EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

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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]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Katherine Edwards, Research Associate (Clinical Effectiveness), LR*i*G, University of Liverpool

Angela Boland, Director, LR*i*G, University of Liverpool

Sophie Beale, Director, HARE Research, North Yorkshire

Rebecca Harvey, Director, Cabourn Statistics Ltd, Manchester

Rachel Houten, Health Economic Modeller, LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Joseph Sharif, Consultant Haematologist, Manchester University NHS Foundation Trust

Correspondence to: Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

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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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LIST OF ABBREVIATIONS

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.

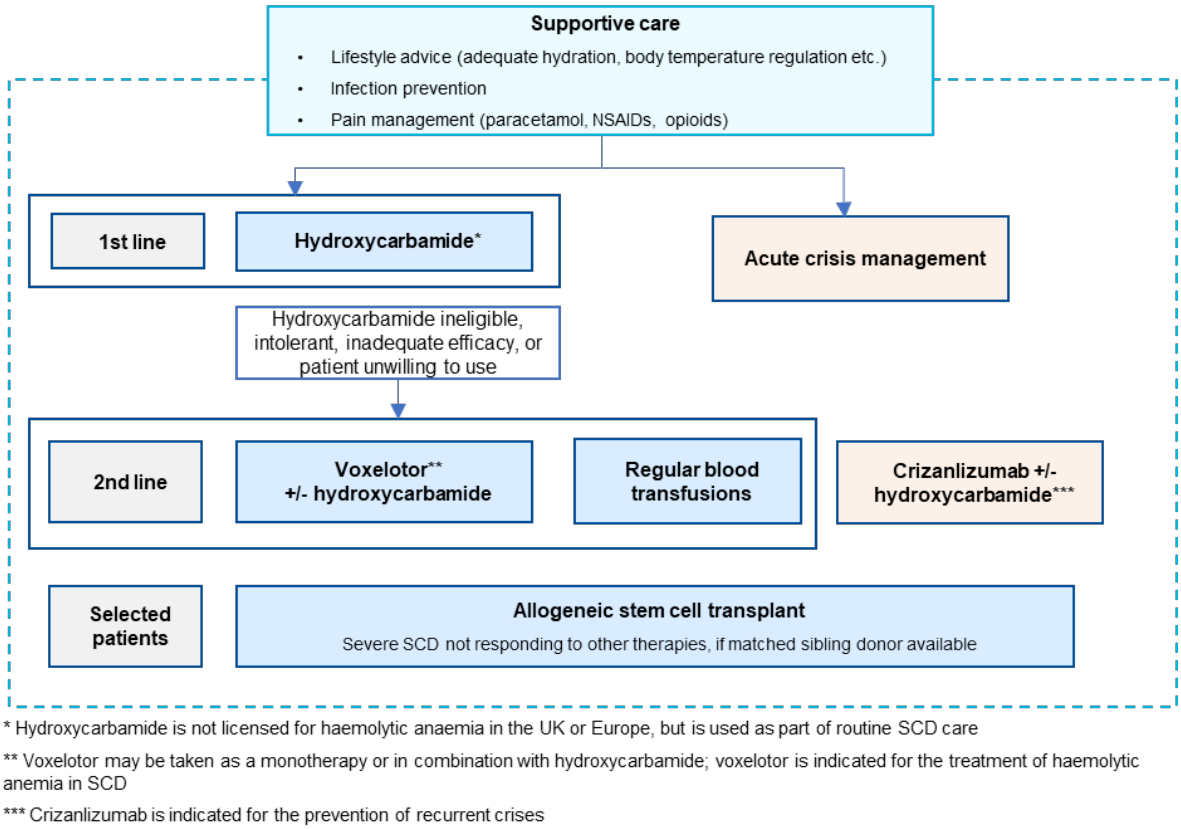
3.2 Population

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[ł] 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

[ł] 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%

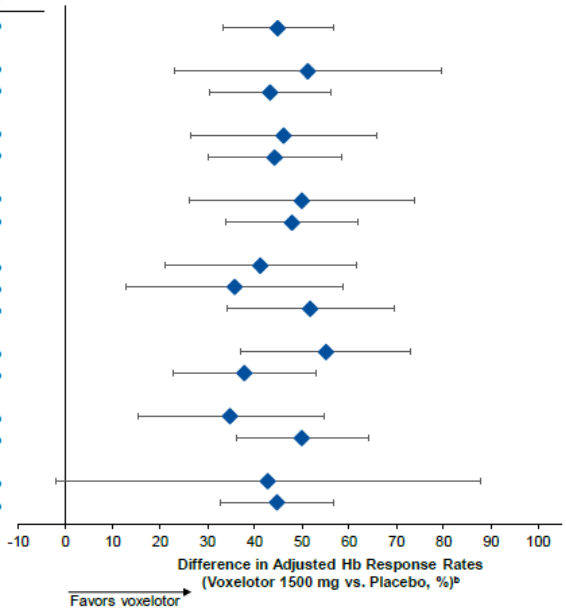


Figure 2 Hb response by subgroup at Week 24

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.

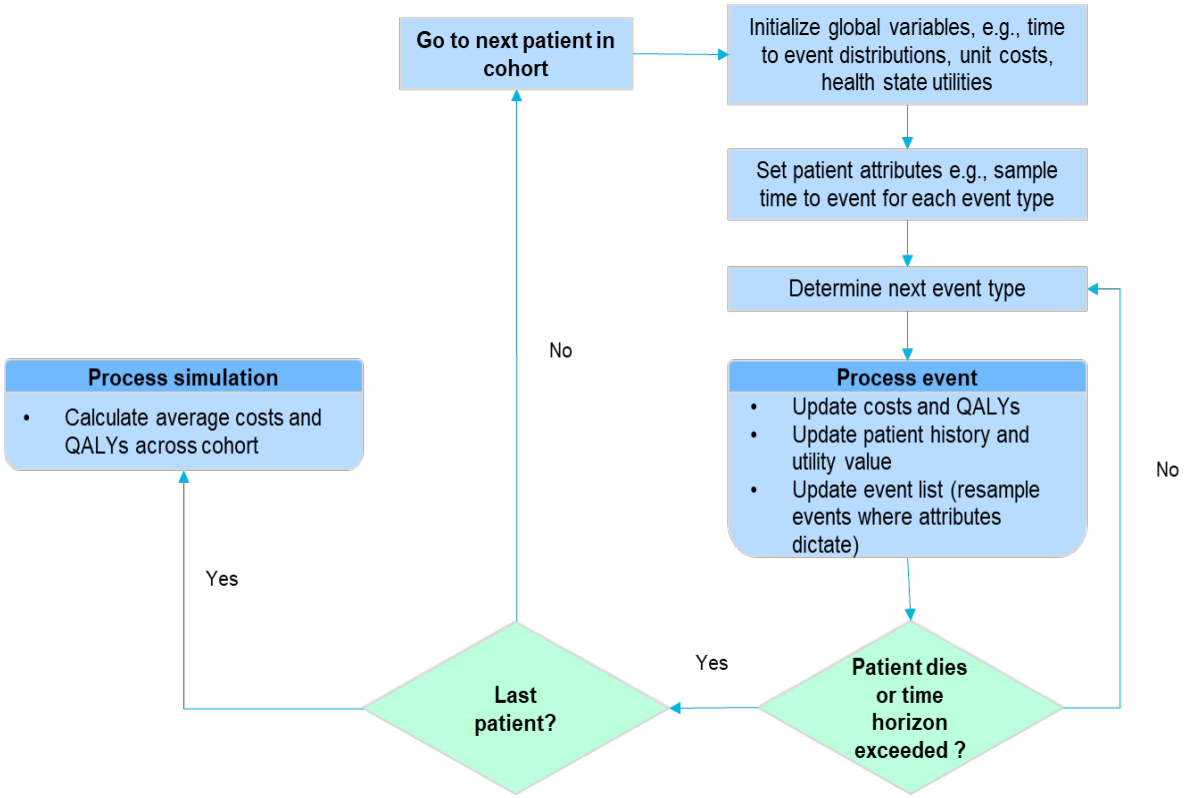


Figure 3 Company simplified discrete event simulation algorithm

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.

7 REFERENCES

1. Egton Medical Information Systems. Sickle Cell Disease and Sickle Cell Anaemia. 2020; Available from: https://patient.info/allergies-blood-immune/sickle-cell-disease-sickle-cell-anaemia. Accessed 27 July 2022.
2. National Institute for Health and Care Excellence. Clinical Knowledge Summaries - Sickle Cell Disease. 2021; Available from: https://cks.nice.org.uk/topics/sickle-cell-disease/. Accessed 27 July 2022.
3. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. New England Journal of Medicine. 2017; 376:1561-73.
4. Sickle Cell Society. Standards for clinical care of adults with sickle cell disease in the UK: Sickle Cell Society 2018.
5. NHS. National Haemoglobinopathy Registry Annual Data Report 2019/20. 2020; Available from: https://nhr.mdsas.com/wp-content/uploads/2021/01/2020_12_NHR_AnnualReport201920_Final.pdf. Accessed 27 July 2022.
6. Public Health England. Sickle cell and thalassaemia screening: data report 2018 to 2019. 2021; Available from: https://www.gov.uk/government/publications/sickle-cell-and-thalassaemia-screening-data-report-2018-to-2019. Accessed 27 July 2022.
7. Public Health England. Sickle cell and thalassaemia screening: programme overview. 2013; Available from: https://www.gov.uk/guidance/sickle-cell-and-thalassaemia-screening-programme-overview. Accessed 27 July 2022.
8. Ashley-Koch A, Yang Q, Olney RS. Sickle hemoglobin (HbS) allele and sickle cell disease: A HuGE review. American Journal of Epidemiology. 2000; 151:839-45.
9. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L*, et al.* Sickle cell disease. Nature Reviews Disease Primers. 2018; 4:1-22.
10. Pleasants S. Epidemiology: A moving target. Nature. 2014; 515:S2-S.
11. Shah N, Bhor M, Xie L, Paulose J, Yuce H. Sickle cell disease complications: Prevalence and resource utilization. PloS one. 2019; 14:e0214355-e.
12. Vora SM, Boyd S, Denny N, Jackson E, Roy NBA, Howard J*, et al.* Expanded eligibility for emerging therapies in sickle cell disease in the UK – crizanlizumab and voxelotor. British Journal of Haematology. n/a.
13. Kato GJ, Steinberg MH, Gladwin MT. Intravascular hemolysis and the pathophysiology of sickle cell disease. Journal of Clinical Investigation. 2017; 127:750-60.
14. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. Jama. 2005; 293:1653-62.
15. NHS. Sickle Cell Disease. 2019; Available from: https://www.nhs.uk/conditions/sickle-cell-disease/. Accessed 27 July 2022.
16. Gardner K, Douiri A, Drasar E, Allman M, Mwirigi A, Awogbade M*, et al.* Survival in adults with sickle cell disease in a high-income setting. Blood. 2016; 128:1436-8.
17. The King's Fund. What is happening to life expectancy in England? 2022; Available from: https://www.kingsfund.org.uk/publications/whats-happening-life-expectancy-england?gclid=EAIaIQobChMI_Mb1qYiU-QIVpoBQBh1QLAQ3EAAYASAAEgK-wPD_BwE. Accessed 17 August 2022.
18. European Medicines Agency. Oxbryta: EPAR - Public Assessment Report. 2022; Available from: https://www.ema.europa.eu/en/documents/assessment-report/oxbryta-epar-public-assessment-report_en.pdf. Accessed 27 July 2022.
19. National Institute for Health and Care Excellence. Voxelotor for treating haemolytic anaemia in people with sickle cell disease [ID1403]: final scope. 2022; Available from: https://www.nice.org.uk/guidance/gid-ta10505/documents/final-scope. Accessed 27 July 2022.
20. Medicines & Healthcare Products Regulatory Agency (MHRA). Voxelotor: Public Assessment Report (PAR). 2022; Available from:

https://www.gov.uk/government/publications/voxelotor-in-the-treatment-of-sickle-cell-disease/voxelotor-public-assessment-report-par Accessed 17 August 2022.
21. Liverpool Reviews and Implementation Group (LRiG). Personal communication with the SPS Horizon Scanning Service. 2022.
22. Food and Drug Administration (FDA). FDA approves voxelotor for sickle cell disease. 2019; Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-voxelotor-sickle-cell-disease. Accessed 20 July 2022.
23. Symphony Health. Putting healthcare data to work for you. 2020; Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://s3.us-east-1.amazonaws.com/prahs-symphony-health/resources/Symphony_IDV-Sheet_FINAL_JULY.pdf?mtime=20200702132440%26focal=none. Accessed 17 August 2022.
24. National Institute for Health and Care Excellence. Sickle cell disease: managing acute painful episodes in hospital. 2012; Available from: https://www.nice.org.uk/guidance/cg143. Accessed 26 July 2022.
25. Qureshi A, Kaya B, Pancham S, Keenan R, Anderson J, Akanni M*, et al.* Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. British Journal of Haematology. 2018; 181:460-75.
26. National Institute for Health and Care Excellence. Spectra Optia for automatic red blood cell exchange in people with sickle cell disease. 2016; Available from: https://www.nice.org.uk/guidance/mtg28. Accessed 17 August 2022.
27. National Institute for Health and Care Excellence. Crizanlizumab for preventing sickle cell crises in sickle cell disease: Committee discussion. 2021; Available from: https://www.nice.org.uk/guidance/ta743/chapter/3-Committee-discussion#comparators. Accessed 17 August 2022.
28. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N*, et al.* Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. British Journal of Haematology. 2017; 176:179-91.
29. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N*, et al.* Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion. British Journal of Haematology. 2017; 176:192-209.
30. European Medicines Compendium. Hydroxycarbamide medac 500 mg capsule, hard. 2021; Available from: https://www.medicines.org.uk/emc/product/254/smpc#gref. Accessed 27 July 2022.
31. Howard J, Ataga KI, Brown RC, Achebe M, Nduba V, El-Beshlawy A*, et al.* Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Haematology. 2021; 8:e323-e33.
32. Achebe M, Hassab H, Alkindi S, Brown RCC, Telfer P, Biemond BJ*, et al.* Long-term safety and efficacy of voxelotor for patients with sickle cell disease: results from an open-label extension of the phase 3 HOPE trial (Poster). American Society of Hematology Annual Meeting & Exposition 2021; December 11-142021.
33. Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A*, et al.* A phase 3 randomized trial of voxelotor in sickle cell disease. New England Journal of Medicine. 2019; 381:509-19.
34. European Medicines Agency. Xromi: EPAR. 2022; Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/xromi. Accessed 17 August 2022.
35. European Medicines Agency. Oxbryta: EPAR. 2022; Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/oxbryta. Accessed 17 August 2022.
36. Han J, Saraf SL, Gordeuk VR. Systematic review of voxelotor: a first-in-class sickle hemoglobin polymerization inhibitor for management of sickle cell disease.

Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2020; 40:525-34.
37. National Institute for Health and Care Excellence. Crizanlizumab for preventing sickle cell crises in sickle cell disease. 2021; Available from: https://www.nice.org.uk/guidance/ta743/chapter/1-Recommendations. Accessed 17 August 2022.
38. National Institute for Health and Care Excellence. Voxelotor for treating haemolytic anaemia in people with sickle cell disease [ID1403]: response to consultee and commentator comments on the draft remit and draft scope (pre-referral). 2022; Available from: https://www.nice.org.uk/guidance/gid-ta10505/documents/scope-consultation-comments-and-responses. Accessed 17 August 2022.
39. MAPI Research Trust. Clinical Global Impressions scale - Improvement, Severity, Change and Efficacy (CGI-I, CGI-S, CGI-C and CGI-E). 2022; Available from: https://eprovide.mapi-trust.org/instruments/clinical-global-impressions-scale-improvement-severity-change-and-efficacy. Accessed 27 August 2022.
40. EuroQoL Research Foundation. EQ-5D. 2022; Available from: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/ Accessed 17 July 2022.
41. Burke L, Hobart JC, Fox K, Lehrer-Graiwer J, Bridges K, Kraus M*, et al.* The 10-Item Sickle Cell Disease Severity Measure (SCDSM-10): A novel measure of daily SCD symptom severity developed to assess benefit of GBT440, an experimental HbS polymerization inhibitor. Blood. 2016; 128:4760-.
42. Global Blood Therapeutics. GBT440-031 A phase 3, double-blind, randomized, placebo-controlled, multicenter study of voxelotor administered orally to patients with sickle cell disease: final clinical study report.2020.
43. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Process and methods [PMG9]. Published date: April 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed 12 July 2022.
44. Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in healthcare. University of York; 2009; Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed 12 July 2022.
45. National Cancer Institute. Common terminology criteria for adverse events (CTCAE), version 4.03,. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm. Accessed 28 July 2022.
46. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). MedDRA® the Medication Dictionary for Regulatory Activities, version 22.0,. Available from: https://www.meddra.org. Accessed 28 July 2022.
47. Achebe M, Hassab H, Alkindi S, Brown RCC, Telfer P, Biemond BJ*, et al.* Long-term safety and efficacy of voxelotor for patients with sickle cell disease: results from an open-label extension of the phase 3 HOPE trial. Blood. 2021; 138:3114.
48. Shah N, Lipato T, Alvarez O, Delea T, Lonshteyn A, Weycker D*, et al.* Real-world effectiveness of voxelotor for treating sickle cell disease in the US: a large claims data analysis. Expert Rev Hematol. 2022; 15:167-73.
49. PRISMA. Transparent reporting of systematic reviews and meta-analyses. 2021; Available from: https://prisma-statement.org/. Accessed 17 August 2022.
50. Adel AA, Abushanab D, Hamad A, Al-Badriyeh D, Yassin MA. L-Glutamine and Crizanlizumab for Adults with Sickle Cell Disease (SCD) in Qatar:A cost-effectiveness analysis. Blood. 2021; 138:4945.
51. Alashgar A, Holdford D, Pontinha V. PRO51 Cost effectiveness of crizanlizumab compared to hydroxyurea for minimizing the frequency of vaso-occlusive (VOC) pain episodes in patients with sickle cell disease from a payer perspective. Value in Health. 2020; 23:S699.

52. Cherry M, Greenhalgh J, Osipenko L, Venkatachalam M, Boland A, Dundar Y*, et al.* The clinical effectiveness and cost-effectiveness of primary stroke prevention in children with sickle cell disease: a systematic review and economic evaluation. NIHR Health Technology Assessment programme: Executive Summaries. 2012.
53. DeMartino P, Haag MB, Hersh AR, Caughey AB, Roth JA. A budget impact analysis of gene therapy for sickle cell disease: the Medicaid perspective. JAMA pediatrics. 2021; 175:617-23.
54. Karnon J, Tolley K, Oyee J, Jewitt K, Ossa D, Akehurst R. Cost-utility analysis of deferasirox compared to standard therapy with desferrioxamine for patients requiring iron chelation therapy in the United Kingdom. Current medical research and opinion. 2008; 24:1609-21.
55. Pontinha V, Almutairi M, Holdford DA. POSB156 Cost-Utility Analysis of Crizanlizumab and Hydroxyurea in Preventing Vaso-Occlusive Events in Patients with Sickle-Cell Disease: A Lifetime Model from a Payer's and Societal Perspectives. Value in Health. 2022; 25:S91.
56. Rizvi AH, Smith KJ, Ragni MV. Cost-Effectiveness Of Thromboprophylaxis In Pregnant Women With Sickle Cell Disease. American Society of Hematology Washington, DC; 2013.
57. Salcedo J, Bulovic J, Young CM. Cost-effectiveness of a hypothetical cell or gene therapy cure for sickle cell disease. Scientific reports. 2021; 11:10838.
58. Spackman E, Sculpher M, Howard J, Malfroy M, Llewelyn C, Choo L*, et al.* Cost-effectiveness analysis of preoperative transfusion in patients with sickle cell disease using evidence from the TAPS trial. European Journal of Haematology. 2014; 92:249-55.
59. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2022; Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Accessed 17 August 2022.
60. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. British Medical Journal. 1996; 313:275.
61. Global Blood Therapeutics. Voxelotor: Summary of Product Characteristics. 2022; Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/oxbryta#product-information-section. Accessed 17 August 2022.
62. da Cunha Gomes EG, Machado LAF, de Oliveira LC, Neto JFN. The erythrocyte alloimmunisation in patients with sickle cell anaemia: a systematic review. Transfusion Medicine. 2019; 29:149-61.
63. DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, Sarnaik SA*, et al.* Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. New England Journal of Medicine. 2014; 371:699-710.
64. Franco JM, Borges CCL, Ansaloni MA, Mauro RDL, Souza Y, Braga JAP. Chronic transfusion therapy effectiveness as primary stroke prophylaxis in sickle cell disease patients. Hematology, Transfusion and Cell Therapy. 2020; 42:12-7.
65. Miller ST, Wright E, Abboud M, Berman B, Files B, Scher CD*, et al.* Impact of chronic transfusion on incidence of pain and acute chest syndrome during the Stroke Prevention Trial (STOP) in sickle-cell anemia. The Journal of Pediatrics. 2001; 139:785-9.
66. Mirre E, Brousse V, Berteloot L, Lambot-Juhan K, Verlhac S, Boulat C*, et al.* Feasibility and efficacy of chronic transfusion for stroke prevention in children with sickle cell disease. European Journal of Haematology. 2010; 84:259-65.
67. National Heart Lung and Blood Institute. Evidence-based management of sickle cell disease. 2014; Available from: https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Accessed.

68. Strouse JJ, Jordan LC, Lanzkron S, Casella JF. The excess burden of stroke in hospitalized adults with sickle cell disease. American Journal of Hematology. 2009; 84:548-52.
69. Global Blood Therapeutics. HealthiQ HES/CPRD analysis of SCD patients report. Data on File. 2021.
70. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. York: Centre for Health Economics; 1999; Available from: https://www.york.ac.uk/che/pdf/DP172. Accessed 17 August 2022.
71. Global Blood Therapeutics. Data on file. 2021.
72. NHS. National cost collection for the NHS 2019/2020. 2021; Available from: https://www.england.nhs.uk/national-cost-collection/#ncc1819 Accessed 27 August 2022.
73. NHS. Proposed Dispensing Feescales for GMS Contractors, England and Wales - 2021, October release. 2021; Available from: https://digital.nhs.uk/data-and-information/publications/statistical/proposed-dispensing-feescales-for-gms/proposed-dispensing-feescales-for-gms-contractors-england-and-wales---2021-october-release. Accessed 17 July 2022.
74. National Institute for Health and Care Excellence. British National Formulary. 2022; Available from: https://bnf.nice.org.uk/drug/. Accessed 17 July 2022.
75. Guest JF, Fuller GW, Vowden P. Venous leg ulcer management in clinical practice in the UK: costs and outcomes. International Wound Journal. 2018; 15:29-37.
76. Ataga KI, Gordeuk VR, Agodoa I, Colby JA, Gittings K, Allen IE. Low hemoglobin increases risk for cerebrovascular disease, kidney disease, pulmonary vasculopathy, and mortality in sickle cell disease: A systematic literature review and meta-analysis. PloS one. 2020; 15:e0229959.
77. Allali S, Taylor M, Brice J, de Montalembert Md. Chronic organ injuries in children with sickle cell disease. Haematologica. 2021; 106:1535-44.
78. Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Kantor E, Bao Y*, et al.* Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics. 2010; 28:935-45.

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.