Voxelotor for treating haemolytic anaemia in people with sickle cell disease

Part 1 slides for public – Fully redacted

Technology appraisal committee D [14th June 2023] – 2nd Appraisal Committee Meeting

Chair: Dr Megan John

Evidence assessment group: Liverpool Reviews and Implementation Group

Technical team: Nigel Gumbleton, Caron Jones, Linda Landells

Company: Pfizer

Key issues from ACM1

Recommendation: Voxelotor is not recommended, within its marketing authorisation, for treating haemolytic anaemia caused by sickle cell disease, with or without hydroxycarbamide, in people 12 years and older

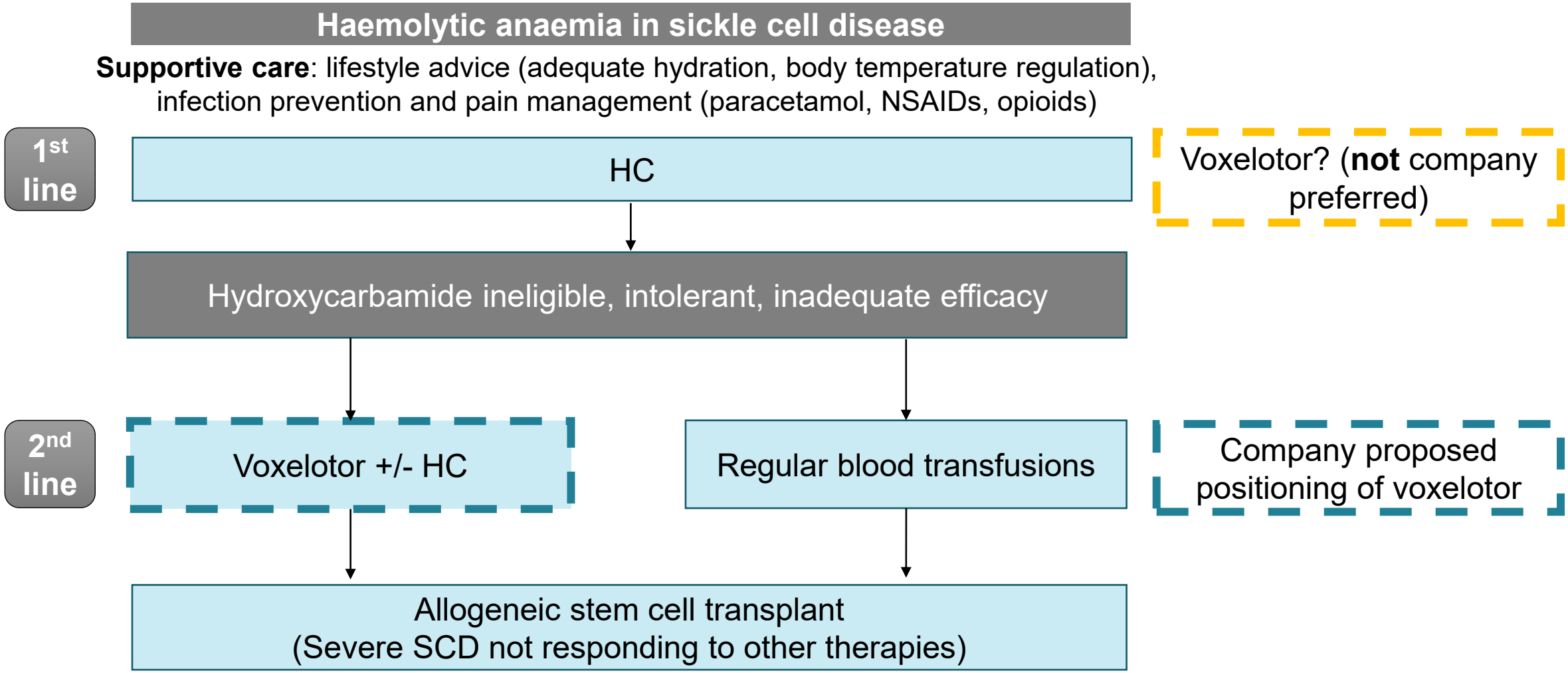
Table 1. Key issues from ACM1

Issue	Committee's considerations
Equalities	Willing to take health inequality into account in its decision making
Positioning of voxelotor	Company proposed 'second-line' positioning not supported by trial evidence
Model population	Model population not reflective of population that would receive voxelotor in clinical practice
Comparators	Most appropriate comparator uncertain. Likely HC or RTT or a mix of both, and may differ depending whether voxelotor used as monotherapy or combination
Long-term complications	Clinically plausible voxelotor could reduce long-term complications in SCD, but high uncertainty around nature and extent of any effect
Rates of RTT	High uncertainty of rates of RTT in each arm. Large impact on cost-effectiveness results. Company could explore impact of alternative assumptions
Utilities	1 g/dL increase in Hb likely associated with improved QoL. However, uncertainty could be reduced by exploring alternative approaches
Change in Hb following RTT	[redacted] g/dL increase in Hb

Abbreviations: Hb, haemoglobin; RTT, regular transfusion therapy; SCD, sickle cell disease; QoL, quality of life

Treatment pathway

Figure 1. Treatment pathway for haemolytic anaemia in sickle cell disease



Abbreviations: HC, hydroxycarbamide; NSAIDs, non-steroidal anti-inflammatory drugs; SCD, sickle cell disease

Voxelotor (Oxbryta, Pfizer)

Table 2. Voxelotor information

Marketing authorisation	• Treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with HC
Mechanism of action	• Voxelotor is a haemoglobin S (HbS) polymerisation inhibitor increasing the affinity of Hb for oxygen. Voxelotor inhibits RBC sickling and improves RBC deformability.
Administration	• Recommended dosage of voxelotor is 3 x 500 mg film-coated tablets taken orally once daily with or without food
Price	• List price 90 x 500mg tablets: £5,917.81 (BNF) • A confidential patient access scheme in the form of a simple discount has been submitted and approved by NHS England

Abbreviations: BNF, British National Formulary; HC, hydroxycarbamide; RBC, red blood cell; SCD, sickle cell disease

DG recommendation: Voxelotor is not recommended

Why the committee made these recommendations

- Uncertainties around the proposed positioning of voxelotor
- The most appropriate comparator was uncertain
- The committee recognised it was clinically plausible that voxelotor could reduce long-term complications in SCD, but because of the lack of evidence, there were high levels of uncertainty around the nature and extent of any effect
- Recognised the uncertainty in the clinical evidence for utility benefit, but noted this could be reduced by exploring alternative approaches
- Model populated with uncertain data that did not reflect the population that would be expected to receive voxelotor in NHS practice

Abbreviations: SCD, sickle cell disease

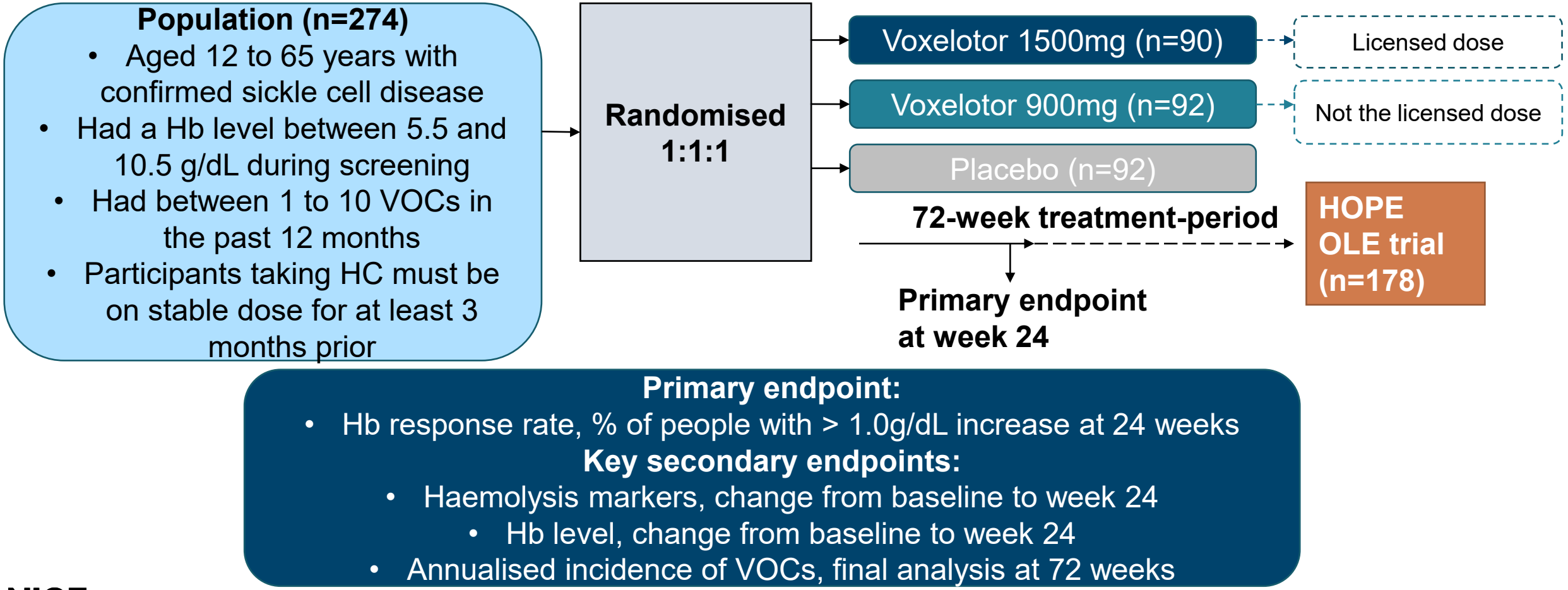
Clinical effectiveness recap

NICE National Institute for Health and Care Excellence

Key clinical trial - HOPE

- 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)

Figure 2. HOPE study design



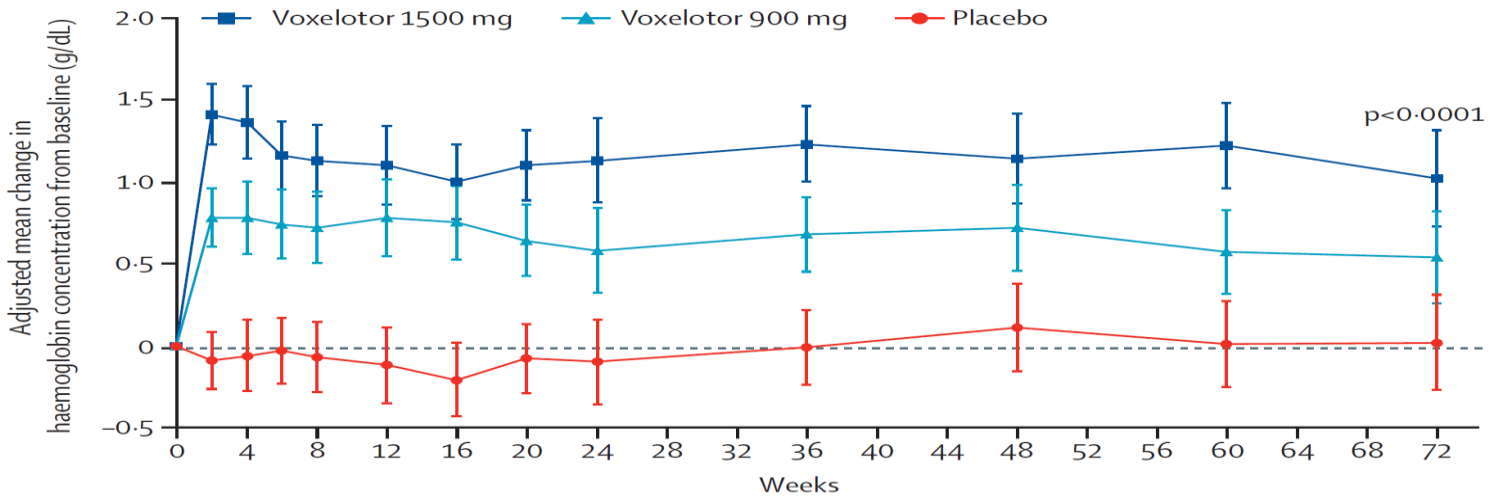
Abbreviations: Hb, haemoglobin; HC, hydroxycarbamide; OLE, open-label extension; RCT, randomised controlled trial; SCD, sickle cell disease; VOC, vaso-occlusive crisis

HOPE trial results

At week 24, voxelotor 1500mg* has higher proportion of people with Hb increase of >1g/dL than placebo

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

Figure 3. Secondary outcome, Hb change from baseline, ITT population



To inform the economic model, treatment effect data from voxelotor 1500mg arm of HOPE stratified by use of HC. The impact of Hb changes on SCD complications is based on time-to-event analysis using evidence from UK CPRD-HES database

NICE

*1500mg is licensed dose. People on placebo & 900mg switched to 1500mg in OLE extension trial

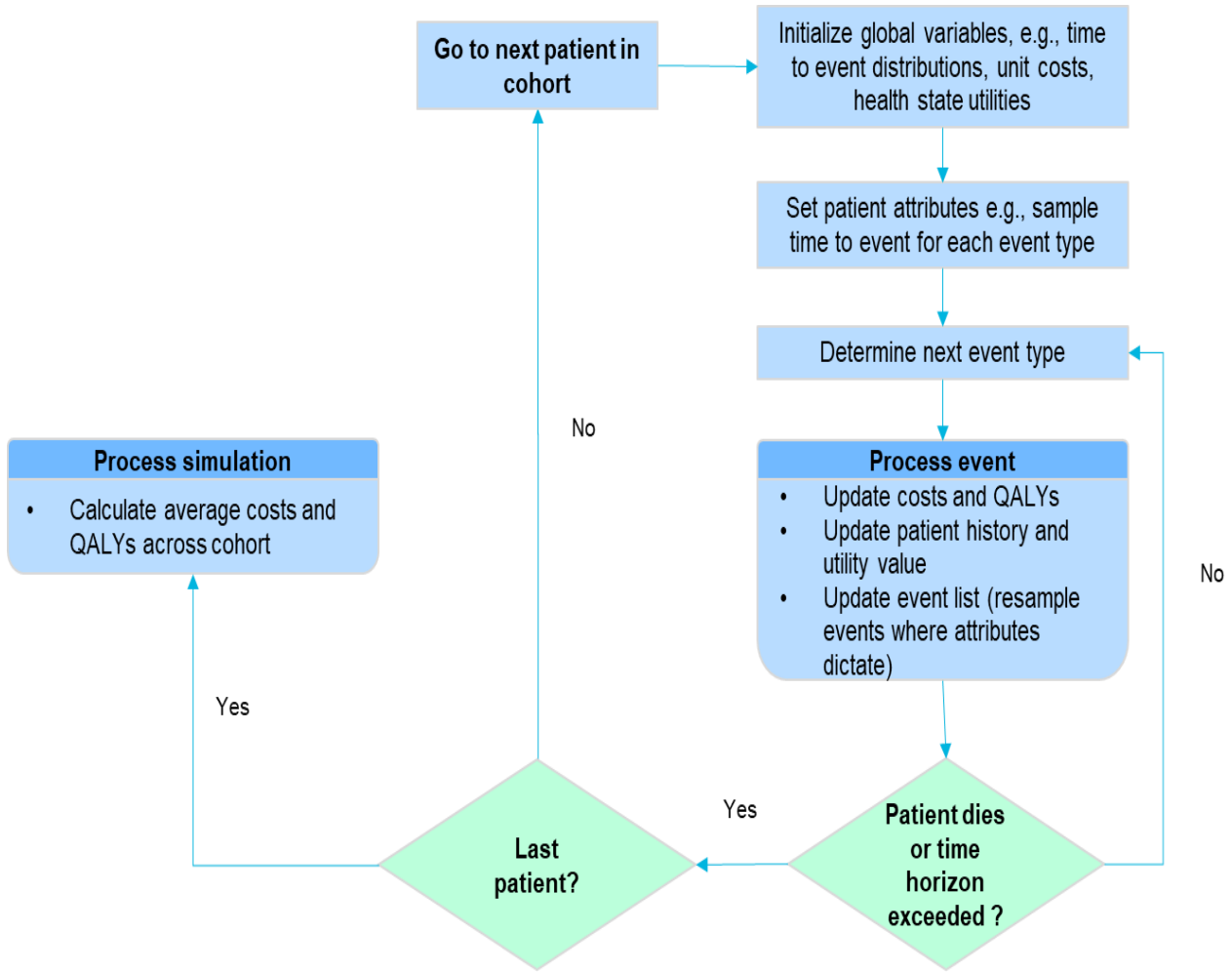
Abbreviations: CI, confidence interval; Hb, haemoglobin; ITT, intention to treat; SCD, sickle cell disease; VOC, vaso-occlusive crisis

Cost effectiveness recap

NICE National Institute for Health and Care Excellence

Company's model overview

Figure 4. Company model structure



- DES model where possible events are modelled on time to event basis.
- Events modelled were SCD-related complications and death, treatment discontinuations
- Biggest model driver is proportions of people in voxelotor and SoC arms who receive RTT
- Complications included: ARF, arrythmias, CKD, ESRD, gallstones, heart failure, leg ulcers, osteomyelitis, osteonecrosis, pulmonary hypertension, sepsis, stroke, VOC

Abbreviations: ARF, acute renal failure; CKD, chronic kidney disease; DES: Discrete Event Simulation; ESRD, end stage renal disease; HC, hydroxycarbamide; RTT, regular transfusion therapy; SCD, sickle cell disease; SoC, standard of care; VOC, vaso-occlusive crisis

Response to consultation

NICE National Institute for Health and Care Excellence

Consultation responses [1]

Consultation comments

Comments received from:

- **Pfizer** (company – manufacturer of voxelotor)
- **Professional organisations**: British Society of Haematology General Haematology Task Force, National Haemoglobinopathy Panel, NHS England, Royal College of Physicians
- **Patient organisation**: Sickle Cell Society
- **2 x Clinical experts**
- **Web comments** (n=3)

Pfizer

- New population sample for people entering the model that is better reflective of population eligible for voxelotor in clinical practice by matching certain characteristics in HOPE
- Hb increase for those on regular transfusion therapy is [redacted] g/dL
- Costs with new evidence obtained from a SCD population using the HES-CPRD database
- PAS has been updated
- Consider a 1.2 QALY weighting should apply, as QALY shortfall is likely to be an underestimate
- Have not submitted a managed access proposal

Abbreviations: CPRD, Clinical Practice Research Database; Hb, haemoglobin; SCD, sickle cell disease; HES, hospital episode statistics; QALY, quality adjusted life year

Consultation responses [2]

Professional organisations

- Insufficient evidence available to recommend voxelotor to all people with SCD over the age of 12
- Subgroup with history of severe, life-threatening complications related to blood transfusion, not able to access voxelotor → support voxelotor treatment in people with SCD who are intolerant of HC, are untransfusable, and who have symptomatic anaemia with Hb consistently <60 g/L
- Voxelotor may have a useful role in treatment of anaemias in SCD under the following circumstances:
  1. People with SCD over 12 years old who are untransfusable or difficult to transfuse
  2. In preparation for surgery in people in category (1)
  3. People with chronic severe anaemia (Hb < 60 g/L), despite use of HC, and who are also in category (1)

Patient organisations

- Committee did not hear from patient expert who could share experience of voxelotor during the clinical trial
- Sufficient weight not applied in NICE decision making to address health inequalities
- Question value of HC as a comparator
- Do not see why voxelotor could not be a candidate for a managed access agreement
- Provided written testimony from an individual who has had voxelotor:
  - "*Within a few months I could feel the difference it [voxelotor] was making to my QoL*"
  - "*reduced tiredness*", "*reduced frequency and level of painful episodes*", "*improved well-being and feeling less vulnerable*", "*improving self-dignity*", "*medium term planning with independence*"

Abbreviations: Hb, haemoglobin; HC, hydroxycarbamide; SCD, sickle cell disease; QoL, quality of life

Consultation responses [3]

Clinical experts

- Negative recommendation could deprive some people of effective therapy e.g., those with severe anaemia who are untransfusable and non-responsive to HC → have a cohort of people with SCD who meet these criteria who are responding well to voxelotor with improved QOL and improved Hb
- Not taken into account heterogenous and multisystem nature of SCD. Prevention of long-term complications (by reversal of anaemia) will only be proven with significant time
- No patient expert who had actually had long-term experience in taking voxelotor
- Uncertainties expected in a rare, poorly researched condition → suggest more flexible approach taken to these uncertainties to address potential health inequalities faced by people with SCD

Abbreviations: Hb, haemoglobin; HC, hydroxycarbamide; SCD, sickle cell disease; QoL, quality of life

Consultation responses [4]

Web comments

- Important to consider benefit of voxelotor for certain people with SCD who are in extreme need for treatment
- Voxelotor is a life changing and life prolonging drug for many people who cannot have other treatment
- For those where transfusions cannot be given, voxelotor improves Hb by reducing haemolysis
- *"Voxeletor has benefitted all those I have treated with it (6 in total) with marked improvements in QOL".* These are people who are difficult to transfuse. Not having access to voxeletor would be detrimental to this group who have had very little in the way of novel therapies for many years
- *"Since I started voxelotor, my everyday life changes drastically. It's almost a year and I feel like a new person/like a normal person"*

Abbreviations: Hb, haemoglobin; SCD, sickle cell disease; QoL, quality of life

Committee preferred assumptions and conclusions

Company explored some of the committee's preferred assumptions

Committee preference at ACM1	Resolved
Positioning of voxelotor - Company proposed 'second-line' positioning not supported by trial evidence	No
Model population - modelled patient population is not reflective of the population that would receive voxelotor in clinical practice	No
Comparators - RTT as a comparator	No
Long-term complications - high levels of uncertainty around nature and extent of any effect	No
Rates of RTT - Company could explore the impact of alternative assumptions	No – removal of RTT not explored by company
Utilities - uncertainty could be reduced by exploring alternative approaches	No
Change in Hb following regular transfusion therapy to be [redacted] g/dL	Yes

Abbreviations: Hb, haemoglobin; RTT, regular transfusion therapy

Committee discussion at ACM2

Parameter	Key question	ICER impact
Equalities	What account for health inequalities should be made in the evaluation of voxelotor for treating haemolytic anaemia in people with sickle cell disease?	Unknown
Positioning	Is the company positioning of voxelotor appropriate?	Unknown
Model population	Is the updated company approach to better match the model population to HOPE trial suitable for decision making? Does the model population reflect the NHS population that would be eligible for voxelotor?	Unknown
Comparators	What are the most appropriate comparators for voxelotor?	Unknown
Long term complications	Is the evidence provided by the company sufficient to suggest voxelotor improves long-term complications of SCD compared with HC?	Unknown
Rates of RTT	Is the evidence provided by the company sufficient to suggest voxelotor will reduce or stop the need for RTT? Is [redacted]% in voxelotor arm and [redacted]% in SoC arm requiring RTT at baseline appropriate?	Large
Utilities	Is there evidence for the impact of voxelotor on increasing Hb by 1g/dL on HRQoL? What utility benefit per 1g/dL Hb increase on voxelotor is most appropriate?	Unknown
QALY weighting	Has the company model accurately captured severity of disease? What, if any, QALY weighting should apply?	Large
Innovation	Have any benefits of voxelotor not been captured in the model? Is voxelotor a step-change in treatment of SCD?	Unknown

Abbreviations: Hb, haemoglobin; HRQoL, health related quality of life; RTT, regular transfusion therapy; SoC, standard of care

Managed access

The company have not submitted a managed access proposal

- To consider a recommendation with managed access, the committee need a managed access proposal (requested as part of the company submission) along with a feasibility assessment from NICE (normally expected approximately 4 weeks prior to the committee meeting)
- The managed access team have been in contact with the company to discuss managed access and request a managed access proposal
- The company has **not** made a managed access proposal for this medicine → Managed access recommendation not possible

Equalities

Health and socio-economic inequalities affect people with SCD

Company DG response:

- Disappointed with committee's conclusion "…that it had not been given robust enough analyses to adequately assess the cost effectiveness of voxelotor, given the historic challenges associated with SCD."
- Aware of historic and ongoing challenges associated with SCD, including underfunding of research
- The All Party Parliamentary Group's No One's Listening report highlighted long-standing lack of investment in sickle cell research describing it as "woefully inadequate"
- Worked to represent a complex disease most accurately with evidence available, and where possible conducting de novo research to fill evidence gaps
- Need for flexibility given challenges with rare diseases, particularly SCD; without this flexibility, concerned historic challenges will continue to disadvantage people with SCD
- Voxelotor may reduce stigma around seeking pain relief. RWE shows voxelotor leads to a reduction in use of opioids; better pain management and less frequent seeking of pain relief

Clinical expert:

- Uncertainties are to be expected in a rare, poorly researched condition
- Suggest a more flexible approach to these uncertainties to address potential health inequalities faced by people with SCD

What account for health inequalities should be made in the evaluation of voxelotor for treating haemolytic anaemia in people with sickle cell disease?

NICE

Abbreviations: RWE, real world evidence; SCD, sickle cell disease

Key issue: Positioning of voxelotor [1]

Committee comments at ACM1

- Company proposed 'second-line' positioning not supported by trial evidence

Company DG response

- In principle, some people eligible for RTT had they not been in HOPE trial
- HOPE excluded RTT → differs from model population. Does not mean effects in HOPE are not comparable
- HOPE population expected to have similar treatment history to model population, as HC is available in all participating countries and recommended as first line
- Model intervention and comparator arms consider independent 'world with' and 'world without' voxelotor
- Proposed positioning does not imply people already having RTT would switch to voxelotor, but those at treatment decision would be treated with voxelotor instead of RTT in 'world with' voxelotor
- Position supported by EAMS: People with SCD ≥12 years old, with haemolytic anaemia (≤10.5 g/dL) and one of:
    1) haemolytic phenotype who are untransfusable or very difficult to transfuse due to previous transfusion reactions or significant alloimmunisation or not consenting to regular blood transfusions
    2) poor response, toxicity or not consenting to hydroxycarbamide
    3) have symptomatic anaemia who cannot be transfused

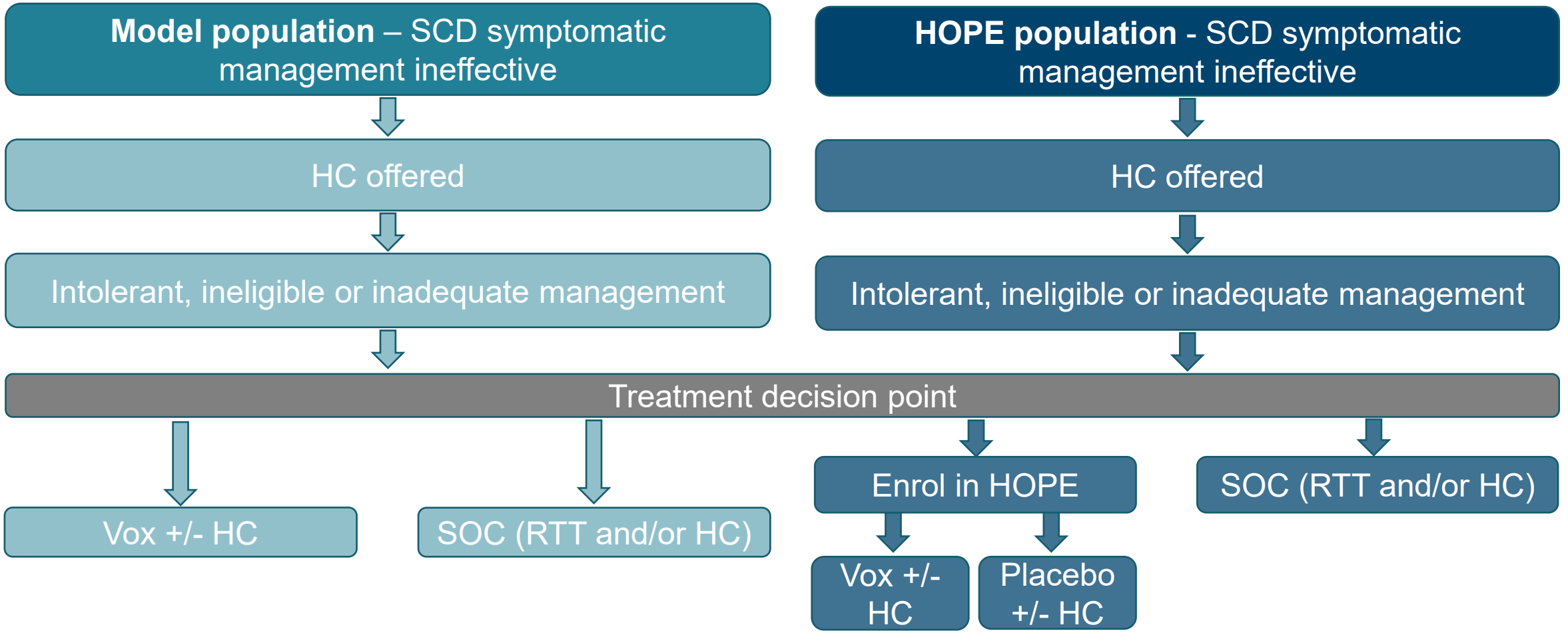
Abbreviations: EAMS. Early Access to Medicines Scheme; HC, hydroxycarbamide; RTT, regular transfusion therapy; SCD, sickle cell disease

Key issue: Positioning of voxelotor [2]

Comparison of HOPE trial and model population

Company DG response

Figure 5. Comparison of model and HOPE trial population in "world with" and "world without" voxelotor scenario



Abbreviations: HC, hydroxycarbamide; RTT, regular transfusion therapy; SCD, sickle cell disease; SOC, standard of care; vox, voxelotor

Key issue: Positioning of voxelotor [3]

Clinical expert comments

- Company suggest people who are taking HC with a good response, and those treated with RTT for whom switching to voxelotor would not be supported by current evidence (e.g., those being regular transfused for stroke prevention), would not have voxelotor
- Positioning is consistent with clinical needs and clinical practice with current EAMS scheme
- Good data from HOPE for voxelotor combined with HC
- Combination of voxelotor with RTT is not being proposed, or be generally clinically appropriate
- Currently recommend RTT for people who do not have another treatment option
- Most services unable to provide transfusion to all people who might benefit because of capacity and funding problems

Is the company positioning of voxelotor appropriate?

Abbreviations: EAMS, Early Access to Medicines Scheme; HC, hydroxycarbamide; RTT, regular transfusion therapy

Key issue: Model population

Company adjusted model population to better match population in HOPE

Committee comments at ACM1

- Company used HES-CPRD to derive TTE probabilities. HES-CPRD population differed from characteristics of people in HOPE trial

Company DG response

- Applied inclusion criteria for VOCs in HOPE (1≤ VOC ≤10) to HES-CPRD linked population
- Weighted MAIC so age, gender, and number of VOCs in previous year matched pooled HOPE population

	HOPE trial population	Updated base case model
Mean age, years	28.000	27.58
Mean Hb, g/dL	8.600	8.91

EAG comments

- Populating model with TTE data from population that more closely matches HOPE reduces company base case ICER
- Revision fails to address/explore uncertainty around nature and extent of raising Hb levels on long-term SCD complications

- Is the updated company approach to better match the model population to HOPE trial suitable for decision making?
- Does the model population reflect the NHS population that would be eligible for voxelotor?

Abbreviations: Hb, haemoglobin; HES-CPRD, Hospital Episode Statistics-Clinical Practice Research Database; MAIC, matching adjusted indirect comparisons; TTE, time to event; VOC, vaso-occlusive crisis

Key issue: Comparators [1]

Most appropriate comparators are uncertain

Committee comments at ACM1

- Distinguish between medical contraindications to HC, and those who choose not to take it for other reasons
- Most appropriate comparator uncertain. But likely to be HC or RTT or a mix of both, and this may differ depending on whether voxelotor is used as monotherapy or in combination

Company DG response

- Population updated to "second-line treatment after HC consideration in people who are ineligible for, intolerant of HC, or for whom HC alone is insufficiently effective."
- Proposed position defined by clinical experts and supported by clinical experts in ECM1, who would not offer voxelotor in place of HC at present → impossible to estimate how prescribing of a new intervention may change based on future evidence and emerging treatments
- Voxelotor not expected to displace ad hoc 'rescue' transfusions. In contrast, voxelotor anticipated to displace a proportion of RTT use
- Agree conducting an ITC between voxelotor and RTT would be informative, however, not feasible due to lack of data

Abbreviations: HC, hydroxycarbamide; ITC, indirect treatment comparison; RTT, regular transfusion therapy; SOC, standard of care

Key issue: Comparators [2]

EAG comments

- Acknowledge merits of an ITC comparing voxelotor with RTT but agree with company that due to lack of RTT efficacy data, this analysis would not be possible
- Most appropriate comparator(s) uncertain

Clinical expert comments

- Very common in adults with SCD not to accept to take HC
- Potential of voxelotor to be used in place of RTT, in particular automated red cell exchange transfusion (ARCET), has not been adequately evaluated
- ARCET only partially implemented in NHS and hugely challenging regarding resources of staff, equipment and blood stocks
- Most clinicians consider voxelotor an alternative to transfusion for some transfusion indications in SCD
- Proportion of people either being treated with RTT, or considered for transfusion could potentially be considered for voxelotor therapy → provide savings for NHS in staffing and blood utilisation

What are the most appropriate comparators for voxelotor?

NICE

Abbreviations: HC, hydroxycarbamide; ITC, indirect treatment comparison; RTT, regular transfusion therapy; SCD, sickle cell disease

Key issue: Long-term complications [1]

Impact of voxelotor on long-term complications uncertain

Committee comments at ACM1

- Clinically plausible that voxelotor could reduce long-term complications in SCD, but because of lack of evidence, there were high levels of uncertainty around nature and extent of any effect

Company DG response

- Recognise uncertainty around nature and extent of effect due to challenges in generating long-term data, especially in rare diseases with high unmet needs
- HOPE showed voxelotor causes improvements in Hb
- Link between lower Hb and worse outcomes is biologically plausible and demonstrated across epidemiological studies → level 2 surrogate relationship according to NICE manual
- In rare diseases with high unmet need such as SCD it may be unethical to conduct long-term trials, limiting opportunity to demonstrate a level 1 relationship
- Strength of surrogate relationship not been recognised by committee, despite support from clinical experts
- Model updated to include costs of complications using data from HES-CPRD population that was used to generate the TTE equations for complications

Abbreviations: Hb, haemoglobin; RTT, regular transfusion therapy; SCD, sickle cell disease; TTE, time to event

Key issue: Long-term complications [2]

EAG comments

- Updated complication management costs are substantially higher than costs during ACM1. As complication incidence rates are not substantially different, updated costs has minimal effect on cost effectiveness results
- However, impact of voxelotor on long-term complications remains highly uncertain

Clinical expert:

- Concerned not taken into account heterogenous nature of SCD and multisystem nature of condition
- Prevention of complications (by reversal of anaemia) will only be proven with significant time
- Suggest flexible approach, given mechanism of action of voxelotor, which addresses primary cause of SCD (polymerisation of Hb)
- HOPE shows significant improvement in Hb level, which is as a consequence of reduced damage to RBC because of reduced polymer formation

- Is the evidence provided by the company sufficient to suggest voxelotor improves long-term complications of SCD compared with HC?

NICE

Abbreviations: Hb, haemoglobin; HC, hydroxycarbamide; RBC, red blood cells; SCD, sickle cell disease

Key issue: Rates of RTT [1]

Rates of RTT have large impact on cost-effectiveness

Background

- Necessary to include RTT as a treatment in model → Consulted 9 English SCD clinicians in a modified Delphi panel exercise. At ACM1, assumed [redacted]% in voxelotor arm and [redacted]% in SOC arm require RTT at baseline

Committee comments at ACM1

- Not clear why rates of RTT varied at baseline in model
- Given extremely high uncertainty of rates of RTT in each arm, and impact on cost-effectiveness results, company could explore impact of alternative assumptions

Company DG response

- Difference in RTT rates between arms reflects voxelotor being available instead of RTT following HC. It is not a result of people already having RTT switching to voxelotor
- Model considers 2 scenarios independently → 'world with' and 'world without' voxelotor
- % having RTT in 'world without' voxelotor may be a conservative estimate:
  - Clinicians limited by capacity and long waiting lists
  - 'No One's Listening' report a specific recommendation that dedicated funding should be made available for NHS Trusts to improve apheresis capacity → if implemented, proportion having RTT in 'world without' voxelotor should be expected to increase

Abbreviations: HC, hydroxycarbamide; RTT, regular transfusion therapy; SCD, sickle cell disease; SOC, standard of care

Key issue: Rates of RTT [2]

Company scenarios varying rate of RTT in SOC arm

Company DG response

- Further consultation with haematologists in March-April 2023 → [redacted]% of people in line to have RTT but currently not doing so for various reasons including capacity, waiting lists, lifestyle and religious beliefs → strong unmet need for alternative treatments such as voxelotor
- Company base case value for % RTT in SOC arm ([redacted]%) a conservative estimate

Table 3. Scenarios for % RTT in SOC arm provided by company

Scenario/Source of RTT in SoC arm	% RTT in SOC arm
Company base case - Delphi panel	[redacted]%
March-April 2023 clinician survey	[redacted]%
Market research among [redacted] practicing UK clinicians (2020)	[redacted]%
Clinical Practice Research Database and linked Hospital Episode Statistics	[redacted]%

- Wide variation in estimates → HES-CPRD data routinely captures all GP prescribed treatments, does not fully record treatments administered in secondary care or emergency care
- RTT administered in secondary care → under-recorded in HES-CPRD → underestimate true RTT use
- RTT % in SOC arm of company base case ([redacted]%) derived from modified Delphi panel is most appropriate value and falls within range of 2 clinician surveys ([redacted]%–[redacted]%)

Abbreviations: HES-CPRD, Hospital Episode Statistics-Clinical Practice Research Datalink; RTT, regular transfusion therapy, SOC, standard of care;

Key issue: Rates of RTT [3]

EAG – no evidence for RTT rate in voxelotor arm

EAG comments

- EAG satisfied with evidence to support company base case SOC RTT rate of [redacted]%
- However, company not provided any further evidence to support voxelotor RTT rate of [redacted]%
- Any increase in RTT rate in voxelotor arm, will make voxelotor less cost effective
- RTT rates account for substantial % of total treatment costs in SOC arm ([redacted]), compared with vastly reduced % of total treatment costs in voxelotor arm ([redacted])
- HOPE trial excluded RTT and results do not show a difference in proportions of RTT in the two arms. Therefore, no clinical trial evidence demonstrating effect of voxelotor on reducing RTT → primary driver of cost differences between voxelotor and SOC (except voxelotor cost) is based on assumption

Clinical expert comments

- Experience in EAMS and Symphony database → voxelotor and RTT would not be used in combination
- Voxelotor an alternative to RTT. For most people, not clinically advisable to treat with combination of voxelotor and RTT → Using together might be counter-productive as it might interfere with effects of transfused blood by reducing oxygen delivery of normal haemoglobin
- Company model is choice between voxelotor and RTT, therefore groups will inevitably be unbalanced

- Is the evidence provided by the company sufficient to suggest voxelotor will reduce or stop the need for RTT?
- Is [redacted]% in voxelotor arm and [redacted]% in SoC arm requiring RTT at baseline appropriate?

Abbreviations: EAMS, early access to medicines scheme; RTT, regular transfusion therapy, SOC, standard of care;

Key issue: Utility values [1]

Hb increase may provide a utility benefit but amount is uncertain

Background

- In HOPE, no significant difference in EQ-5D between voxelotor and SOC arms at 72 weeks
- Company used analysis of EQ-5D from Patient Journey Survey of people with SCD
- Company state limitations of EQ-5D from HOPE → missing data, high baseline values, long-term complications not captured and validity of EQ-5D in SCD

Committee comments at ACM1

- Increase in Hb of 1 g/dL likely associated with improvement in QoL for people with SCD and therefore utility benefit in model. However, uncertainty could be reduced by exploring alternative approaches

Company DG response

- Voxelotor improvement in QoL shown by CGI-C→ 74% treated with voxelotor described as “very much improved” or “moderately improved” compared to 47% in placebo arm
- Attempted excluding HOPE EQ-5D values higher than general population norms at baseline (>0.9, >0.8 and >0.74) → data set too small and not qualitatively different from those already presented
- Literature review explore alternative approaches to capture impact of a 1 g/dL change in Hb on QoL in SCD
- Identified range of utilities: 0.0114 to 0.109 for a 1 g/dL increase in Hb → current estimate of [redacted] within this range; however, reinforces uncertainty, therefore provided scenarios using 0.028, 0.075 and 0.109

Abbreviations: CGI-C, Clinical Global Impression of Change; Hb, haemoglobin; SOC, standard of care; QoL, quality of life

Key issue: Utility values [2]

EAG – No utility benefit from Hb increase should be in the model

EAG comments

- Considers company scenario analysis useful to explore effect of different utility values
- Modelling should adhere to NICE Reference Case → use of clinical trial EQ-5D data
- HOPE EQ-5D showed no statistically significant difference between arms from baseline to Week 72
- At Week 72, SoC arm experienced a numerically larger improvement in utility than voxelotor arm
- No HOPE trial evidence to support voxelotor improves QoL (measured using EQ-5D) compared with SoC → no utility gain should be modelled

Clinical expert comments

- "*I have a cohort of people who are responding well to voxelotor with improved QOL and improved Hb*"

Technical team comments

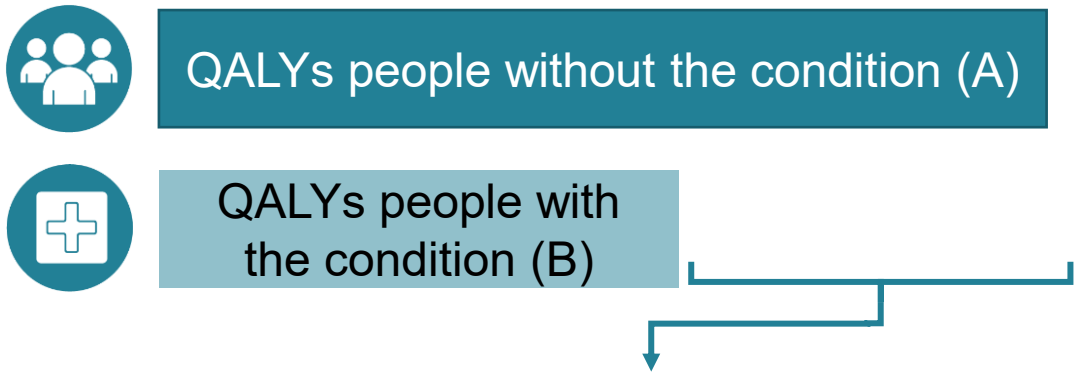
- NICE Health Technology Evaluations: the manual, states "EQ-5D reported by patients and/or carers in a relevant study" is preferred
- However, also considers EQ-5D can be sourced from literature and when more than 1 plausible set of EQ-5D data is available, sensitivity analyses should be done to show the effect of alternative utility values

- Is there evidence for the impact of voxelotor on increasing Hb by 1g/dL on HRQoL?
- What utility benefit per 1g/dL Hb increase on voxelotor is most appropriate?

Abbreviations: Hb, haemoglobin; MAIC, matching adjusted indirect comparisons; QOL, quality of life; TTE, time to event; VOC, vaso-occlusive crisis

QALY weightings for severity [1]

New severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall (AS)	Proportional shortfall (PS)
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year

QALY weightings for severity [2]

	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment	**Absolute QALY shortfall**	**Proportional QALY shortfall**
Company base case	[redacted]	[redacted]	[redacted]	[redacted]
1.5% discount rate	[redacted]	[redacted]	[redacted]	[redacted]

X1 QALY weight

X1.7 QALY weight

Company

- Consider 1.2 weighting should apply, as QALY shortfall calculation likely an underestimate:
  - average age in NHS practice likely lower than model age → SCD inherited disease and voxelotor licensed aged ≥12. Reduction in population age produces a QALY shortfall > 1.2 threshold
  - uncertainty in true QALY loss in SCD → may be attributed to paradoxical finding people with chronic conditions from an early age adapt to levels of disability, often reporting better QoL than expected due to altered perception of disease. Reported in long-term conditions e.g. haemophilia
  - QALY shortfall calculation highly sensitive to discount rates. Impact of discounting even larger in inherited chronic diseases like SCD, discounting applied on outcomes from young age. SCD is chronic in nature, severely debilitating and benefits of voxelotor are rapid and expected to be sustained over full lifespan → believe flexibility should be given to consider non-reference case discount rate of 1.5% when applied to health effects in severity modifier calculations
  - In PSA, the AS would exceed threshold for 1.2 severity modifier in 60% of simulations

NICE Abbreviations: AS: absolute shortfall SCD, sickle cell disease; SoC, standard of care; PSA, probability sensitivity analysis; QALY, quality-adjusted life year; QOL, quality of life;

QALY weightings for severity [3]

EAG comments

- [redacted] is best estimate from model. Allowing rounding would lower threshold to [redacted], therefore inappropriate
- If average age in NHS lower than company model, implications for generalisability of model results to NHS
- Company not provided source to support claim people who have chronic conditions from birth learn to live with their disabilities and how this impacts perceptions of HRQoL when completing EQ-5D. Mean utility in SoC arm in the model is [redacted]; suggests significant utility loss already captured for people with SCD
- Evidence to support long-term benefit of voxelotor not provided by company
  - People with SCD likely to have shorter life expectancy than general population. However, in company base case, voxelotor provides an additional [redacted] life years compared to SoC and increases mean utility from [redacted] (SoC) to [redacted] (voxelotor) → 1.5% discount rate not appropriate
- NICE Health Technology Evaluations: the manual does not stipulate percentage of PSA iteration QALY shortfall results greater/lower than 12 is required before a severity modifier should/should not be applied

Technical team comments

- NICE Health Technology Evaluations: the manual, states “the committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects, if, in the committee's considerations, all of the following criteria are met:
  - the technology is for people who would otherwise die or have a very severely impaired life
  - it is likely to restore them to full or near-full health
  - the benefits are likely to be sustained over a very long period

Has the company model accurately captured severity of disease? What, if any, QALY weighting should apply?

Abbreviations: HRQoL, health related quality of life; SCD, sickle cell disease; SoC, standard of care; QALY: quality-adjusted life year

Uncaptured benefits/Innovation

Company consider voxelotor innovative

Company

- Number of important benefits of voxelotor not captured in model
- As an alternative to RTT, voxelotor will reduce:
  - need for transfusion-related hospital visits
  - travel to specialist centres
  - anxiety over potential adverse effects from transfusions
- Reduced need for transfusions will benefit NHS through reduced pressure on blood supplies and transfusion clinic time
- Voxelotor potentially limiting long-term complications also benefit of reduced anxiety relating to future outcomes

- Have any benefits of voxelotor not been captured in the model?
- Is voxelotor a step-change in treatment of SCD?

NICE

Abbreviations: RTT, regular transfusion therapy; SCD, sickle cell disease

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

- Company base case ICER is below the threshold normally considered as an effective use of NHS resources
- Scenario analyses varying the rate of RTT results in ICERs above the threshold normally considered as an effective use of NHS resources

Cost-effectiveness results and scenarios

Analyses with voxelotor PAS and confidential mid-point CMU prices

Company analysis

Company base case assumptions post consultation

- Utility increment of [redacted] per 1g/dL increase in Hb
- RTT rate of [redacted]% in voxelotor arm and [redacted]% in SoC arm
- Increase in Hb with RTT of [redacted] g/dL
- Multiplicative utility values for SCD complications
- TTE dataset from HES-CPRD
- HOPE trial Hb evaluation at 24 weeks
- Updated PAS discount

→ Base case ICER post consultation **< £20,000/QALY**

EAG scenarios applied to company base case

1a. No direct utility benefit associated 1g/dL increase in Hb

1b. 0.028 utility benefit associated 1g/dL increase in Hb

1c. 0.075 utility benefit associated 1g/dL increase in Hb

1d. 0.109 utility benefit associated 1g/dL increase in Hb

→ ICERs **< £20,000/QALY**

2a. RTT rate for voxelotor arm set to [redacted]%

2b. RTT rate for voxelotor arm set to [redacted]%

2c. RTT rate for voxelotor arm set to [redacted]%

→ ICERs **>> £30,000/QALY**

NICE

Abbreviations: CMU, commercial medicines unit; Hb, haemoglobin; HES-CPRD, Hospital Episode Statistics-Clinical Practice Research Database; ICER, incremental cost effectiveness ratio; PAS, patient access scheme; RTT, regular transfusion therapy; SCD, sickle cell disease; SOC, standard of care; TTE, time to event

Patient perspective summary

ACM1 recap: patient organisation comments

- SCD is a debilitating condition. Severe painful crises are unpredictable and common
- High unmet need for effective additional disease modifying treatments for SCD
- Burden of SCD is significant. Profound impact on QoL, including education, work and relationships

Patient organisation DG response

- Voxelotor potentially very beneficial for some people living with SCD (those with primarily haemolysis driven symptoms)
- Do not see why voxelotor could not be a candidate for a managed access agreement
- Sufficient weight not applied in NICE decision making to address health inequalities

Patient DG response quotes

- "*Within a few months I could feel the difference it [voxelotor] was making to my QoL*"
- "*Reduced tiredness which meant I was able to do more for myself without having to rely on others such as preparing meals. This helped greatly with improving my self-dignity*"
- "*Reduction in the frequency and level of painful episodes including hospitalisation. This meant less disruptions to my everyday living and I can actually do some medium term planning with independence*"
- "*Improved well-being and feeling less vulnerable as I am able to do more for myself including holding on to my job*"
- "*Since I started voxelotor, my everyday life changes drastically. It's almost a year and I feel like a new person/like a normal person*"

Abbreviations: SCD, sickle cell disease; QoL, quality of life

Committee discussion at ACM2

Parameter	Key question	ICER impact
Equalities	What account for health inequalities should be made in the evaluation of voxelotor for treating haemolytic anaemia in people with sickle cell disease?	Unknown
Positioning	Is the company positioning of voxelotor appropriate?	Unknown
Model population	Is the updated company approach to better match the model population to HOPE trial suitable for decision making? Does the model population reflect the NHS population that would be eligible for voxelotor?	Unknown
Comparators	What are the most appropriate comparators for voxelotor?	Unknown
Long term complications	Is the evidence provided by the company sufficient to suggest voxelotor improves long-term complications of SCD compared with HC?	Unknown
Rates of RTT	Is the evidence provided by the company sufficient to suggest voxelotor will reduce or stop the need for RTT? Is [redacted]% in voxelotor arm and [redacted]% in SoC arm requiring RTT at baseline appropriate?	Large
Utilities	Is there evidence for the impact of voxelotor on increasing Hb by 1g/dL on HRQoL? What utility benefit per 1g/dL Hb increase on voxelotor is most appropriate?	Unknown
QALY weighting	Has the company model accurately captured severity of disease? What, if any, QALY weighting should apply?	Large
Innovation	Have any benefits of voxelotor not been captured in the model? Is voxelotor a step-change in treatment of SCD?	Unknown

Abbreviations: Hb, haemoglobin; HRQoL, health related quality of life; RTT, regular transfusion therapy; SoC, standard of care

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Thank you.