal approach to treating sickle cell disease in the same way that has had so much success in myeloma. The unmet need being met is the total lack of choice of treatment for people living with sickle cell disorder!
21. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In my experience with my patients it has been remarkably well tolerated. Care needs to be taken with patients on concomitant EPO treatment that the Hb doesn't rise to quickly and therefore a lower starting dose may be appropriate here
22. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes they do. I personally would have designed the trial differently and potentially focused more on exercise tolerance and energy levels and ability to perform ADLs. Pain is a very hard endpoint to judge as is subjective. I think the real world data brings more useful information to this area.
23. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

24. How do data on real-world experience compare with the trial data?	More impact on VOCs in real world data than in trial. Significant reductions in admissions and in transfusions and therefore in chelation. The early data on improvements in renal function are also potentially very interesting
25. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	The main equality issue facing my patients is the massive lack of therapies that they can access, how they are treated by society and unfortunately by the majority of health care professionals. Not being considered appropriate for vox due to their stroke risk is the least of their concerns I would say.

Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

The company's positioning of voxelotor is problematic	I disagree that positioning it as an additional or second line therapy is entirely appropriate and its use in patients who are hard to transfuse in certain clinical situations
It is unclear if an increase in haemoglobin of >1g/dL is clinically meaningful for people with haemolytic anaemia in sickle cell disease	I think that is up to the patients and clinicians to decide – given the real world evidence I would say that it is
The impact of voxelotor on long-term complications is unknown	That was the same for HU 30 years ago. Or indeed on any of the cancer drugs that are funded on a seemingly weekly basis.

Methods used by the company to generate time to event probabilities are not robust	Cannot comment on this
The modelled impact of treatment with voxelotor on health-related quality of life is not supported by trial evidence	This is likely due to the not fit for purpose nature of QOL questionnaires used in the majority of trials
Inappropriate regular transfusion therapy rates	I do not understand this statement
The company model generates clinically implausible individual patient simulations	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Patients deserve a choice of therapies

Some patients will significantly benefit from vox as there are no other options for them currently

Appropriate as a second line or additional treatment in patients without significant pain

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR in section 1.1. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Friday 14th October 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

NICE National Institute for Health and Care Excellence

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

Part 1: Treating haemolytic anaemia in people with sickle cell disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Paul Telfer
2. Name of organisation	Queen Mary University of London and Barts Health NHS Trust
3. Job title or position	Clinical Professor of Haemoglobin Disorders and Haematology (QMUL), and Honorary Consultant Haematologist (Bart's Health NHS Trust)
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with haemolytic anaemia in sickle cell disease? ☒ A specialist in the clinical evidence base for haemolytic anaemia in sickle cell disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links with tobacco industry

8. What is the main aim of treatment for haemolytic anaemia in people with sickle cell disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	1. To improve symptoms of anaemia (including fatigue, poor concentration, reduced exercise tolerance, reduced ability to undertake expected activities of daily living, impaired function in employment or in undertaking study) 2. To reduce the risk of chronic complications of sickle cell disease associated with anaemia and haemolysis 3. To reduce the effects of severe anaemia during an acute complication of sickle cell disease (acute pain crisis, acute chest crisis, severe infection etc)
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A sustained increase in haemoglobin level by 1g/dl (10g/l) without a concomitant increase in frequency of vaso-occlusive episodes
10. In your view, is there an unmet need for patients and healthcare professionals in haemolytic anaemia in people with sickle cell disease?	Yes, I agree with the company summary of unmet needs
11. How is haemolytic anaemia in people with sickle cell disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Treatment of haemolytic anaemia is not explicitly covered in current clinical guidelines (1. BSH Hydroxyurea guideline (Qureshi et al, BJ Haem 2018)- Hydroxyurea not specifically recommended for treatment of anaemia 2. BSH transfusion guideline (Davis et al, BJ Haem 2017): Transfusion is not recommended to treat steady state anaemia provided that Hb has not fallen over a period of time to symptomatic levels (e.g. with developing chronic kidney disease) (Grade 1C). 3. American Society of Haematology Guideline Excepting chronic severe, symptomatic anaemia, the pathway of care for chronic anaemic in sickle cell disease is not well defined in the NHS, and in my

	experience of working with colleagues in other European and North American health care systems, the same is true in these. The company has provided a good summary of the current evidence of the associations of anaemia with chronic end organ damage. The efficacy of long-term therapies aimed at treatment of anaemia and consequent prevention of chronic illness is difficult to study in a short-term randomised controlled trial, and require careful documentation in long-term follow up cohorts. These data are not yet available. In my view it is not acceptable to continue a conservative approach towards the anaemia associated with sickle cell disease, or to wait for further data to be acquired in long-term studies. The available data presented by the company justify a change in treatment pathway and to offer therapy to treat anaemia provided it meets the criteria I have suggested in Question 9.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Voxelotor would be offered as second line treatment for haemolytic anaemia in patients with SCD who are intolerant, ineligible, unwilling to take or have an inadequate response to, hydroxycarbamide. The proportion of SCD patients being offered treatment to modify the course of SCD would not change substantially from current care. It would be used in secondary and tertiary care only. I expect that the decision to initiate treatment would be made through consultation between specialist in the local haemoglobinopathy centre and specialist haemoglobinopathy centre. Dosing and monitoring could be done in local centre with advice from specialist centre when needed. I expect voxelotor treatment would follow a national treatment protocol. I do not expect additional facilities or equipment would be needed to introduce voxelotor therapy.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Based on my knowledge of the literature, and experience in treating paediatric and adult patients in Phase 2 and 3 clinical trials and early access schemes, I would expect an improvement in symptoms of anaemia and in quality of life in those who respond compared to current care. There is no evidence yet to determine if life expectancy in increase. My expectation based on mechanism of action and results of clinical trials and real world evidence is that reducing haemolytic anaemia will improve life expectancy.
14. Is voxelotor expected to show improved clinical outcomes and health-related quality of life compared with standard care?	Yes
15. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It would not be appropriate at this stage to use voxelotor for primary or secondary stroke prevention or to prevent progression of cerebro-vascular disease. The relative efficacy compared to established treatment (regular transfusion) would need to be formally evaluated in a clinical trial before switching. For patients with frequent vaso-occlusive crises (at least 2 per year requiring hospital admission), and who have not responded to hydroxyurea or who have not tolerated, or not willing to take, there is evidence that regular simple transfusion or exchange transfusion can control crises effectively, and this is also my experience in practice. I would not recommend switching such patients to voxelotor.
16. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Initiating and monitoring therapy will be similar to what is required for hydroxycarbamide. No additional treatments or tests are required for monitoring therapy.
17. How long are people expected to be treated with voxelotor for?	Long term therapy (as in the case of hydroxycarbamide) for those who have a good response and absence of significant adverse effects

18. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	See above concerning groups of patients who would not be suitable. Otherwise, inclusion and exclusion criteria would be those in the SMPC.
19. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	In my experience, patients treated with voxelotor may have improvement in symptoms of fatigue and poor concentration. In addition, unpredictable fluctuations in symptoms are less apparent. This appears to impact on ability to undertake normal activities at home- cleaning, child care, shopping etc, improved attendance and functionality while at work, and also reduces stress and time commitment of regular carers. If this therapy is shown to be effective as a substitute for regular transfusion for a subset of patients, the inconvenience, time and travel requirements for the patient to access the transfusion facility, as well as the reduction in health care resource utilization at the transfusion facility would be significant.
20. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	See above. This a first in class anti-polymerization agent which targets the underlying pathophysiology of polymerization of deoxygenated haemoglobin within the red blood cell. There are currently only a few available treatments for SCD, and all of these have limitations because of inadequate efficacy, adverse effects, and unacceptability from the patient perspective. There is a particular unmet need in treating patients with severe symptomatic anaemia who are untransfusable or very difficult to transfuse (for a variety of reasons, including allo-immunization, severe transfusion reactions, very difficult venous access and religious objections to transfusion). In my experience, this is about 5% of the adult SCD population.
21. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	From the literature, and in my experience, the adverse effect profile of voxelotor is not severe. Patients often experience mild to moderate gastrointestinal side effects during the first 1-2 weeks of therapy, but these tend to resolve without dose reduction. Rarely, a severe cutaneous reaction may require discontinuation. In my experience, most patients and carers welcome the prospect of an additional oral medication for treating SCD which does not have the potential adverse effects associated with hydroxycarbamide (which are

	referred to in the product information leaflet for the drug (suppression of cell division, reduced sperm count, potential malignant transformation)
22. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Please see above. Although primarily positioned to treat anaemia and prevent long-term complications, I would expect any drug being used to treat SCD to improve the experience of acute crises. The HOPE 3 trial and real world data suggest that voxelotor does reduce crisis frequency to a moderate degree. In my experience in the expanded access scheme, some patients have continued to experience acute crises, and these patients, if not responding adequately to hydroxycarbamide, should be offered regular exchange transfusion.
23. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The UK and European Early Access to Medicines scheme is generating real world data on use of voxelotor
24. How do data on real-world experience compare with the trial data?	The real world data from the Symphony dataset seem to be broadly consistent with the HOPE 3 results
25. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.	Several reports (including the All Party Parliamentary Group report 'No one is listening) highlight the inequality in NHS health care and inadequate social support available to patients and carers living with SCD compared to chronic conditions such as haemophilia and cystic fibrosis. SCD is a condition which is common in people whose family origins are African and African Caribbean. Patients are disadvantaged particularly on account of race and socioeconomic status.

Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

The company's positioning of voxelotor is problematic	I think the company's positioning of voxelotor is clear and makes clinical sense. In my view, there is no problem in considering therapy second line, when first line therapy has been offered, but refused by the patient. This is important in the context of Hydroxyurea (hydroxycarbamide), which is acknowledge to be first line therapy for most patients with SCD, but in practice, a significant proportion of adult patients and parents refuse to take it, even after a long period of time during which information and encouragement are given by health care specialists in the clinic. There is a persisting, intractable perception in some parts of the community that hydroxyurea is ineffective and/or toxic, and that adverse effects outweigh benefits.
It is unclear if an increase in haemoglobin of >1g/dL is clinically meaningful for people with	I agree that an increase in haemoglobin is a surrogate. It is yet to be shown that the increased risk of certain chronic complications associated with a haemoglobin level reduced by 1g/dL in steady state however, can be ameliorated through raising haemoglobin level by 1g/dL during therapy with voxelotor. This is an area of uncertainty which will be hard to resolve until results of long-term follow-up studies on

haemolytic anaemia in sickle cell disease	treatment are available. An amelioration of the risk and time to onset of these chronic complications would certainly be meaningful. In my experience of treating patients in the clinical trials and early access schemes, an improved haemoglobin during therapy with voxelotor is associated with improved energy levels and improved functionality. In addition, there is a subgroup of patients with very low haemoglobin level at steady state, for whom transfusion is not possible (usually as a result of allo-immunization). These patients would have a clinically meaningful benefit from treating the anaemia. I would be more confident and expect a better increment in haemoglobin level for these patients treated with voxelotor compared to hydroxyurea therapy.
The impact of voxelotor on long-term complications is unknown	See above.
Methods used by the company to generate time to event probabilities are not robust	I am not able to comment on this
The modelled impact of treatment with voxelotor on health-related quality of life is not supported by trial evidence	From my experience in managing a large number of patients across paediatrics, adolescent and adults I think the trial evidence does not adequately capture the range of decrement in quality of life experienced by people living with SCD who might be eligible for this treatment.
Inappropriate regular transfusion therapy rates	Chronic transfusion therapy, particularly with automated exchange transfusion, is being increasingly used in the NHS for long-term management of adolescents and adults with SCD. A proportion of these patients could potentially be switched to voxelotor, however this group were not eligible for the HOPE 3 study and further clinical trials of observational studies are needed to determine how best to switch treatment.

The company model generates clinically implausible individual patient simulations	I am not able to comment on this
Are there any important issues that have been missed in EAR?	For a subset of patients with very low haemoglobin, symptomatic anaemia and who are untransfusable, voxelotor may be the only treatment option, and if not available on the NHS, would deprive these patients of potentially life-saving therapy

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

People living with Sickle cell disease are disadvantaged, particularly on account of race and socio-economic status
Sickle cell disease is associated with severe impairment of health and life expectancy which could be improved if more therapeutic options were available
There is good data from a Phase 3 supported by long-term follow-up and real world evidence that voxelotor is effective in treating sickle cell disease
The company's submission which positions voxelotor as a second line agent is clinically appropriate
For a subset of patients with low haemoglobin, symptomatic anaemia and who are untransfusable, voxelotor may be the only treatment option available

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR in section 1.1.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Global Blood Therapeutics UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nothing to disclose**

Executive Summary

Thank you for the opportunity to respond to the technical considerations and areas of uncertainty as identified through the External Assessment Group (EAG) report. We have carefully considered the issues highlighted by the EAG and have developed a comprehensive and robust response which addresses these uncertainties. In addition, we have provided further evidence and materials which support voxelotor as a clinically and cost-effective treatment of haemolytic anaemia in patients with sickle cell disease (SCD). In summary our response includes and addresses the following:

1. Further clarification and argumentation is provided in relation to the clinical benefit of voxelotor. This includes further discussion of the relevance of the Company's 2L positioning, as well as further contextualisation of the relevance of an improvement in haemoglobin and the impact of voxelotor on future complications. In addition, further clarification and evidence is provided to support the positive impact of voxelotor on quality of life for patients and why it is appropriate to capture this improvement in the economic model.

2. An updated and revised economic model has been presented which addresses the EAGs concerns regarding robustness and is suitable for health technology assessment (HTA) decision making. The economic model also includes alternative base case model assumptions which further strengthen the robustness of the economic case.

3. [redacted]. The impact of the PAS and the post-technical engagement ICER are presented below within this Executive Summary. A full set of updated economic results are presented in the supporting Appendix 1: technical engagement analysis addendum.

4. Updated supporting documentation such as Appendices P and Q – derivation of HES and Symphony time to event (TTE) analyses respectively, are provided which present updated equations and correct any typographical errors. In addition, an

updated Appendix U – Delphi panel report, is available which contains further clarification regarding the derivation of the proportion of patients on regular transfusion therapy (RTT).

Updated agreed PAS discount for voxelotor

The agreed PAS discount for voxelotor has been updated from [redacted] to [redacted]. The updated PAS has been applied within this response and for reference, the base case from the Clarification stage of the process is presented in Table 1, alongside the company's preferred base case post-technical engagement. Please note that the preferred base case post technical engagement includes the adoption of additional base case assumptions which are presented in full in the supporting Appendix 1: technical engagement analysis addendum.

Table 1: Cost-effectiveness results

	Post-clarification base case	Post-technical engagement base case
ICER versus SOC	[redacted]	[redacted]
ICER: incremental cost-effectiveness ratio; SOC, standard of care		

HTA context and health inequalities

Health inequalities are unfair and avoidable differences exist in health across the population, and between different groups within society.[1] In the recent appraisal for crizanlizumab (TA743)[2] it was acknowledged that there is an unmet need for effective treatments for people with SCD. People with SCD face health inequalities because the condition is not well understood, results in disability, and is more common in people of African or African-Caribbean family origin, who tend to have poorer health outcomes and experience higher levels of social deprivation than other ethnicities in the UK.

Tackling health inequalities forms parts of the NHS long term plan. The COVID-19 pandemic, with its disproportionate impact on those already disadvantaged in society, has brought the issue of health and wider inequalities into sharp focus. The NICE 2021-2026 strategy refers to the organisation's need to enhance their offer and strengthen the role it plays in reducing health inequalities.[3]

Conclusion

As outlined in the company submission, voxelotor address an important and relevant unmet need for safe and effective treatments for patients with haemolytic anaemia due to SCD. The company's 2L positioning is appropriate and reflects where voxelotor will be used in clinical practice following robust consultation with clinicians. The inclusion of an [redacted] and revised model assumptions address the uncertainties as reported by the EAG and the updated base case ICER is within a threshold considered cost-effective by NICE, for medicines for severe diseases in neglected patient populations. Therefore, we believe that voxelotor represents a clinically and cost-effective treatment option in a disease area with a high unmet need and significant patient inequity and should be made available for patients within the National Health Service (NHS).

Key issues for engagement

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: The company's positioning of voxelotor is problematic	No	The company has used the term 'second line' (2L) to describe the positioning of voxelotor in the submission, following consultation with clinical experts (see Delphi panel report, CS appendix U). The company recognises that terminology around lines of treatment is not exact and is open to different interpretations. The detailed rationale for the choice of this population, and for its designation as 2L is set out below. This population corresponds well to that in the HOPE study; the rationale for this is also given below. **Definition of 2L** Hydroxycarbamide (HC) is an established treatment that is recommended by the British Society of Haematology for all SCD patients.[4] HC can thus be regarded as 'first line treatment', insofar as HC will be considered for every patient ***prior to*** any other treatment. This characterisation is widely confirmed by health-care professionals, treatment guidelines and by the company. The company defined 2L patients as patients who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective; this is the positioning of voxelotor for the submission. These patients can be described as follows:

		• Ineligible for HC: patients who are contraindicated for HC and therefore have never received it, so require a different treatment. These patients will receive voxelotor monotherapy. • Intolerant to HC: have been treated with HC for a period but are unable to tolerate it due to adverse effects and therefore require a different treatment. These patients will receive voxelotor monotherapy. • Unwilling: unwilling to start taking HC, or to continue taking it, because of safety or fertility concerns, or because of impacts it has had on them. These patients therefore require a different treatment and will receive voxelotor monotherapy. • HC insufficiently effective: these patients are receiving some benefit from HC but remain inadequately treated due to a partial response or inability to receive a sufficient therapeutic dose (e.g. dose reductions to avoid neutropenia or intolerance). These patients require an additional treatment and take voxelotor in combination with HC. **Choice of population and position in therapy** The population for the submission is "adults and paediatric patients aged 12 years or older with SCD who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective." (CS, B1.1). This is the population in which voxelotor is likely to be used in clinical practice in the NHS, as confirmed by: • UK clinicians consulted for the modified Delphi panel (CS Appendix U). • The submission by the Royal College of Pathologists (RCP) (TE papers item 3e) confirms that some patients are assessed as ineligible, intolerant or unwilling for HC and require alternatives. The RCP respondent states that "There is a need for an alternative treatment that can improve haemoglobin and haemolysis in sickle cell disorder. Hydroxycarbamide has the potential to improve both to a similar level as voxelotor, but a number of people do not tolerate hydroxycarbamide or are 'non-responders'. Because of concerns about fertility and fears of using an anti-cancer drug, patients are sometimes reluctant and prefer to opt out of treatment for these reasons. Blood transfusion (exchange or top up) will also improve these parameters, but is more invasive than an oral treatment. There is a risk of iron overload in the more anaemic sickle cell patients.

		Some patients become hard to transfuse due to the development of allo-antibodies. A number of sickle cell patients are members of Jehova's Witness communities and do not wish to receive blood products. Voxelotor fulfils the need for disease-modifying treatment in these groups." This population is clearly defined, clinically appropriate and reflects the position where voxelotor is likely to be used in the NHS (consistent with NICE recommendations that assessments reflect clinical practice). **Differing interpretations of the term "2L" should not be a barrier to consideration of this population by NICE. If NICE prefers, the designation "2L" can be modified and the population can be referred to simply as "patients who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective."** **The trial evidence is applicable to the submission population** The inclusion criteria for the HOPE trial did not require documentation that patients were ineligible for, intolerant of or unwilling to take hydroxycarbamide, or had inadequate efficacy from hydroxycarbamide alone. However, as previously stated in the CS (B.1.1 and B.2.12.2) and the CQ response, it is reasonable to assume that most patients in HOPE fell into this category: • Two-thirds of patients (64% and 63% in voxelotor 1500 mg and placebo groups, respectively) were already taking HC when they and their physicians decided they should enter a trial of an investigational product. It is reasonable to assume that this decision was made because current management of their SCD was not optimal (i.e. they had inadequate efficacy from HC alone, and therefore fall within the submission population). o A prespecified subgroup analysis showed that the effect of voxelotor on Hb was not significantly different between patients who were on HC and those who were not. o Given the different mechanisms of action of HC and voxelotor, there is no reason to assume that voxelotor would have a different treatment effect (as measured by

		haemoglobin (Hb) response) in patients who were documented as ineligible, intolerant or unwilling for HC compared with the effect seen in the HOPE trial population. • There is an international consensus that all patients with SCD should be offered HC; this is reflected in numerous guidelines, including those from the British Society of Haematology.[4] HC is available in all the countries in which HOPE was conducted. In clinical trials it is common practice to only enrol patients who have no licenced alternatives that are suitable for that patient. It is thus unlikely that for patients in HOPE who were not taking HC, HC had not been either considered or used for them in the past. However, the reasons for patients not being on HC at baseline were not captured in the case report form. In summary, the population in HOPE is sufficiently representative of the submission population.
EAG Response		Patients who had previously taken, were currently taking, and who had never taken hydroxycarbamide were enrolled in the HOPE trial. The EAG agrees with the company that patients who had taken hydroxycarbamide but had stopped taking it at, or prior to, baseline, would be taking voxelotor as a second-line treatment. Patients who were taking hydroxycarbamide at baseline and continued to take hydroxycarbamide would also be taking voxelotor as part of a second-line (combination) treatment. However, the EAG considers that patients who were ineligible for, intolerant of or unwilling to take hydroxycarbamide would be taking voxelotor as a first-line treatment given that they had not received prior treatment with hydroxycarbamide, regardless of whether it had been offered. Therefore, the EAG still considers that it is not appropriate to label voxelotor as a second-line treatment.
Issue 2: It is unclear if an increase in haemoglobin of >1g/dL is clinically meaningful for people with haemolytic anaemia in sickle cell disease	Yes. The full analysis by Telfer et al.[5] was not available at the time of the original	The clinical relevance of an Hb increase of >1g/dL seen with voxelotor is evidenced by several different factors, described below. **Clinical relevance has been confirmed by regulatory bodies** The European Medicines Agency (EMA) has stated that: “there is a high unmet need for medicines to treat haemolytic anaemia, which is experienced to various degrees by all SCD patients.”[7]

	submission. The figure from Howard 2019[6] was not presented in the original submission.	Voxelotor was approved for haemolytic anaemia in SCD by the EMA and Medicines and Healthcare products Regulatory Agency (MHRA) on the basis of the proportion of patients achieving an increase in Hb of >1g/dL with voxelotor. The EMA states that: "Treatment with voxelotor has resulted in a beneficial effect in terms of reduction in haemolysis and an increase in Hb, which are considered of clinical relevance to the patients."[8] **Increased Hb with voxelotor is a marker of reduced disease activity** Haemolytic anaemia in SCD results from increased rates of haemolysis (breakdown of red blood cells), caused by repeated sickling due to the polymerisation of HbS (the abnormal Hb present in SCD). As set out in the CS (B.1.3.1.1): • HbS polymerisation results in a cascade of pathological events, starting with RBC sickling and haemolysis and leading to haemolytic anaemia, blood vessel damage (vasculopathy) and vaso-occlusion (including VOCs). This results in reduced oxygen delivery to the tissues, and chronic sterile inflammation caused by the presence of free cell contents in the blood.[9,10] • Together, these pathologies cause a range of acute and chronic severe complications, including progressive organ damage and associated symptoms and comorbidities. Voxelotor acts by inhibiting HbS sickling, which reduces haemolysis and thereby both increases Hb levels and reduces the other effects of haemolysis the pathological cascade as described above. **The increase in Hb levels seen with voxelotor is therefore a marker of reduced disease activity, rather than simply an isolated occurrence.** The same is not true for transfusions, where an increase in Hb is not related to an improvement in disease activity. The effect of voxelotor on the percentage of irreversibly sickled cells is shown in Figure 1 below.

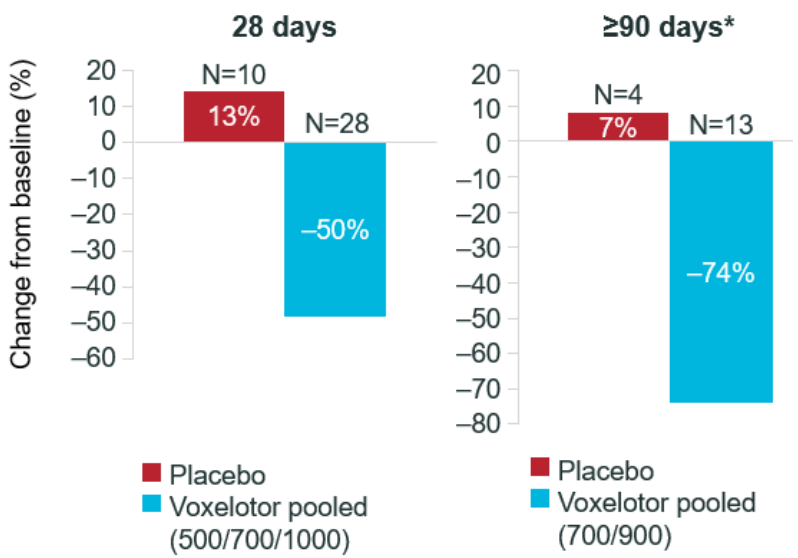


Figure 1 Percentage change in irreversibly sickled cells from baseline after treatment with voxelotor or placebo.

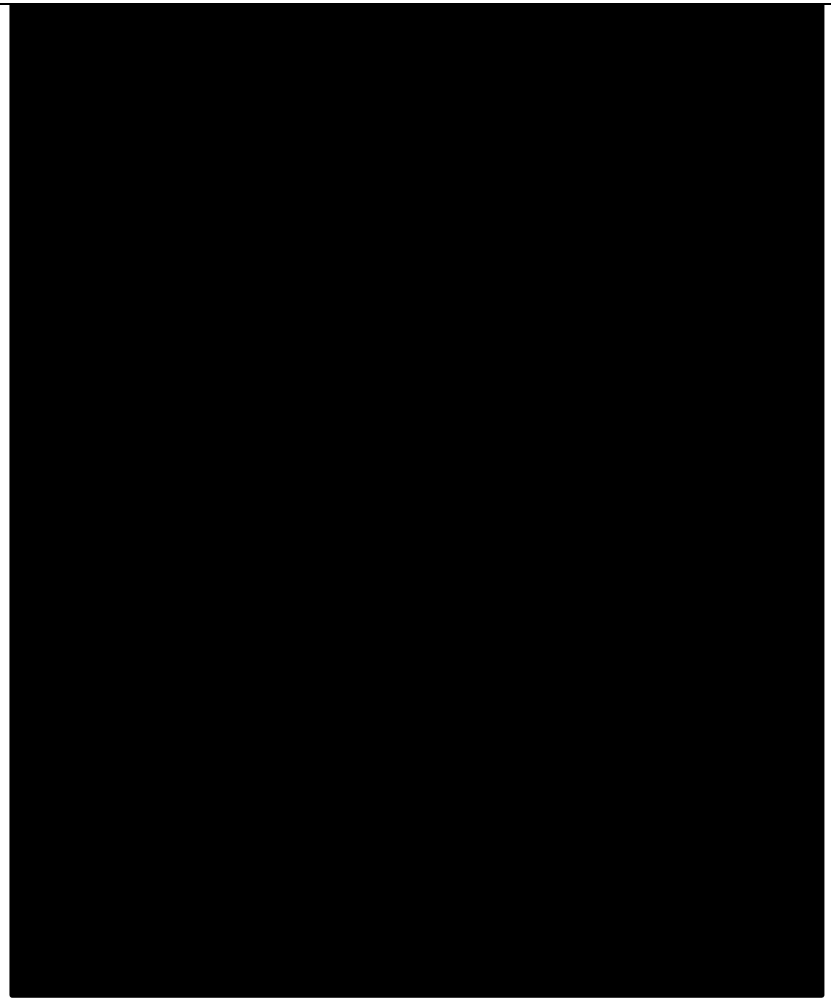
Data from Howard et al. 2019[6]. *90 days to 6 months of dosing (two patients had 90 days of dosing, one patient had 118 days of dosing, and four patients had 6 months of dosing).

Voxelotor's effect in reducing disease activity at the physiological level explains the association between higher Hb levels and improved outcomes, described below.

The RCP submission (TE papers item 3e, p. 3) stated that: "Voxelotor has a unique ability to keep oxygen bound to haemoglobin which results in less cell destruction and improvement of anaemia as well as rate of haemolysis. Some of the long-term morbidities in sickle cell disorder are directly related to the degree of anaemia and/or haemolysis and voxelotor has the option to target both. The reduced strain on bone marrow can also improve fatigue and quality of life for people with this chronic disorder."

		Increased Hb is associated with improved outcomes in SCD There is considerable evidence for the relationship between higher haemoglobin (Hb) and improved outcomes in SCD (and lower Hb and poorer outcomes), as presented in the CS p. 123-124 and summarised here: • A meta-analysis by Ataga et al. of 41 studies (mainly retrospective and prospective cohort studies) showed lower haemoglobin concentration was consistently associated with higher incidence or history of stroke, silent cerebral infarct, increased transcranial doppler (TCD) velocity, albuminuria, pulmonary hypertension and mortality, in SCD patients of all ages (see Section B.1.3.1.2).[11] • Ataga et al. also conducted a risk-reduction meta-analysis, and found that the modelled risk reduction for negative clinical outcomes decreased at all modelled levels of increased Hb concentration. An increase in Hb of ≥1 g/dL predicted risk reductions of 41% for stroke/silent cerebral infarct, 53% for albuminuria, 57% for elevated estimated pulmonary artery systolic pressure (PASP) and 64% for death.[11] The authors concluded that even modest increases in Hb may be beneficial in SCD. • An association between Hb levels and TTE for a range of outcomes was found in the Symphony health claims database see appendix P (revised version submitted at technical engagement) for details. • An association between Hb levels and TTE for a range of outcomes was also found in the HES/CPRD database see Appendix Q (revised version submitted at technical engagement) for details. • Figure 2 demonstrates the hazard ratio per 1 g/dL increase in Hb for the risk of complications from the Symphony and HES/CPRD databases. Across both datasets there is generally very good alignment for most complications, showing a robust link between Hb and risk of complications. • An additional analysis of HES/CPRD by Telfer et al.[5] found that an increase in Hb of 1 g/dL was associated with a statistically significant reduction in risk for six common end organ damage outcomes and clinical complications (leg ulcer, pulmonary hypertension, chronic kidney disease, end-stage renal disease, acute chest syndrome and stroke; see

		Section B.1.3.1.2 for details) over a 12-year period. Evidence is also available from a number of studies published after the inclusion date for the Ataga et al. meta-analysis, as described in Section B.1.3.1.2. • Analysis of data from approximately 4,000 SCD patients, who at enrollment ranged from birth to 66 years, from the Cooperative Study of Sickle Cell Disease (CSSCD), showed patients with the lowest Hb levels had an increased risk of death.[12] Subsequent analyses from this long-term cohort dataset were also included in the Ataga et al. meta-analysis.[11]

		 **Figure 2 Hazard ratio for each 1 g/dl increase in Hb derived from the Symphony TTE analysis weighted to HES-CPRD vs the HES-CPRD analysis.**

		Evidence on non-Hb outcomes with voxelotor Evidence on non-Hb outcomes seen with voxelotor, e.g. a reduction in leg ulcers in the HOPE trial, and reduction in hospitalisations and use of concomitant medication in the Symphony database, also support the clinical benefits arising from treatment. This is described in more detail under Issue 3. **Summary** The positive decision by the regulatory authorities, the status of Hb level with voxelotor as a marker of disease activity in SCD, the evidence showing that higher Hb is associated with improved outcomes in SCD, and the evidence of real-world patient-relevant benefits with voxelotor, all confirm that the Hb increase of 1g/dL seen with voxelotor is clinically meaningful. The use of real-world evidence to resolve gaps in knowledge is one of the stated aims of the NICE Real World Evidence Framework and the real-world evidence provided by the company meets NICE's standards for data quality.[13]
EAG Response		HOPE trial results showed a statistically significant difference in favour of voxelotor over placebo in the number of patients who had a Hb response (defined as an increase in Hb >1g/dL from baseline to Week 24). However, the effect of this improvement in Hb level on long term outcomes for the HOPE trial population is not known.
Issue 3: The impact of voxelotor on long-term complications is unknown	No	The chronic complications resulting from the pathology of SCD evolve over time, and worsen as patients get older. The HOPE trial was not designed to show an effect on chronic complications, as these require a longer time scale, and different population at baseline as well as potentially more patients for evaluation. The link to long-term outcomes in the modelling is therefore made using associations between Hb concentration and outcomes of interest based on TTE equations derived from the HES/CPRD databases and validated using equations derived from the Symphony database. These are all typical when modelling treatments for chronic conditions, where surrogate endpoints are frequently used. The relationship between Hb and these outcomes is robust, as discussed in relation to Issue 2, above. **Non-Hb outcomes with voxelotor**

		In HOPE The principal endpoints in HOPE were Hb-related and the trial was not designed or powered to study the impact on VOCs or other SCD-related complications. However, patients treated with voxelotor had numerically lower incidences of VOCs than the placebo group[14] and there was a potential clinical benefit for patients with leg ulcers;[15] although these differences did not reach statistical significance, for either outcome. Leg ulcers are a painful and often debilitating complication of SCD. A published post hoc analysis of leg ulcers in HOPE over 72 weeks showed that 5 of 5 patients with leg ulcers in the voxelotor 1500 mg group and 8 of 9 in the 900 mg group had their leg ulcers improve or resolve by week 72, compared with 5 of 8 in the placebo group.[15] During the 72-week treatment period, nine additional patients developed new leg ulcers: one in the voxelotor 1500 mg group (mild severity), three in the 900 mg group (two mild, one moderate), and five in the placebo group (three mild, two moderate).[15,16] This suggests that voxelotor has a potential clinical benefit on leg ulcers, [15] (See CS Section B.2.6.7). The HOPE open label extension study (OLE) is ongoing, with a currently planned end-date in Oct 2024. HOPE OLE will continue to deliver Hb and haemolysis data to demonstrate the sustainability of the treatment effect with voxelotor and report on long-term safety. However, the OLE is not designed to deliver data on other outcomes as it does not contain a comparator arm and does not allow for meaningful comparisons to baseline. In addition, the drop-out of patients over time, e.g. due to voxelotor becoming commercially available in additional countries, reduces patient numbers and introduces bias. ***Real-world evidence for voxelotor*** Voxelotor has been commercially available in the US since 2019, and the positive clinical impact of voxelotor has also been confirmed by real-world evidence from there. A published analysis of voxelotor-treated patients in the Symphony database demonstrated statistically significant and clinically meaningful reductions in annualised rates of hospitalisations, transfusions and vaso-occlusive (VOC) events, and reduced use of iron chelation and opioids[17] (presented in CS Section B.2.6.9).

		According to the NICE RWE framework, RWE can be used to reduce uncertainties and resolve gaps in evidence. The use of RWE in situations where trials are based on unvalidated surrogate outcomes is specifically mentioned in the RWE framework.[13] The company respects the hierarchy of evidence highlighted in the RWE Framework and is confident that real world data submitted by the company meets the standards on data quality (specifically, with regard to provenance, transparency and minimisation of bias) set out in the RWE Framework. To ensure fair and transparent implication by NICE of its own methods and processes, this evidence should be considered. The company will continue to analyse Symphony data and are conducting a prospective registry in the US. **Summary** Data on the effect of voxelotor on the incidence of long-term complications of SCD are not yet available. However, there is strong evidence that meets NICE's standards for acceptability, to support the link between Hb levels and outcomes in SCD, which in turn supports the expectation that voxelotor will reduce the risk of long-term complications.
EAG Response		The EAG considers that the RWE analysis of the Symphony database which, as it is a simple before and after study, is at a high risk of bias. Further, the Symphony database analysis results showed changes in event rates for patients treated with voxelotor that were not reflected in the HOPE trial results.
Issue 4: Methods used by the company to generate time to event probabilities are not robust	Yes, Cost-effectiveness analysis has been conducted using updated TTE equations, shown in Appendix 1: technical	To address the EAG's comments in the EAR, the company has made several changes to our approach in the base case outlined below: • Appendices P and Q, containing the reports of the TTE analyses, have been updated and supplied as part of the technical engagement response. Updated tables of the equations used in the model, have also been supplied in the revised results addendum following technical engagement. An updated appendix R was not required for the updated analysis so has not been supplied. • Following a suggestion in the EAR, the HES-CPRD dataset was used directly to derive TTE equations. This means that the model TTE equations are derived directly on the linked HES-CPRD records of a sub-set of the entire UK SCD population. Thus, there is no longer the requirement to match patients in the US Symphony database to the UK

	engagement analysis addendum	SCD population. The updated validation section (Appendix 1: technical engagement analysis addendum; Section 3, pg.23) shows very good agreement between our model simulations for event occurrence at 5 years, and Kaplan Meier estimates from the HES-CPRD analysis.
		• The parameterisation of the TTE equations has been adjusted as follows:
		  • The number of VOCs in the prior year was changed from a continuous variable and replaced with two categorical variables (1) 1–4 VOCs and (2) ≥ 5 VOCs.
		  • The interaction term between the number of VOC events in the prior year and the Hb level was removed. The continuous variable and interaction terms were causing some issues with model stability. For patients entering the model with a very high number of VOCs, some degree of runaway effect was observed, where the incidence rate of VOCs and then the events that depend on VOCs gets ever higher throughout the model.
		• Cardiomegaly and priapism as events were removed from the model. These events had very little impact in either terms of cost (cardiomegaly) or utility (priapism) and no impact on mortality (both). In the interests of simplifying the model equations and the model itself, it was felt that these events could be removed without biasing the results in either direction.
		• Following the prior changes, during model validation it was observed that the incidence rate of VOCs over the first 5 years was less than the mean number of VOCs in the year prior to baseline in the HES cohort. We tested other TTE equation forms and found that the log-logistic equation best fitted the 5-year event occurrence and incidence rate for VOC.
		With the implementation of the changes described above, along with the correction of typographical errors in appendices P and Q, the reliability of both the methods used and the TTE equations generated thereby is assured,

EAG Response		The EAG remains concerned about the methods used by the company to generate TTE probabilities.

		Inclusion criteria The analysis included patients who had had ≥3 confirmed SCD secondary care interactions before a baseline Hb level had been recorded. The company states that this was "to identify a subgroup of patients with SCD who experienced severe disease requiring hospital treatment which may indicate unmet clinical need, despite standard treatment, and thus may benefit from novel treatments" (Appendix P page 7). Only [redacted]% of patients in the analysis had had a VOC during the 12 months before the index Hb level was recorded. In contrast, all HOPE trial patients had had at least one VOC during the 12 months before enrolment and approximately 60% had had at least two VOCs during the 12 months before enrolment. It is, therefore, not clear whether the company TTE analysis relates to a population with more or less severe disease than the HOPE trial population; however, there is evidence that disease severity differs between the two populations. Given that the number of previous VOCs and/or previous secondary care interactions were not included in the NICE scope description of the population of interest, and that the purpose of the TTE analysis was to link Hb levels to the likelihood of complications, it is not clear why the company did not include data from all patients. If the reason was that the company considered that the effect of Hb level on long-term complications varied depending on disease severity, then it is not clear why the company did not limit the analysis to data from patients who met the HOPE trial VOC inclusion criterion, i.e., those who had had between one and ten VOCs during the previous 12 months. The EAG also notes that the mean age of patients who provided data for the TTE analysis was [redacted] years and that the median age of patients enrolled in the HOPE trial was 24 years. This age difference also suggests that the TTE analysis probabilities may not be directly applicable to the HOPE trial population. The EAG is also concerned that using index Hb level to generate TTE probabilities is overly simplistic. The company TTE probabilities relate to only one Hb level at a specific point in time and not to how changes to this Hb level affect the probability of experiencing a complication.

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<td>Issue 5: The modelled impact of treatment with voxelotor on health-related quality of life is not supported by trial evidence</td>
<td>Yes, additional sources of evidence supporting the association between changes in Hb and HRQoL.</td>
<td>
The Company does not agree that modelling an Hb-related utility benefit is inappropriate. It is common for phase 3 trials, and more so in rare diseases, to show no significant difference in HRQoL scores between treatment arms, as they are powered for efficacy outcomes only.

Why was a benefit in utility in favor of voxelotor not demonstrated in the HOPE trial when a statistically significant increase in Hb was demonstrated?

Limitations of the EQ-5D data in HOPE
Several factors may explain the fact that voxelotor showed no significant effect on HRQoL as measured by EQ-5D in HOPE. Of note, HRQoL was also measured using the Clinical Global Impression of Change (CGIC) measure, and more patients in the voxelotor 1500 mg were rated as improved compared with the placebo arm. These points are elaborated below.

Missing data
The power of the HOPE trial to assess HRQoL outcomes was limited by the large amount of missing data for EQ-5D; only [redacted] of 90 patients in the placebo group and [redacted] of 90 in the voxelotor 1500 mg group had a baseline value. The number who had a change from baseline value at Week 24 was [redacted] and [redacted] respectively, falling to [redacted] in both arms at Week 72 (CSR Table 14.2.15.1, summarised in Table 1 below).
The power of between-arm comparisons at different time points is also limited by missing data: the number of patients with data was 63 and 64 for placebo and voxelotor 1500 mg respectively at Week 24, with lower numbers at the preceding assessments. At 72 weeks the number fell to [redacted] and [redacted]. The amount of missing data further reduces the statistical power to detect significant between-arm differences in scores, and reduces confidence in the robustness of the data, as values may not be missing at random

Table 1 Number of patients with EQ-5D data available at each time point, HOPE trial
<table>
<tr><th></th><th>Placebo
(N=92)</th><th>Voxelotor 1500mg
(N=90)</th></tr>
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Timepoint, weeks	Patients with data N (%)	Patients with CFB value N (%)	Patients with data N (%)	Patients with CFB value N (%)
0 (baseline)	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]

CFB: change from baseline
Source: CSR Table 14.2.15.1

High baseline EQ-5D levels

As noted in the CS [p. 87 and 136], the mean utilities recorded in both groups in HOPE were unexpectedly high: they were very close to population norms for the UK and higher than utilities reported in the literature for SCD patients.[18,19] This value may not reflect the considerable burden of the disease.[20] The high baseline makes it difficult to detect improvements. In addition, as noted by the EAG, EQ-5D may also be insufficiently sensitive to capture all the HRQoL effects associated with SCD.

Effect of long-term complications on HRQoL is not captured in HOPE

HRQoL in SCD will be strongly influenced by the presence of long-term complications, which develop over a longer timescale than that covered by the HOPE trial. Complications are associated with reduced HRQoL (utility decrements), as can be seen from the literature (see CS

		Section B.3.4.4.2, p. 131, Table 36). Due to its mechanism of action, as described in Issues 2 and 3 above, voxelotor is expected to slow the development of these complications. This in turn is expected to slow the decline in patients' HRQoL that would occur in the absence of disease-modifying treatment. Thus, an important part of voxelotor's HRQoL benefit will be realised through prevention of HRQoL decline, and this aspect is not captured in the trial EQ-5D data as the duration is too short. ***Validity of EQ-5D in SCD*** The Office of Health Economics (OHE) report that generic measures of HRQoL like EQ-5D in certain contexts fail to capture relevant aspects of QoL. They highlight in the case of SCD there has been relatively little research testing the validity of EQ-5D in SCD, which in part may be explained by the lack of funding for research in SCD compared to other similar diseases, such as cystic fibrosis. Furthermore, fatigue, a major component of SCD, is not captured explicitly in the EQ-5D and therefore, EQ-5D may lack validity in SCD patients, as it does in multiple sclerosis.[21] This may explain, in part, why improvements in HRQoL were not detected by EQ-5D in the HOPE trial. **Evidence to support the association between Hb level and HRQoL** The NICE RWE framework outlines that in the absence of randomised controlled trial data or where randomised evidence is not sufficient, RWE should be used to fill evidence gaps. RWE has already been widely used in evaluating the effects of medical devices and procedures and is becoming more frequently used in regulatory approval of medicines. An analysis was performed on data from the Patient Journey survey, a study enrolling patients (n = 253) with SCD from the UK (17.19%), France (17.79%), Brazil (17.79%), Germany (13.04%), Spain (11.86%), Italy (11.86%), and Canada (9.88%). Survey data collected included demography, symptoms, current and previous treatments, Hb levels, and HRQoL, among others. HRQoL was measured in the survey using the EQ-5D-3L questionnaire. To assess the relationship between Hb levels and HRQoL, linear models of utilities as a function of Hb were adopted including patient age as a covariate (See CS Section B 3.4.4.3 and Appendix T for

more details). The resulting estimated utility increment per 1g/dL increase in Hb was calculated to be 0.047 (p <0.00001**Error! Reference source not found.**). This relationship was applied in the model to all patients, irrespective of treatment arm.

Justification for modelling an Hb-related utility benefit

SCD is a systemic progressive disease associated with a range of chronic and acute events. SCD-related adverse outcomes extend far beyond the list of comorbidities explicitly modelled in the economic model.

For example, as part of the National Heart Lung and Blood Institute Cure Sickle Cell Initiative, Johnson et al.[22] recently identified 26 acute and chronic events that were considered, by a wide range of stakeholders, as critically relevant and have a significant impact of HRQoL and resource use (Figure 3).

The set of complications explicitly modelled in the CS was determined in part by the need for simplification inherent to any model and, on the other hand, the limitations of the data available.

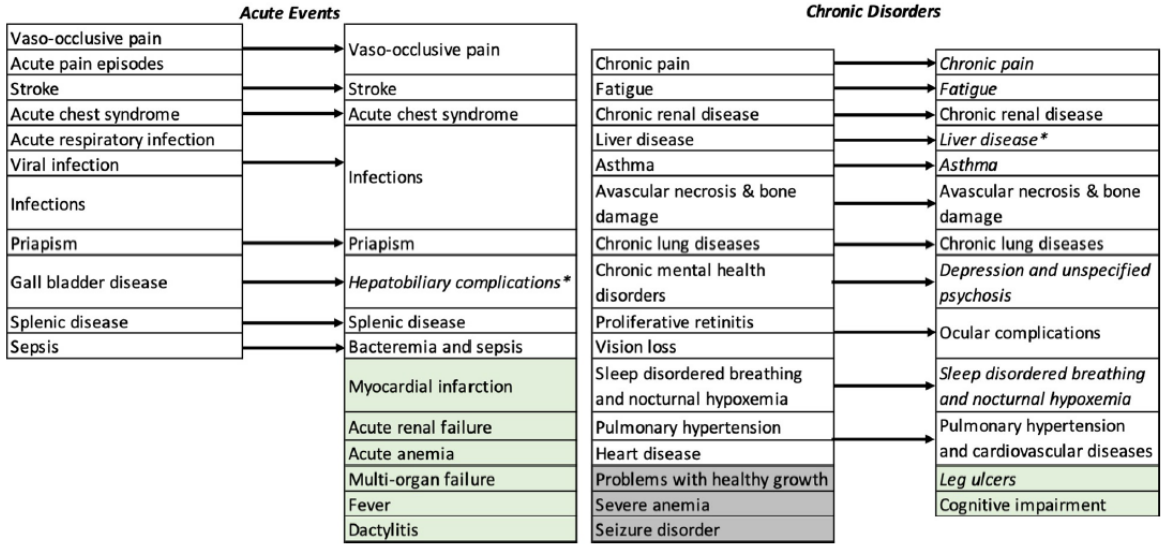
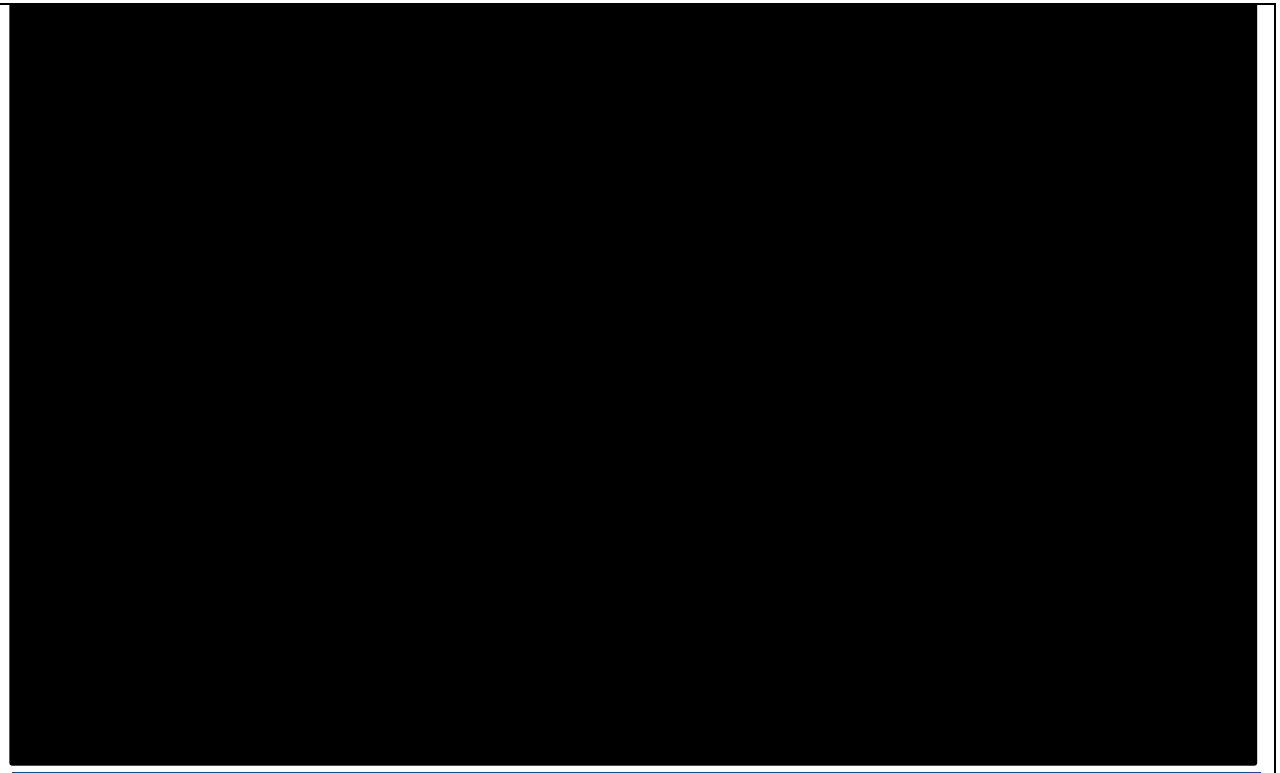


Figure 3 List of critically relevant complications identified by Johnson et al.[22]

		Several complications with well-established links to lower HRQoL in non-SCD patients were not included in the CS model due to data limitations, such as fatigue, anaemia, hypoxemia, fever, cognitive impairment and retinopathy. It is reasonable to assume that these events would impact SCD patients a similar way they impact non-SCD patients. The link between increasing Hb levels and reduced incidence of some of these excluded complications has been demonstrated (anaemia by definition, cognitive impairment,[23] nocturnal and diurnal hypoxemia[24], retinopathy[25], silent cerebral infarct[26], fat embolism syndrome[27], etc). Furthermore, the incidence of others, such as acute hepatopathy[28] result from the sickling process and are therefore expected to be, at least partially, prevented by increases in healthy red blood cells. While some of these adverse outcomes occur infrequently or have a limited impact on HRQoL, SCD is a chronic and progressive disease and over their lifetime the number of complications that SCD patients are at risk of causes a major impact on HRQoL. Demonstrated by patient experts consulted in the context of the NICE TA743[29] ***"(…) build-up of complications over time and resulting organ damage significantly affects their quality of life***." This applies especially in the target population being considered for voxelotor which is a subset of SCD patients with a high unmet need, where the disease *is* progressing, and end-organ damage *is* occurring despite treatment with available options. Excluding these comorbidities from the CS model would result in an underestimation of the treatment effect of voxelotor. To capture the long-term benefits of increased Hb level without adding comorbidities/events and overcomplicating an already sophisticated model, a benefit associated with increased Hb was considered. Of note, in the model, this benefit is assumed to apply to both treatment arms irrespectively. Based on expert opinion, ***such an assumption is conservative***. According to expert opinion consulted on October 10th 2022, the impact of regular red blood cell transfusions (RTT) on HRQoL is limited since patients feel a boost within the first couple of weeks post transfusion but they feel progressively worse over the course of the following weeks leading up to the next transfusion session 6-8 weeks from the previous. More than that, according to the experts

		consulted, the improvement in HRQoL observed in the first couple of weeks seems to occur at the early stages of the program but reduces as time on RTT increases. **Summary** Considering the evidence presented above describing the relationship between Hb levels in SCD patients and the development of complications, which adversely impact HRQoL, the company believe that the approach taken to model HRQoL benefits associated with Hb is appropriate. The response also explained why improvements in HRQoL were not able to be demonstrated in the pivotal clinical, and therefore, why an alternative source was required to estimate HRQoL. Furthermore, there is precedent for NICE to consider submissions where utility benefits were undetected in the pivotal trial, further reiterating the difficulty of capturing HRQoL improvements in SCD patients. Finally, it justifies attributing a benefit to voxelotor as a reasonable approach.
EAG Response		The EAG disagrees with the company assertions that i) the HOPE trial utilities are very close to population norms and ii) the EQ-5D questionnaire is not able to accurately measure HRQoL for patients with SCD. In the HOPE trial, patients in the voxelotor arm had a mean age of 24 years and a mean utility of 0.86. i) The mean utilities reported by Kind 1999[1] for people in the UK aged 24 years or under and those aged 25 to 34 years are 0.94 and 0.93 respectively. HOPE trial data suggest, therefore, that compared with the general population, the utility decrement for people with SCD who are not receiving RTT is approximately 0.08. ii) The size of the company HOPE trial utility decrement (0.08) suggests that the EQ-5D questionnaire is a reasonable tool to measure the utility of patients with SCD; the EAG highlights that the company carried out a separate study (unpublished) in which the EQ-5D questionnaire was used to measure utility for patients with SCD and used these values in the model. The company model assumes that there is a linear relationship between utility values and Hb level. Following a visual inspection of the Hb levels reported in Appendix T (shown below) the

		EAG considers that the relationship between Hb level and utility is complex and unlikely to be linear. The company is correct to point out that the EQ-5D questionnaire completion rates were not 100% at baseline and declined over time; the EAG does not consider that this invalidates the HOPE trial finding that change in utility value over time was not statistically significant. The potential explanations, provided in the EAG report, as to why there was no statistically significant difference in utility values between HOPE trial voxelotor and placebo arms still stand. **EAG scenario analysis** The EAG has run a scenario in which the utility gain directly associated with an increase in Hb levels was removed from the model. This increased the ICER for the comparison of voxelotor versus Soc to [redacted] per QALY gained.

		 Source: CS, Appendix T References 1. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. Discussion paper 172. University of York (1999) https://www.york.ac.uk/che/pdf/DP172.pdf
Issue 6: Inappropriate regular transfusion therapy rates	No, Delphi panel updated only	The EAG considers that “at baseline, the SoC arm of the company model should not include RTT as a treatment” and states that “The company should have assumed the same proportions

	to provide clarification	of patients were receiving RTT in both arms or, preferably, modelled the risk of having RTT." [EAG Report p.13] Patients on regular transfusion therapy (RTT) were not eligible for inclusion in the HOPE trial as transfusions would have confounded the Hb-related endpoints. Nevertheless, the Company recognises that blood transfusions are an important part of second line treatment for patients with haemolytic anaemia in SCD, as set out in British society of Haematology guidelines on transfusions[30,31] and the NICE Spectra Optia guidance.[32] Because they are an important part of management for some patients, the Company believes it is appropriate and necessary to include RTT as a treatment in the SoC arm. **Source of RTT rates in the economic model** • The company consulted nine practising English clinicians who are experts in SCD in a modified Delphi panel exercise (report presented as CS Appendix U), following NICE DSU guidelines. In the absence of any other data on the proportion of patients receiving RTT, this is best available data source. • The proportion of patients receiving RTT in the model was [redacted]%. This was derived from the Delphi panel as follows: Given that "Table 6. Treatment utilisation before and after voxelotor introduction among adults with SCD", in Appendix U refers to patients willing to take hydroxycarbamide, a follow-up question was sent to the experts asking how patients unwilling to take hydroxycarbamide are currently treated. • A weighted average between the willing and unwilling was calculated as per the following (Table 8 in Appendix U the revised Delphi panel report, shown below) [redacted]

Age 18+	Without voxelotor			With voxelotor		
Treatment options	[redacted]	[redacted]	Weighted average	[redacted]	[redacted]	Weighted average
Percent of patients (from question 4.5.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

		[redacted]

Hydroxycarbamide	[redacted]																						
Regular transfusions	[redacted]																						
Voxelotor	[redacted]																						

* It was assumed that the proportion of patients on regular transfusions + voxelotor is independent of willingness to take HC status
Abbreviations: HC = Hydroxycarbamide

Treatment of RTT in the crizanlizumab appraisal

The company notes in the recent crizanlizumab submission in SCD the submitting company included a proportion of regular transfusion therapy in the SoC arm, despite patients on RTT being excluded in the SUSTAIN registrational trial. Thus there is a precedent to this approach

EAG Response		The potential cost effectiveness of voxelotor is heavily dependent on preventing RTT. If treatment with voxelotor does not reduce RTT, then the ICER for the comparison of voxelotor versus SoC would be [redacted] per QALY gained. The HOPE trial results showed no difference in the use of transfusion therapy between the voxelotor and placebo arms. The only evidence source to estimate RTT use was a Delphi panel. The Delphi panel provided a wide range of responses to the question about the level of use of RTT for patients treated with voxelotor and those not treated with voxelotor. Reponses from the panel for RTT use without voxelotor (with HC) ranged from [redacted]% to [redacted]%, whilst those for patients treated with voxelotor ranged from [redacted]% to [redacted]%. The company states that the value used to populate the model was estimated by taking a weighted average of Delphi panel responses (the approach used to weight responses is not reported). The EAG highlights that the value used to populate the voxelotor arm of the model was [redacted]%, which does not appear a likely weighted average given the range was between [redacted]% and [redacted]%. During the NICE appraisal of crizanlizumab (TA743), the Appraisal Committee accepted that treatment with crizanlizumab led to a reduction in the need for RTT. The (redacted) level of reduction that was accepted by the Appraisal Committee was derived from analysing data,

		rather than from a Delphi panel, and was considered by the Appraisal Committee as being highly uncertain.
Issue 7: The company model generates clinically implausible individual patient simulations	Yes, an updated model has been supplied see Appendix 1: technical engagement analysis addendum for further details	The EAR highlighted the EAG's concerns that the model was generating substantial numbers of clinically implausible patient simulations. The EAR suggests that one of the reasons for this was that post-event mortality for certain events was not being accurately accounted for. While the prior model was incorporating the long-term excess risk of mortality from these events it was considered that the risk of mortality immediately after certain events wasn't being captured. Reviewing the literature, the company determined that there were several events for which the immediate risk of death wasn't included. Using sources derived from the literature the company added additional one-off mortality risk to ARF, Arrhythmias, Heart Failure, and Sepsis. After the addition of these excess one-off mortality rates, the proportion of patients with a large number of certain events was considerably reduced. In their report the EAG called into question the face validity of the model with the explanation that there were meaningful numbers of clinically implausible patient profiles generated in the base case analysis (e.g., a patient with over 100 cardiomegaly admissions). Whilst it is almost impossible to state with any degree of certainty when a clinically implausible patient profile becomes plausible, it is acknowledged that there were several modelled patients with event counts, for example in acute renal failure, where survival would not be likely. To illustrate this visually, we constructed event histograms. In the model analysis submitted at CQs, although the number of patients having large numbers of ARF events is low, there were patients who experienced over 100 events (Figure 4). In the revised modelling submission (Figure 5), we can see clearly that the number of patients experiencing large numbers of events has reduced, indeed the total proportion of patients in the model experiencing 100 or more, 50 or more, and 20 or more events was [redacted]%, [redacted]% and [redacted]% respectively, compared to [redacted]%, [redacted]% and [redacted]% in the previous version. This is expected model behaviour with the revised mortality parameterisation, as now each ARF event has a one-time risk of mortality of [redacted]% (Appendix 1: technical engagement analysis addendum; Section 1.1.2, pg.9). This pattern is repeated across all recurring events in the model with the exception of VOC, which is to be expected given that VOC events do recur frequently in the population used in the model.

		 **Figure 4 – Event frequency distribution for ARF in the standard of care arm (as of per the prior base case model supplied in the first results addendum)**

		 **Figure 5 Event frequency distribution for ARF in the standard of care arm (as of per the current base case model supplied in the second results addendum)** Another criticism the EAG made of the model was that the mean utility value generated in the SoC arm was lower than estimated using company data (vs approx. for age matched estimate from the real-world analysis of the relationship between age and EQ-5D based utility among 220 SCD patients in the UK (Appendix T). The revised model now predicts mean utility in the SoC arm of (Appendix 1: technical engagement analysis addendum; Section 3.1, pg.23), which agrees very well with the company estimates.

		An additional change made to address the plausibility issue was that gallstones has been changed to non-recurring event. The cost applied in the model is for gallstones removal, therefore this should only be allowed to happen once.
EAG Response		The EAG is satisfied that the new company model does not generate individual simulations that are clinically implausible. A teleconference was held between NICE, the company and the EAG on 3 November 2022 to try to resolve new model related issues identified by the EAG, namely: • Life year gain for patients treated with voxelotor even when all clinical parameters for the voxelotor and SoC arms were set to be the same • Model results were substantially different depending on the version of Excel used to run the model; in one version of Excel top up transfusions were reported • The EAG was unable to replicate the company base case ICER per QALY gained The EAG acknowledges the support provided by the company to resolve the new model issues; however, these issues remain unresolved. The company has provided analyses that demonstrate that the life-year gain issue is related to the algorithm relating to voxelotor treatment discontinuation and the effect of any error in this algorithm is small (perhaps just 0.01 life years in favour of treatment with voxelotor). However, the EAG highlights that the actual consequences of correcting this error are unknown. The company was unable to explain why different versions of Excel generated different results. This means that the EAG has been unable to replicate company base case cost effectiveness results and remains unable to verify that the new model outputs are robust.

EAG concluding remarks

The EAG considers that the validity of the new company model cost effectiveness results is highly uncertain. Three key uncertainties described in the EAG report remain unresolved:

- the methods used by the company to generate TTE probabilities is not robust (see EAG response to Issue 4)
- modelled impact of treatment with voxelotor is not supported by HOPE trial evidence (see EAG response to Issue 5)
- inappropriate RTT rates (see EAG response to Issue 6 and below).

The EAG reiterates that there is no robust clinical evidence that treatment with voxelotor reduces the need for RTT, and RTT should not have been incorporated into the company base case model. However, the company model does include RTT and the EAG has the following concerns about the approach to modelling RTT taken by the company:

i) effect of RTT on Hb level
ii) disutility associated with RTT
iii) RTT costs
iv) RTT for patients who discontinue voxelotor.

i) Effect of RTT on Hb level

In the new company model, patients who receive RTT experience an increase in Hb level of [redacted] g/dL. This value is based on results from an analysis of Symphony data and clinical advice Analysis of Symphony data showed that, 28 days after a transfusion, patients experienced an increase in Hb level of [redacted] g/dL. Clinical advice to the company was that RTT involves a transfusion every 6 weeks, and that the increase in Hb level that occurs following a transfusion declines after 3 weeks. The company, therefore, considered that it was appropriate to divide the value derived from the Symphony data analysis ([redacted]g/dL) in half (i.e., [redacted]g/dL). The EAG considers this approach to deriving an estimate for the effect of RTT on a patient's Hb level is not logical. The Symphony data analysis relates to Hb level at 4 weeks following a transfusion, and therefore the Hb increase seen at 3 weeks should be at least as high as the increase seen at 4 weeks. Increasing the size of the Hb level gain associated with RTT will increase the ICER per QALY gained for the comparison of voxelotor versus SoC.

EAG scenario analysis

The EAG has carried out a scenario analysis in which patients who receive RTT experience an increase in Hb level of [redacted]g/dL. Results from this scenario increase the company base case ICER for the comparison of voxelotor versus SoC to [redacted] per QALY gained. The EAG highlights that this scenario generated counterintuitive results as SoC arm QALYs remained unchanged whilst there was a decrease in voxelotor arm QALYs. This result should therefore be treated with caution.

ii) Disutility associated with RTT

The company has increased the disutility associated with RTT from 0.03 to 0.18. The EAG agrees that the value of 0.03 obtained from an incorrect interpretation of the source study, but notes that the value now used by the company is from a TTO study in the general population using vignettes (as was the case with the original source study), not from patients.

In the company base case, the QALY loss associated with RTT ([redacted]) accounts for 45.6% of the difference, over the model time horizon, in QALYs ([redacted]) between the voxelotor and SoC arms. It is, therefore, unfortunate that there is considerable uncertainty around the true magnitude of the disutility associated with RTT.

The EAG also considers that as, in the company base case, RTT costs [redacted] per year, generates a disutility of [redacted] and has limited effect on Hb level (and, therefore, on long term complications), it raises questions about whether the model is failing to adequately capture the benefits of RTT.

iii) RTT costs

The EAG was unable to identify the source of the RTT costs used in the model.

iv) RTT for patients who discontinue treatment with voxelotor

In the new company model, it is unclear whether patients who receive voxelotor and do not receive RTT at baseline, go on to receive RTT if they are a non-responder to voxelotor or discontinue treatment for any other reason. If any patients in the voxelotor arm receive RTT after stopping treatment with voxelotor and this is not accounted for in the model, this will increase the ICER per QALY gained for the comparison of voxelotor versus SoC.

EAG scenario analysis results

Table 2 EAG scenario 1: no direct utility increase associated with an increase in Hb level (voxelotor PAS price)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Voxelotor	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CMU=Commercial Medicines Unit; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; SoC=standard of care

Table 3 EAG scenario 2: setting the RTT rate to be [redacted]% for the voxelotor and Soc arms (voxelotor PAS price)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Voxelotor	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CMU=Commercial Medicines Unit; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; SoC=standard of care

Table 4 EAG scenario 3: Hb level increases by [redacted]g/dL for patients receiving RTT (voxelotor PAS price)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Voxelotor	[redacted]	[redacted]			
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CMU=Commercial Medicines Unit; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; RTT=regular transfusion therapy; SoC=standard of care

Additional issues

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Is voxelotor expected to show improved clinical outcomes and health-related quality of life compared with standard care? [Issue raised by EAG]	Issues 2, 3 and 5	No	Yes, voxelotor is expected to show improved clinical outcomes and health-related quality of life compared with standard care. Voxelotor is indicated by the MHRA for the treatment of haemolytic anaemia due to sickle cell disease in adult and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide (hydroxyurea).[33] The population covered by the submission is "adults and paediatric patients aged 12 years or older with SCD who are ineligible for, intolerant of or unwilling to take hydroxycarbamide, or for whom hydroxycarbamide alone is insufficiently effective." SoC for these patients (which is the comparator in the economic model) consists of HC only, regular transfusion therapy (RTT), RTT + HC, or symptomatic (supportive) care only. These patients currently have no pharmacological disease-modifying options for the treatment of haemolytic anaemia; RTT results in a temporary increase in Hb that wanes between transfusions, but is not indicated for the treatment of haemolytic anaemia (as confirmed by BSH guidelines[31] and by clinicians consulted by the Company at Technical Engagement phase). On its approval of voxelotor, the

			EMA noted that there is a high unmet need for treatments for haemolytic anaemia.[7] The MHRA Public Assessment report states that "There is an unmet need in significant proportion of patients with sickle cell disease who do not respond adequately to currently available treatments or in whom these treatments cannot be administered due to intolerability." Voxelotor is the first and only medicine approved specifically for the treatment of haemolytic anaemia in SCD, and was approved on the basis of beneficial effects on haemolysis and Hb levels, which were considered as being clinically relevant for patients.[8] The MHRA states that "The observed improvement in blood haemoglobin levels after treatment with voxelotor therefore offers a significant benefit in the management of patients with sickle cell disease.[33]" The evidence confirming that the impact of voxelotor on Hb is clinically meaningful is set out in response to Issue 2, and the evidence supporting voxelotor's expected beneficial impact on long-term complications of SCD is set out in response to Issue 3. As occurs with many trials, the EQ-5D data collected in the HOPE trial do not show a significant difference in HRQoL between treatment arms. Potential reasons for this are discussed in the response to Issue 5, together with real-world evidence indicating that patients do experience improvements to their health status with voxelotor. The HRQoL benefit of voxelotor is expected to become further apparent over time due to the expected reduction in patients' risk of long term

			SCD-related complications, compared with standard of care. Taken together, the information presented in the TE responses clearly indicates that patients experience improved clinical outcomes and HRQoL compared with standard of care, and that the difference between voxelotor and SoC can be expected to increase over time.
EAG Response	In the company model, the health-related quality of life gain with voxelotor is generated directly from (i) raised Hb levels and (ii) a reduction in RTT with voxelotor. The EAG remains concerned that this key economic outcome remains poorly evidenced.		
Additional issue 2: How long are people expected to be treated with voxelotor for? [Issue raised by EAG]		No	No additional evidence or discussion is provided regarding this issue at this stage.

Summary of changes to the company's cost-effectiveness estimate(s)

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 4: Methods used by the company to generate time to event probabilities are not robust	• TTE equations were derived using the Symphony database, matched to the HES patient population • VOCs were considered as a continuous variable • Model included cardiomegaly and priapism events	**Change 1** • Used the HES-CPRD dataset directly to derive TTE equations • Altered the parameterisation of VOCs, to a categoric variable, in the TTE equations • Removed cardiomegaly and priapism as events in the model. • See Appendix 1: technical engagement analysis addendum; Section 1.1.1, pg.23	[redacted] (+20.7% vs prior base case)
	• VOC TTE equation was exponential	**Change 2** • Changed VOC TTE equation to log-logistic	[redacted] (-18.2% vs change 1)
Issue 7: The company model generates clinically implausible individual patient simulations	• Long-term excess risk of mortality was applied for ARF, arrhythmias, heart failure, and sepsis events	**Change 3** • Additional one-off mortality risk to ARF, arrhythmias, heart failure, and sepsis. Sources derived from literature	[redacted] (+6.9% vs change 2)

	• Patients could experience multiple gallstones events	**Change 4** • Gallstones has been changed to non-recurring event	[redacted] (+0.5% vs change 3)
Issue 6: Inappropriate regular transfusion therapy rates	• No change in Hb levels for RTT	**Change 5** • Increase in Hb level of [redacted] g/dl for RTT	[redacted] (+14.0% vs change 4)
	• Utility decrement for patients on RTT previously 0.038	**Change 6** • Utility decrement for patients on RTT changed to 0.18	[redacted] (-31.3% vs change 5)
NA – Changes to address NICE resource impact assessment	• Cost per ARECT transfusion: [redacted] • Cost per simple transfusion £608.38	**Change 7** • Cost per ARECT transfusion: £3,674.37 • Cost per simple transfusion £493.28	[redacted] (-8.6% vs change 6)
NA – Updated patient access scheme discount	• Annual cost of voxelotor [redacted] (assumes [redacted] discount)	**Change 8** • Annual cost of voxelotor [redacted] (assumes discount)	[redacted]

Sensitivity analyses around revised base case

Further sensitivity analyses around the revised base case are reported in Appendix 1: technical engagement analysis addendum (Section 1.3)

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