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Crizanlizumab for preventing sickle cell crises in sickle cell disease

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR)

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Contributions of authors

Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Hannah Penton acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Heleen Vellekoop, Valerie Wester, Kathi Abraham, Philip Klein, Steve Ryder and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Annette Chalker and Vanessa Huertas Carrera acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Isaac Corro Ramos acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report, and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

Abbreviations

ACS	Acute chest syndrome
AE	Adverse event
AiC	Academic in confidence
AIC	Akaike information criterion
ASCT	Allogenic stem-cell transplant
ASH	American Society of Hematology
AWMSG	All Wales Medicines Strategy Group
BC	Base-case
BIC	Bayesian information criterion
BNF	British National Formulary
BPI	Brief Pain Inventory
BSH	British Society for Haematology
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Central Register of Controlled Trials
CfB	Change from baseline
CG	Clinical guideline
CiC	Commercial in confidence
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRC	Crisis Review Committee
CRD	Centre for Reviews and Dissemination
Criz.	Crizanlizumab
CRU	Cost resource use
CS	Company submission
CSR	Clinical study report
DARE	Database of Abstract Reviews of Effects
DSA	Deterministic sensitivity analysis
EED	Economic Evaluation Database
EHA	European Haematology Association
EMA	European Medicines Agency
eMIT	Electronic Marketing Information Tool
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
Haemo-QoL-A	Haemophilia-specific Quality of Life Questionnaire
Hb	Haemoglobin
HbS	Homozygous haemoglobin S
HbSβ	Haemoglobin S-beta plus
HbSβ0	Haemoglobin S-beta zero
HbSC	Sickle cell–hemoglobin C
HC	Hydroxycarbamide
HES	Hospital Episode Statistics
HLA	Human leucocyte antigen
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
HSUV	Health state utility value
HTA	Health technology assessment
HTAD	Health Technology Assessment database
HU	Hydroxyurea

HUI	Health utility index
ICER	Incremental cost effectiveness ratio
incr.	Incremental
IQR	Inter-quartile range
IRR	Incident rate ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
IXRS	Interactive voice/web response system
kg	Kilogram
KSR	Kleijnen Systematic Reviews
LS	Least squares
LYG	Life years gained
mg	Milligram
NCPE	National Centre for Pharmacoeconomics
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drugs
PAS	Patient Access Scheme
PICOS	Population, Intervention(s), Comparator(s), Outcomes, Study Type
PP	Per-protocol
PRISMA	Transparent reporting of systematic reviews and meta-analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PY	Patient year
QALY	Quality-adjusted life year
QoL	Quality of life
RBC	Red blood cell
RCT	Randomised controlled trial
RDI	Relative dose intensity
SAE	Serious adverse event
SCD	Sickle cell disease
ScHARR	School of Health and Related Research
ScHARRHUD	School of Health and Related Research Health Utilities Database
SCPC	Sickle cell-related pain crises
SD	Standard deviation
SF-36	36-Item Short Form Health Survey
SF-36v2	36-Item Short Form Health Survey version 2
SF-6D	Short form-six dimensions
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SPS	Specialist Pharmacy Service
SoC	Standard of care
TEAE	Treatment-emergent adverse event
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale
VOC	Vaso-occlusive crises
WTP	Willingness-to-pay

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1. Summary

1.1 Critique of the decision problem in the company's submission

1.1.1 Population

The final scope issued by the National Institute for Health and Care Excellence (NICE) defined the population of interest as people with sickle cell disease (SCD) aged 16 years and older.

The population presented in the company submission (CS) is narrower than that defined in the NICE final scope as, in line with the anticipated licensed indication, it specifically related to the use of crizanlizumab for the prevention of recurrent vaso-occlusive crises (VOC) in people with SCD. In addition, the identified trial, SUSTAIN, included participants 16 to 65 years of age, i.e. results may not be applicable to participants older than 65 years.

Therefore, conclusions should only be made in the narrower population addressed in the CS.

1.1.2 Intervention

Crizanlizumab with or without hydroxycarbamide was defined as the intervention of interest.

The intervention used in the CS is broadly in line with the intervention defined in the NICE scope. However, it should be noted that patients in the SUSTAIN trial *"were prescribed HC/HU* [hydroxy–carbamide/hydroxyurea] *for at least six months and were dose-stable for at least three months prior to the beginning of the study"* which might limit the applicability of the results to clinical practice in the United Kingdom (UK).

1.1.3 Comparator

According to the final NICE scope, the relevant comparators are established clinical management without crizanlizumab including 1) HC, 2) blood transfusions (exchange and top-ups), 3) allogenic stem-cell transplants (ASCTs) and 4) best supportive care.

The comparators in the CS are in line with those defined in the NICE scope with the exception of ASCT *"as it not expected that crizanlizumab would displace ASCT as a treatment option of last resort, or necessarily alter the number of patients with SCD that would ultimately receive ASCT"*. The Evidence Review Group (ERG) agrees with the company, however, the omission of ASCT should be noted by the committee.

1.1.4 Outcomes

The final NICE scope listed the following outcomes as relevant:

- Mortality
- Number and severity of sickle cell crises
- Recurrent event
- Complications arising from VOC (including stroke, acute chest syndrome (ACS), organ damage)
- Adverse effects of treatment
- Health-related quality of life

1.1.5 Other relevant factors

A Patient Access Scheme (PAS) for crizanlizumab has already been agreed and included within the submission. The CS states that the company intend to discuss the potential for a Managed Access

Agreement with NICE and National Health Service (NHS) England in order to improve the cost effectiveness of crizanlizumab.

1.2 Summary of the key issues in the clinical effectiveness evidence

A single set of searches was undertaken to identify clinical effectiveness and adverse events data. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were searched, including additional grey literature resources and reference checking. Searches were well conducted and documented, making them transparent and reproducible.

The primary evidence used in the CS came from the SUSTAIN trial, a double-blind, placebo-controlled, randomised controlled, phase II trial evaluating the efficacy and safety of crizanlizumab compared to placebo for the prevention of VOC in patients aged 16 to 65 years with SCD. SUSTAIN compared two doses of crizanlizumab (2.5 mg/kg and 5 mg/kg) administered intravenously 14 times over 52 weeks with placebo (results after longer follow-up not available). Most participants included in SUSTAIN described their race as "black" ([redacted]). None of the trial centres were in the UK or Europe.

Randomisation was stratified by concomitant use of HU and the number of sickle cell-related pain crises (SCPC) in the previous 12 months (two to four or five to 10). The primary endpoint was the annual rate of SCPC, defined as acute episodes of pain with no medically defined cause other than a vaso-occlusive event which resulted in a medical facility visit and treatment with oral or parenteral narcotics or a parenteral non-steroidal anti-inflammatory drugs (NSAIDs). ACS, hepatic sequestration, splenic sequestration, and priapism were also considered to be crisis events.

At the end of the 52-week treatment period the median annual SCPC rate in the high-dose crizanlizumab group (1.63, inter-quartile range (IQR) 0 to 3.97) was significantly lower than placebo (median 2.98, IQR 1.25 to 5.87, P =0.01 for difference vs. placebo), see Table 1.1.

Table 1.1: SUSTAIN primary endpoint annual rate of SCPC (ITT population)

	High-dose crizanlizumab (5 mg/kg), N=67	**Low-dose crizanlizumab (2.5 mg/kg), N=66**	**Placebo, N=65**
Median annual rate (IQR)	1.63 (0.00 to 3.97)	2.01 (1.00 to 3.98)	2.98 (1.25 to 5.87)
P-value (difference vs. placebo)	0.01	0.18	-
Number with zero rate at trial end	24	12	11
Based on Table 9 of the CS P-value from stratified Wilcoxon rank sum test CI = confidence interval; CS = company submission; IQR = inter-quartile range; ITT = intention-to-treat; kg = kilogram; mg = milligram; SCPC = sickle cell-related pain crises			

Time to the first SCPC was significantly longer with high-dose crizanlizumab compared to placebo (hazard ratio (HR) 0.50, 95% confidence interval (CI) 0.33 to 0.74, P=0.001) but not with low-dose crizanlizumab (HR 0.75, 95% CI 0.52 to 1.10, P=0.136). Similarly, the time to the second SCPC was also longer with high-dose crizanlizumab compared to placebo (HR 0.53, 95% CI 0.33 to 0.87, P=0.022) but not with low-dose crizanlizumab (HR 0.69, 95% CI 0.44 to 1.09, P=0.10), see Table 1.2 for results of secondary endpoints.

Table 1.2: SUSTAIN secondary endpoints (ITT population)

Outcome	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab (2.5 mg/kg), N=66	Placebo, N=65
Annual rate of days hospitalised			
Median rate (IQR)	4.00 (0.00–25.72)	6.87 (0.00–18.00)	6.87 (0.00–28.30)
Difference from placebo, %	-41.8	0.00	-
P-value[a]	0.45	0.84	-
Time to first SCPC			
Median time to first crisis (IQR), months	4.07 (1.31–NR)[b]	2.20 (0.95–6.60)	1.38 (0.39–4.90)
HR (95% CI)	0.50 (0.33–0.74)	0.75 (0.52–1.10)	-
P-value[c]	0.001	0.14	-
Time to second SCPC			
Median time to second crisis (IQR), months	10.32 (4.47–NR)[b]	9.20 (3.94–12.16)	5.09 (2.96–11.01)
HR (95% CI)	0.53 (0.33–0.87)	0.69 (0.44–1.09)	-
P-value[c]	0.02	0.10	-
Annual rate of uncomplicated SCPC[d]			
Median rate per year (IQR)	1.08 (0.00–3.96)	2.00 (0.00–3.02)	2.91 (1.00–5.00)
Difference from placebo, %	-62.9	-31.3	-
P-value[a]	0.02	0.12	-
Annual rate of ACS			
Median rate per year (IQR)	0 (0.00–0.00)	0 (0.00–0.00)	0 (0.00–0.00)
Difference from placebo, %	0.0	0.0	-
P-value[a]	0.78	0.87	-

Based on Table 10 of the CS

[a] P-values are for the comparison between the active-treatment group and the placebo group and were calculated with the use of a stratified Wilcoxon rank-sum test; [b] The 75% value for the interquartile range was not observed within the 52-week trial and was considered to be not reported (NR). [c] P-values are for the comparison between the active-treatment group and the placebo group during the treatment phase and were calculated with the use of the log-rank test; [d] Uncomplicated SCPC are defined as crises other than ACS, hepatic sequestration, splenic sequestration, or priapism.

ACS = acute chest syndrome; CI = confidence interval; CS = company submission; HR = hazard ratio; IQR = inter-quartile range; ITT = intention-to-treat; kg = kilogram; mg = milligram; NR = not reported; SCPC = sickle cell-related pain crises

Uncomplicated crises were defined as SCPC other than ACS, hepatic sequestration, splenic sequestration, or priapism. The median rates per year of uncomplicated crises were 1.08 for high-dose crizanlizumab and 2.91 for placebo (reduction of 62.9%, P=0.02). [redacted]

[redacted]

[redacted] There was also no significant difference between groups in the median annual rate of ACS (zero for all groups). Further details of other complications are provided in Table 1.3.

Table 1.3: Treatment-emergent SCPC (safety population)

SCPC event	High-dose crizanlizumab (5 mg/kg), N=66		Low-dose crizanlizumab (2.5 mg/kg), N=64		Placebo, N=62	
	Patients, N (%)[a]	Events, N[a]	Patients, N (%)[a]	Events, N[a]	Patients, N (%)[a]	Events, N[a]
Any SCPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uncomplicated SCPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic sequestration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Splenic sequestration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Priapism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 11 of the CS
Note: Treatment-emergent SCPC are defined as all SCPC which start (or increase in severity) after the date of first dose of study medication. All treatment-emergent SCPC were adjudicated by the CRC.
[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Multiple events for a patient that are in the same event category are counted multiple times in that event category. Multiple events belonging to more than one event category are counted multiple times in each of those event categories; [b] While death was removed as an SCPC event category by Amendment 2 to the Protocol, the CRC subsequently indicated that four events which met the criteria for SCPC should be given the event classification of "death".
ACS = acute chest syndrome; CRC = Crisis Review Committee; CS = company submission; kg = kilogram; mg = milligram; SCPC = sickle cell-related pain crises

Results for the pain severity and interference domains of the Brief Pain Inventory (BPI) are shown in Table 1.4.

[redacted]

Table 1.4: BPI pain severity and interference (ITT population)

	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab (2.5 mg/kg), N=66	Placebo, N=65
Pain severity			
Baseline, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 52 CfB, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab (2.5 mg/kg), N=66	Placebo, N=65
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Treatment difference	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	
Week 58 follow-up[b] CfB, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Treatment difference	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	
Pain interference			
Baseline, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 52 CfB, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Treatment difference	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	
Week 58 follow-up[b] CfB, N	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	
LS mean (95% CI)	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	
Treatment difference	[redacted]	[redacted]	

	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab (2.5 mg/kg), N=66	Placebo, N=65
P-value	[redacted]	[redacted]	

Based on Tables 14 and 15 of the CS
Note: BPI outcomes are calculated as the average of non-missing responses
[a] For patients who discontinue crizanlizumab or placebo, assessments six weeks or more after final dose are considered in the week 58 follow-up windowed visit
BPI = Brief Pain Inventory; CfB = change from baseline; CI = confidence interval; CS = company submission; ITT = intention-to-treat; kg = kilogram; LS = least squares; mg = milligram; SD = standard deviation

The incidence of overall adverse events (AEs) and serious adverse events (SAEs) was comparable across the three arms. In contrast, [redacted] (Table 1.5).

Five participants deaths occurred in the trial [redacted]. Two deaths happened in participants receiving 5 mg/kg crizanlizumab, one participant from ACS and one participant from endocarditis and sepsis. In the lower dose arm, one death occurred involving ACS, aspiration, respiratory failure, and progressive vascular congestion arm. Two participants also died in the placebo arm, one from right ventricular failure and one from a confluence of VOC, ischaemic stroke, coma, sepsis, and venous thrombosis of the right lower limb.

Table 1.5: Overview of adverse events, n (%)

	Crizanlizumab 5 mg/kg (n=66)		Crizanlizumab 2.5 mg/kg (n=64)		Placebo (n=62)	
	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
Any AE	57 (86.4)	459	56 (87.5)	434	55 (88.7)	358
Any drug-related AE	[redacted]	83	[redacted]	73	[redacted]	26
Any SAE	17 (25.8)	25	21 (32.8)	34	17 (27.4)	33
Any drug-related SAE	[redacted]	10	[redacted]	9	[redacted]	3
Any discontinuation due to AE	[redacted]	2	[redacted]	1	[redacted]	7
Death	2 (3.0)	3	1 (1.6)	4	2 (2.3)	6

Based on Table 17 of the CS and Table 14.3.1.1 of the CSR
AE = adverse events; CS = company submission; CSR = clinical study report; kg = kilogram; mg = milligram; SAE = serious adverse events

In line with the NICE final scope, *"pre-specified subgroup analyses of the annual rates of SCPC in the ITT population were performed according to concomitant HC/HU use (yes or no), history of SCPC (2–4 or 5–10 crises in the 12 months prior to the study) and SCD genotype (HbSS or non-HbSS)"*. It was noted that *"across all subgroups, crizanlizumab 5 mg/kg was associated with a lower median annual SCPC rate compared to placebo. The subgroup analyses did not often meet statistical significance (P < 0.05), however the study was not powered to detect differences between treatment arms in these subgroups"*. Detailed results are reported in Table 4.12.

No meta-analysis, indirect comparison and/or multiple treatment comparison was performed.

1.3 Summary of the key issues in the cost effectiveness evidence

A single search was undertaken for cost effectiveness, costs and healthcare resource studies, and a separate search was conducted for health-related quality of life (HRQoL) data. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were searched, including additional grey literature resources and reference checking. Searches were well conducted and documented, making them transparent and reproducible.

The ERG has concerns whether the current model is fit for purpose. The main issue is that the definition of health states in terms of VOC per year (less than one, between one and three, and more than three VOC) does not match with the way it was recorded in SUSTAIN (between two and four, and between five and 10). Consequently, transition probabilities for the model cannot be derived using data from the 52-week SUSTAIN trial. To overcome this limitation, and in the absence of any longer-term data on the use of crizanlizumab, the company re-distributed all alive patients between the VOC health states at the end of every model cycle according to the proportions observed in SUSTAIN. However, this also seems inappropriate since SUSTAIN only provides information about patients with more than two VOC at baseline (how patients with less than two VOC would transition after the first year in the model and following treatment with crizanlizumab is unknown given the 52-week duration of the trial). Furthermore, the company assumed in the model that there is no direct link between SCD-related complications and death. For some complications, like acute chest syndrome, this assumption seems unrealistic. Even though the company indicated that since all-cause mortality (including death from acute chest syndrome) from the Hospital Episode Statistics (HES) database was considered when estimating the baseline mortality hazard and the HRs for the VOC health states of the model, applying a separate risk of death for acute chest syndrome would result in double counting of death*;* it remains unclear to what extent the definitions of VOC in SUSTAIN and HES are equivalent and whether the impact of SCD-related complications on death are properly captured in the model. With the available data, a time to event approach seems more logical and would overcome the concerns raised by the ERG.

There are also widespread uncertainties in terms of inputs used and assumptions made in the model, which have a substantial impact on results. The main source of efficacy data in the model comes from the SUSTAIN trial, which is used to distribute patients in each treatment group between the three VOC health states and determines the mean number of VOCs per treatment group per health state in each cycle. The company argued that patients in SUSTAIN are representative of the population who would be expected to receive crizanlizumab in UK clinical practice i.e. those patients experiencing recurrent VOCs. However, in their base-case the company assumed baseline patient characteristics of age and gender distribution from the HES database and weight from the NICE clinical guideline (CG) 143, arguing that the use of UK based estimates is more appropriate. However, the vast majority of SCD patients in the HES database analysis do not experience recurrent VOC and therefore represent a much broader, and possibly less severe, group of patients than would receive crizanlizumab in practice. The estimated weight from the NICE guideline is also intended to be representative of all SCD patients. Therefore, the ERG would argue that patient characteristics should be have taken from the SUSTAIN trial in the base-case, especially as this source represents the main source of treatment efficacy in the submission as it determines patients health state occupancy and number of VOC events and therefore is a driver of their risk of complications, mortality and their costs and HRQoL.

There were also uncertainties relating to treatment usage in both arms. In their base-case, the company assumed that the proportion of patients receiving HC/HU in each treatment group was better represented by estimates from UK data than from the SUSTAIN trial. Therefore, it was assumed that 14.2% of patients received HC/HU in each treatment arm, based on information from the National Haemoglobinopathy Registry annual report 2018/2019 which included all SCD patients, rather than

[redacted] of patients as seen in the SUSTAIN trial. Given that the aim of HC/HU treatment is to prevent recurrent VOC, it can be assumed that its use would be higher in a population experiencing recurrent VOC. This is supported by the company submission which states that the majority of HC/HU use is expected to be in patients with recurrent VOC, following recommendations by the British Society for Haematology (BSH). The ERG therefore considers that the proportion of patients receiving HC/HU in the SUSTAIN trial should be used in the base-case, as this population reflects the population expected to receive crizanlizumab in clinical practice. The company also assumed that no patients receiving crizanlizumab would receive chronic blood transfusions, while [redacted] of standard of care (SoC) patients would. Again, the assumption of [redacted] was taken from all SCD patients in the HES analysis who did not have a prior diagnosis of stroke (in order to exclude patients receiving transfusions for the prevention of stroke) and not only those experiencing recurrent VOCs who did not have a prior diagnosis of stroke. Therefore, in a recurrent population the usage is likely to be higher. There is no data with which to validate the assumption that no patients treated with crizanlizumab will receive chronic blood transfusion in clinical practice.

The company incorporated treatment effectiveness in the economic model by considering the distribution of patients across the three VOC health states (<1, ≥1-<3, ≥3) and linking the mean annualised VOC rate within each health state to mortality and complications. The distribution of patients and annualised VOC rates were obtained from the SUSTAIN trial, while the estimated association between VOC rates and mortality and complications resulted from statistical analysis on the HES database. In the company's base-case, the distribution of patients into the different health states and the rate of VOCs in each state are assumed to be constant over time within the crizanlizumab and SoC arms. This implicitly assumes a constant lifetime treatment effect for crizanlizumab while on treatment. No data are available on the long-term efficacy of crizanlizumab beyond one year of treatment and yet the base-case assumes a lifetime treatment effect. This is an important area of uncertainty in the model.

The company assumed that patients who discontinue crizanlizumab are subject to a continuing treatment effect for two additional years, based on data from the follow-up trial SUCCESSOR, in which 15 patients who had completed the high dose crizanlizumab treatment arm experienced a similar mean annualised VOC rate in the year post trial completion, compared to in the SUSTAIN trial. In the company's base-case it is assumed that the additional two years of treatment effect applies to all patients who discontinue treatment, including the 32.8% of patients who discontinue treatment in the first model cycle (one year). In their response to the clarification letter, the company indicates two years of treatment effect post-discontinuation to be "the likely *maximum* periods to observe *any* benefits" (italics added). The ERG therefore suspects that assuming two years of post-discontinuation treatment effect would overestimate the actual treatment benefit and reduced the post-discontinuation benefit to one year in the ERG base-case, to reflect the data available from SUCCESSOR. Given that the SUCCESSOR study provides data only for patients who finished one year of treatment, the ERG deemed it more appropriate to allocate the additional post-discontinuation treatment effect only to patients who completed one year of treatment with crizanlizumab. However, the ERG cannot be certain how long post-discontinuation efficacy would last in clinical practice given the small number of patients in SUCCESSOR and the short-term follow up.

The ERG questions the appropriateness of using the patient characteristics in the HES database to link VOC state outcomes for the population in the SUSTAIN trial to mortality and complications, due to the large differences between the two patient populations in terms of VOC state distribution. The ERG would have liked to use the patient characteristics from the SUSTAIN trial (age, gender) in its base-case, in order to better reflect the patient population likely to receive crizanlizumab in clinical practice.

However, the ERG did not feel confident that using the HRs (used to estimate mortality and complications based on mean annualised VOC rate) that were estimated from the HES data set, with a different mean age and gender distribution, would be appropriate to apply.

The company did not provide utility estimates from the SUSTAIN trial, arguing that limitations of the SUSTAIN trial with regards to the collection of HRQoL data (e.g. HRQoL collected at fixed timepoints which may or may not have corresponded to the occurrence of a VOC) and the limited duration of the trial, led to their decision to derive utility values from published studies. The impact of frequent VOC events is captured within the health state utility values used for each VOC state, onto which an additional per event utility decrement is applied for each individual VOC event. The company utilised health state utility values derived from an unpublished analysis of the LEGACY registry data. The per event utility decrements were derived from a study by Anie et al. 2012. The ERG raised concerns regarding the choice of applying the LEGACY health state utility values which differ per VOC health state in addition to the per event decrement for individual VOC events and conducted several additional scenario analyses to explore the influence of changing modelling assumptions for utilities on the cost effectiveness results.

1.4 Summary of the ERG's preferred assumptions and resulting incremental cost effectiveness ratio (ICER)

The ERG preferred assumptions are described in detail in section 7.1.2 of this report and summarised below:

1. In the company's base-case, administration costs were not applied for the additional administration of crizanlizumab in the first year. This was applied in the ERG base-case.
2. The ERG felt it was correct to apply the compliance rate to crizanlizumab administration costs, as it was applied for drug costs.
3. The ERG prefers to use the patient weight from SUSTAIN rather than from CG143 as the SUSTAIN trial is claimed to be reflective of the population who will receive crizanlizumab in UK clinical practice and the estimate from CG143 is based on all SCD patients and not only those experiencing recurrent VOCs.
4. The ERG prefers to assume the HC/HU usage from SUSTAIN, given that the population in SUSTAIN matches the intended use of crizanlizumab in UK clinical practice.
5. The ERG prefers to assume that post-discontinuation efficacy is only maintained for one year, in line with the data provided from SUCCESSOR.
6. The ERG prefers to assume that only patients who complete one year of crizanlizumab treatment receive the post-discontinuation efficacy, in line with the data provided from SUCCESSOR

The cost effectiveness results of the ERG preferred base-case are presented in Table 1.6. The assumptions with the largest impact on the ICER were assuming the HC/HU usage and patient weight from the SUSTAIN trial, which increased the ICER by £158,409 and £132,017, respectively. The base-case ICER in the company submission was £329,868. The ICER based on the ERG preferred assumptions was slightly more than double the company ICER at £693,689.

Table 1.6: ICER resulting from ERG's preferred assumption

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Crizanlizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£693,689

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
Based on electronic model, updated in response to request for clarification ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; QALYs = quality adjusted life years							

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG probabilistic analysis resulted in an ICER of £524,226, which is substantially lower than the deterministic ICER. This issue seems to be due to the inclusion of the distribution of patients between the VOC states in the probabilistic sensitivity analysis (PSA). The cost effectiveness acceptability curve (CEAC) suggested that at willingness-to-pay (WTP) thresholds of £20,000 and £30,000, respectively, the probability that crizanlizumab is cost effective remains at [redacted]. The one-way sensitivity analysis performed on the ERG base-case shows that patient weight, utilities, number of VOC events in the most severe VOC health state, concomitant HC/HU use and compliance for crizanlizumab are the most influential parameters on the ICER.

The ERG considered that the scenario analyses conducted by the company were insufficient to draw overall conclusions over the robustness of the model results. Therefore, the ERG conducted several additional scenario analyses to explore several sources of uncertainty that seem to be relevant for the model results identified by the ERG. From the results of these analyses, shown in Table 1.7, it could be concluded that the ICER was most sensitive to changes in assumptions surrounding the long-term efficacy of crizanlizumab, HC/HU usage, utilities, and patient characteristics. These represent substantial areas of uncertainty in the submission which should be further addressed before any firm conclusions on cost effectiveness can be made.

Table 1.7: Exploratory analyses undertaken by the ERG

Scenario	Section in main ERG report	Crizanlizumab		SoC		ICER £/QALY
		Costs (£)	QALYs	Costs (£)	QALYs	
Patient characteristics						
Age, gender, and weight UK (company BC)	7.2.2.1	[redacted]	[redacted]	[redacted]	[redacted]	£505,666
Age, gender, and weight SUSTAIN		[redacted]	[redacted]	[redacted]	[redacted]	£733,489
Age and gender UK; weight SUSTAIN (ERG BC)		[redacted]	[redacted]	[redacted]	[redacted]	£693,689
HC/HU Usage						
HC/HU use 14.2% (UK estimate) (company BC)	7.2.2.2	[redacted]	[redacted]	[redacted]	[redacted]	£519,073
HC/HU use SUSTAIN (ERG BC)		[redacted]	[redacted]	[redacted]	[redacted]	£693,689
No HC/HU use in either arm (always monotherapy)		[redacted]	[redacted]	[redacted]	[redacted]	£484,103
Everyone HC/HU use in both arms (always combination therapy)		[redacted]	[redacted]	[redacted]	[redacted]	£953,475
Chronic transfusion assumptions						
Criz = 0% SoC = [redacted] (BC)	7.2.2.3	[redacted]	[redacted]	[redacted]	[redacted]	£693,689
Criz = [redacted] SoC = [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	£736,619
Criz = 0% SoC = [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	£652,383
Criz = [redacted] SoC = [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	£715,154
Long term treatment effectiveness						
5-year treatment effectiveness, discontinued treatment	7.2.2.4	[redacted]	[redacted]	[redacted]	[redacted]	£748,970
10-year treatment effectiveness, discontinued treatment		[redacted]	[redacted]	[redacted]	[redacted]	£738,055

Scenario	Section in main ERG report	Crizanlizumab		SoC		ICER £/QALY
		Costs (£)	QALYs	Costs (£)	QALYs	
15-year treatment effectiveness, discontinued treatment		[redacted]	[redacted]	[redacted]	[redacted]	£701,525
5-year treatment effectiveness, continued treatment		[redacted]	[redacted]	[redacted]	[redacted]	£1,439,905
10-year treatment effectiveness, continued treatment		[redacted]	[redacted]	[redacted]	[redacted]	£871,452
15-year treatment effectiveness, continued treatment		[redacted]	[redacted]	[redacted]	[redacted]	£754,456
Post-discontinuation treatment effectiveness						
2 years all patients (company BC)	7.2.2.5	[redacted]	[redacted]	[redacted]	[redacted]	£621,678
2 years in patients completing 1 year of treatment		[redacted]	[redacted]	[redacted]	[redacted]	£667,550
1 year in patients completing 1 year of treatment (ERG BC)		[redacted]	[redacted]	[redacted]	[redacted]	£693,689
1 year in all patients		[redacted]	[redacted]	[redacted]	[redacted]	£668,370
HRQoL assumptions						
Impact VOC through health state and per-event decrement, with VOC impact starting two days prior to hospitalisation (ERG BC)	7.2.2.6	[redacted]	[redacted]	[redacted]	[redacted]	£693,689
Impact individual VOC events captured in health state utility value only		[redacted]	[redacted]	[redacted]	[redacted]	£911,405
Impact VOC events captured as per-event decrement only, using the <1 VOC health state utility as steady-state		[redacted]	[redacted]	[redacted]	[redacted]	£849,796
Impact VOC events captured as per-event decrement only, using the steady-state utility from NICE CG143		[redacted]	[redacted]	[redacted]	[redacted]	£818,111
VOC utility decrement starts at hospitalization		[redacted]	[redacted]	[redacted]	[redacted]	£744,939

Based on electronic model, updated in response to request for clarification

BC = base-case; Criz. = crizanlizumab; ERG = Evidence Review Group; HC = hydroxycarbamide; HRQoL = health-related quality of life; HU = hydroxyurea; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care; UK = United Kingdom; VOC: vaso-occlusive crises

2. Background

2.1 Introduction

In this report, the Evidence Review Group (ERG) provides a review of the provided evidence submitted by Novartis in support of crizanlizumab, trade name Adakveo™, for treating sickle cell crises in sickle cell disease (SCD). In this section, the ERG summarises and critiques the company's description of the underlying health problem and the overview of the current service provision. The information for this critique is based on document B of the company submission (CS).[1]

2.2 Background and underlying health problem

SCD is caused by the occurrence of point mutations in the beta-globin gene, which encode haemoglobin (Hb) in erythrocytes, and impact the shape of the erythrocyte.[1] The most common sickle cell genotype, which includes 67% of SCD patients in the United Kingdom (UK), is homozygous haemoglobin S (HbS).[2] Patients with homozygous HbS tend to experience the most clinically severe form of the disease.[1] Other HbS-related genotypes exist and can present variable levels of disease severity among patients.[3]

In the CS, the company described SCD as a group of inherited haematological disorders, which largely affect individuals of African or African-Caribbean ethnicity.[1] In the UK, SCD has a prevalence of one in 4,600.[1] The company stated that around 14,000 people in the UK live with SCD. SCD is considered to be an orphan condition.[4] In the UK a national screening programme is available for pregnant women, to identify HbS carriers along with additional testing for new born infants.[1] However, according to the CS, SCD remains a neglected disease and the life expectancy for individuals is reduced when compared to the general population.[1, 3, 5] The CS reported the median age of death across patients from North America and Europe to range from 39.7-53.0 years.[1]

Vaso-occlusive crises (VOC) is a major component of SCD and include acute and severe painful episodes.[1] Due to the increased cell-cell interactions between affected erythrocytes, other blood cells, and endothelial cells lining the wall of the blood vessel, this results in the formation of a multi-cellular aggregate within the blood vessel lumen.[6] This impacts on the delivery of oxygen to surrounding tissues, resulting in ischaemic injuries, severe pain, the potential for multi-organ damage, and other acute and chronic complications.[7] The experienced pain from VOC can be debilitating and may result in hospitalisation.[1] However, some patients with VOC will seek medical care at a hospital, some may choose to manage VOC at home due to perceptions about the care they may receive, particularly regarding the act of seeking pain relief at hospital, when appearing healthy.[1]

The CS noted the main severe outcome of VOC to be acute chest syndrome (ACS), which can be a potentially life-threatening, component of SCD.[1] The incidence rate of ACS is 12.8 per 1,000 patient years (PYs) and is responsible for up to a quarter of SCD-related deaths.[1] Other SCD complications can include gallstones, avascular necrosis, ischaemic stroke and silent infarcts, splenic sequestration, leg ulcers, priapism in males, and pulmonary hypertension.[1, 3, 8] SCD signs and symptoms typically present in childhood and are experienced throughout the lifetime.[1, 9] The high symptom burden and risk of comorbidities associated with SCD can result in patients experiencing reduced health-related quality of life (HRQoL).[1] The CS noted that impact of VOC was associated with high rates of absenteeism from work and school.[10, 11]

2.3 Critique of company's overview of current service provision

The CS provides a general overview of the current service provision.[1]

According to the CS, the current approach to VOC management focuses on prevention and supportive therapy in order to reduce pain and the further complications.[9] The company notes VOC should be treated as an acute medical emergency when presented at the hospital, followed by continuous assessment, and offered appropriate analgesics within 30 minutes.[1] The main strategies to prevent VOC occurrences include mainly supportive care, such as hydration and keeping warm.[1]

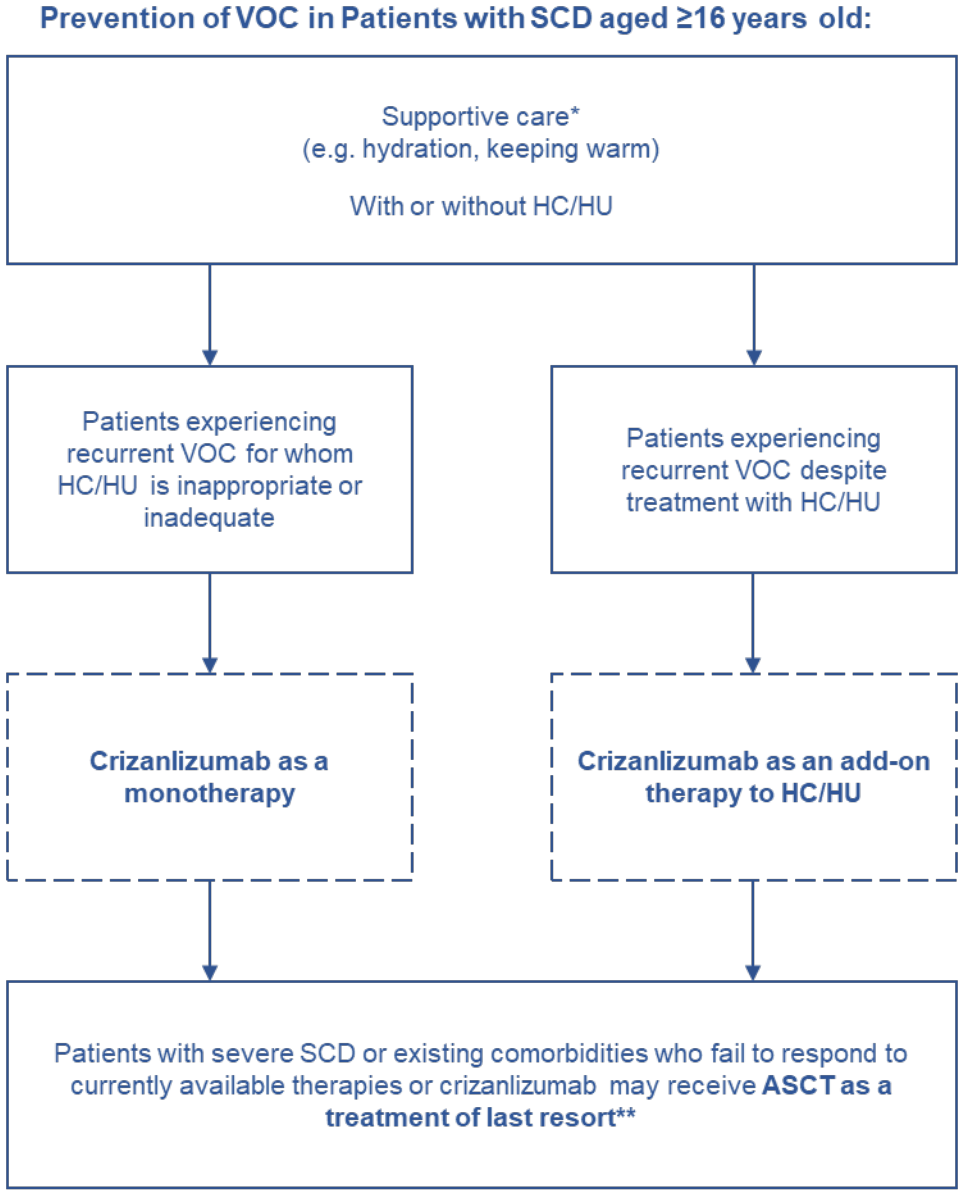
Hydroxycarbamide/hydroxyurea (HC/HU) is identified as the only available pharmaceutical option for addressing the frequency of painful VOC episodes, including ACS, in children older than two years, adolescents, and adults.[1] The CS notes some patients continue to experience pain despite treatment with HC/HU.[12, 13] However, due to the absence of other available treatment options, patients may continue to take HC/HU despite limited success with reducing VOC episodes.[12, 13] The CS reported that 14.2% of all patients with SCD received HC/HU as a treatment in the UK.[14]

Other non-pharmacological approaches can include chronic blood transfusions.[1] However, the company stated that *"blood transfusions are however more commonly used either in an acute context to manage complicated VOC and other complications of SCD (e.g. for ACS and splenic sequestration) or in preparation for surgery, or they are used on a chronic basis for the prevention of stroke and other major complications in high-risk patients"*.[1, 15, 16] The CS noted that the proportion of patients in the UK who receive regular blood transfusions as a method of VOC prevention is expected to be low based on the National Haemoglobinopathy Registry annual report in which 6.6% of SCD patients had limited available transfusion data and data from an audit of transfusion services in the UK and the Republic of Ireland, which suggests that 17% of elective transfusions in adults are for the prevention of recurrent VOC.[1, 14, 17, 18] As an intervention, the use of blood transfusions may be limited based on the availability of blood from suitable donors and the additional antigen matching that must be completed.[19]

For the current CS, crizanlizumab was presented for use as a monotherapy or as an add-on therapy with HC/HU for the prevention for recurrent VOC in SCD patients aged 16 years and older.[1] All SCD patients are expected to have been considered or offered treatment with HC/HU for recurring VOC.[1] The company did not expect patients receiving crizanlizumab to also receive chronic blood transfusions.[1] This is due to the recommended use of blood transfusions in patients who receive treatment using HC/HU, in which blood transfusions would be received if HC/HU is determined to be ineffective.[15]

Figure 2.1 shows the proposed treatment pathway for patients with VOC and the recommended placement of crizanlizumab.[1]

Figure 2.1: Proposed positioning of crizanlizumab in the current treatment pathway as an intervention for the prevention of VOC



Based on Figure 1 of the response to request for clarification[20]

ASCT = allogenic stem-cell transplant; HC = Hydroxycarbamide; HLA = human leucocyte antigen; HU = hydroxyurea; NICE = National Institute for Health and Care Excellence; SCD = sickle cell disease; VOC = vaso-occlusive crises

3. Critique of company's definition of decision problem

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with SCD aged 16 years and over	As per the final scope	Not applicable In line with the anticipated licensed indication, the company submission specifically relates to the use of crizanlizumab for the prevention of recurrent VOC in this population.	Population narrower than NICE scope, see section 3.1 for details
Intervention	Crizanlizumab with or without hydroxycarbamide	As per the final scope	Not applicable	Intervention broadly in line with NICE scope, see section 3.2 for details
Comparator(s)	Established clinical management without crizanlizumab including: • Hydroxycarbamide • Blood transfusions (exchange and top-ups) • Allogenic stem-cell transplants (ASCTs) • Best supportive care	Established clinical management without crizanlizumab including: • Hydroxycarbamide • Blood transfusions (exchange and top-ups) • Best supportive care	Established clinical management for the prevention of VOC consists of supportive care (e.g. hydration with intravenous fluids and keeping warm) with or without HC/HU.[21, 22] HC/HU is currently the only licensed therapy for the prevention of VOC, but is not received by all patients due to concerns from patients about toxicity and perceived side effects of the treatment.[22] HC/HU has demonstrated some efficacy versus placebo in reducing the frequency of VOC, however some patients that receive HC/HU continue to experience high rates of VOC, and due to the lack of other available treatment options, these patients may continue HC/HU treatment.[12, 13] There is therefore a role for crizanlizumab as an add-on therapy to HC/HU, when HC/HU alone does not adequately reduce the number of	ASCT not included as a comparator, see section 3.3 for details

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			VOC, as well as an unmet need for alternative treatments to HC/HU when HC/HU is inappropriate or inadequate. Blood transfusions may also be used for the prevention of VOC in patients who have failed treatment with HC/HU or for whom HC/HU is contraindicated.[15, 17, 23] In practice, the proportion of patients receiving blood transfusions for this purpose is small (less than 10%; and is expected to vary between centres), and evidence of the efficacy of blood transfusions in reducing the frequency of VOC is limited. Given the use of blood transfusions for only a proportion of patients, as part of current standard of care, these have not been included as a direct comparator but are considered as part of established clinical management. Allogeneic stem cell transplantation is primarily used in paediatric SCD patients and is only considered for adults with severe SCD or existing comorbidities (e.g. stroke or pulmonary hypertension) who have failed to respond to currently available treatment.[24] Furthermore, it is only routinely funded by NHS England for patients with a related, fully human leucocyte antigen (HLA) matched donor and so of those patients who are otherwise eligible for transplantation, few undergo transplantation due to a lack of donor availability. Crizanlizumab is expected to be licensed for [redacted], it is not expected that crizanlizumab would displace transplantation as a treatment option of last resort or necessarily alter the number of patients who would ultimately receive a transplant.[25] Allogeneic stem cell transplantation has therefore not been considered as a direct	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			comparator or as part of established clinical management for SCD as part of this submission.	
Outcomes	The outcome measures to be considered include: • Mortality • Number and severity of sickle cell crises • Recurrent event • Complications arising from VOC (including stroke, acute chest syndrome, organ damage) • Adverse effects of treatment • Health-related quality of life	As per the final scope Note: sickle cell crises and VOC, as described in the final scope, are considered to be the same. The definition of VOC used in the SUSTAIN trial is provided in the next column	Annual rate of VOC and time to first and second VOC event were outcomes measured in the SUSTAIN trial (see section 4.2.3).[26] A VOC was defined in SUSTAIN as an acute episode of pain with no medically determined cause other than a vaso-occlusive event, that resulted in a medical facility visit and treatment with pain relief.[26] VOC which did not meet this definition were not captured as an outcome in the SUSTAIN trial. Only the more severe crises experienced by patients (i.e. those that require a medical facility visit) have therefore been considered as an outcome in the submission, and the potential impact of treatment on less severe VOC has not been assessed. Death and other complications were also reported in SUSTAIN but few events occurred during the 52-week trial. The annual rate of acute chest syndrome (ACS), one of the main and severe complications of VOC, was included as an outcome in the SUSTAIN trial. Stroke was not included as a separate outcome in the SUSTAIN trial, however ischaemic stroke was captured as an adverse event.[27] The relationship between VOC and long-term or less frequent outcomes, such as death and SCD-related complications, has been assessed as part of analyses of the Hospital Episode Statistics (HES) database.[28]	Only "more severe crises" have been considered, see section 3.4 for details

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Subgroups to be considered	If evidence allows, the following subgroups will be considered: • Subgroups defined by combination treatment with/without HC • Subgroups defined by genotypes of SCD • Subgroups defined by severity of disease	As per final scope	Evidence from the SUSTAIN trial for the efficacy of crizanlizumab in these subgroups (concomitant HC/HU: yes or no; SCD genotype: HbS or non-HbS; history of VOC: 2–4 or 5–10 crises in the 12 months prior to the study) versus placebo has been presented as part of the submission.	
Special considerations including issues related to equity or equality	Not applicable	Not applicable	In the UK, SCD predominantly affects individuals of African or African-Caribbean ethnicity, and as a group, these individuals tend to have poorer health outcomes compared to other ethnicities, such as White British, as has been seen during the COVID-19 pandemic[29-33] Patients with SCD may be registered disabled due to the morbidity associated with their disease e.g. strokes, chronic leg/foot ulcers and osteonecrosis.[34] Patients with SCD may also experience stigma relating to the management of their condition, which can deter them from seeking medical support.[35] In particular, the use of opioids to manage VOC pain may cause SCD patients to be perceived as drug seeking, especially if healthcare professionals are not aware of the condition and how it is managed.[36, 37] This stigma may be linked to other factors such as patient ethnicity or socioeconomic status.[36, 37] SCD patients are more likely to live in an impoverished area of the UK, with approximately 66% of SCD patients living in one of the lowest two quintiles of deprivation according to the English Index for Multiple Deprivation.[38, 39] In a UK	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			analysis of the Sickle Cell World Assessment Survey (SWAY), 72% of patients with SCD reported that SCD limited their career, whilst 74% of patient reported reducing their working hours due to SCD, which could further negatively impact the socioeconomic status of patients with SCD.[11] Given the aim of reducing inequalities in health, it is important that patients with SCD should not be further disadvantaged should a new, clinically- and cost-effective treatment become available for the prevention of VOC.[40]	

Based on Table 1 of the CS[1]

ACS = acute chest syndrome; ASCT = allogenic stem-cell transplant; COVID-19 = coronavirus disease 2019; CS = company submission; ERG = Evidence Review Group; HbS = homozygous haemoglobin S; HC = hydroxycarbamide; HES = Hospital Episode Statistics; HLA = human leucocyte antigen; HU =hydroxyurea; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; SCD = sickle cell disease; UK = United Kingdom; VOC = vaso-occlusive crises

3.1 Population

In the request for clarification, the ERG asked the company to *"please confirm that the population for which evidence is presented in the CS is narrower than that defined in the final scope by NICE, especially regarding age and previous SCPC episodes"* as *"according to Table 3 of the CS, the population in SUSTAIN included 'patients aged 16–65 years with SCD and history of 2–10 SCPC [sickle cell-related pain crises] in the previous 12 months'"*.[41]

In response, the company stated that *"the population for which the evidence is presented in the CS is narrower than the population defined in the NICE* [National Institute for Health and Care Excellence] *final scope with regards to the number of VOC experienced by the patient before initiation of crizanlizumab, but covers the same population according to age"* and added that *"importantly, the data from SUSTAIN which is presented in the CS is consistent with the expected licenced indication, in that* [redacted] *to receive treatment with crizanlizumab. Therefore, all patients that receive treatment with crizanlizumab are expected to have experienced multiple VOC (i.e. ≥2 VOC) in the previous year. The NICE final scope is therefore considered to be broader than the expected use of crizanlizumab (based on the anticipated indication), rather than the SUSTAIN trial not being reflective of the expected use of crizanlizumab"*.[20]

ERG comment: The population presented in the CS is narrower than that defined in the NICE final scope as, in line with the anticipated licensed indication, it specifically related to the use of crizanlizumab for the prevention of recurrent VOC in people with SCD.[1, 42] In addition, the identified trial, SUSTAIN, included participants 16 to 65 years of age, i.e. results may not be applicable to participants older than 65 years (see Table 4.3 in section 4.2 for further details).

3.2 Intervention

According to the CS, in SUSTAIN *"HC/HU was permitted in any treatment arm provided patients were prescribed HC/HU for at least six months and were dose-stable for at least three months prior to the beginning of the study. HC/HU dosing was not to be altered or terminated throughout the 52-week study treatment period, other than for safety reasons. Patients not on HC/HU at the start of the study were not permitted to initiate treatment with HC/HU during the 52-week study period"* (see Table 4.3 in section 4.2 for further details).[1]

ERG comment: The intervention used in the CS is broadly in line with the intervention defined in the NICE scope.[42] However, it should be noted that patients in the SUSTAIN trial *"were prescribed HC/HU for at least six months and were dose-stable for at least three months prior to the beginning of the study"* which might limit the applicability of the results to clinical practice in the UK.[1]

3.3 Comparators

The final scope issued by NICE lists allogenic stem-cell transplant ASCT) as a comparator.[42] As detailed in section B.1.3.2 of the CS as well as in response to question A1 of the request for clarification, ASCT has *"not been considered as a relevant comparator to crizanlizumab for the treatment of SCD as it not expected that crizanlizumab would displace ASCT as a treatment option of last resort, or necessarily alter the number of patients with SCD that would ultimately receive ASCT"*.[1, 20]

ERG comment: While the ERG agrees with the argument made by the company, the omission of ASCT should be noted by the committee.

3.4 Outcomes

In the SUSTAIN trial, VOC *"were specifically defined as acute episodes of pain with no medically determined cause other than a vaso-occlusive event, which resulted in a visit a medical facility and also receive treatment with oral/parenteral narcotic agents or parenteral non-steroidal anti-inflammatory drugs (NSAID)"* in order to provide *"a more robust outcome for measurement in the trial"*.[20]

The company stated that "*due to the definition of VOC used in the trial, the use of data from SUSTAIN may fail to capture any additional benefits of treatment with crizanlizumab for patients who choose not to seek medical attention for a VOC. However, the decision of a patient on whether to seek medical attention for VOC does not necessarily correspond to the severity of the event. As described in Section B.1.3.1 of the CS, other factors such as poor previous experience in hospital, or a feeling that medical professionals do not understand their disease, are more commonly cited reasons for why patients may manage VOC at home"*.[1, 20]

ERG comment: Only *"the more severe crises experienced by patients (i.e. those that require a medical facility visit)"* were considered. Therefore, results might not be applicable to patients with less severe crises, including those not visiting a medical facility.[1]

3.5 Other relevant factors

Results of subgroup analyses are reported in section 4.2.3.5.

A Patient Access Scheme (PAS) for crizanlizumab has already been agreed and included within the submission. The CS states that the company intend to discuss the potential for a Managed Access Agreement with NICE and NHS England in order to improve the cost effectiveness of crizanlizumab.[1]

4. Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D.1.1 of the CS provides details of a systematic literature review conducted to identify randomised controlled trials (RCTs) of crizanlizumab and relevant comparators, as well as interventional non-RCTs and observational studies of crizanlizumab, for the prevention of VOC in SCD.[43] Searches were conducted in August 2019, with a subsequent update in January 2020. No language or publication date limits were reported. Databases were searched from date of inception. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the clinical effectiveness systematic review

Resource	Host/source	Date ranges	Dates searched
Electronic databases			
MEDLINE, MEDLINE In-Process, MEDLINE Daily and MEDLINE EPub Ahead of Print	Ovid	(i)1946-12.8.19 (ii)1946-24.1.20	(i)13.8.19 (ii)27.1.20
Embase	Ovid	(i)1974-8.10.19 (ii)1974-24.1.20	(i)13.8.19 (ii)27.1.20
Cochrane CDSR	Wiley	(i)Issue 8/12, August 2019 (ii)Issue 1/12, January 2020	(i)13.8.19 (ii)27.1.20
Cochrane CENTRAL			
DARE	CRD website	Issue 2/12, April 2015	(i)13.8.19 (ii)27.1.20
Conference proceedings			
ASH Annual Meeting	Handsearch of online proceedings	2017-2019	(i)September 2019 (ii)January 2020
Annual Congress of the EHA		2017-2019	
Annual Symposium of the Foundation for Sickle Cell Disease Research		2017, 2019	
BSH Annual Scientific Meeting		2017-2019	
Additional resources			
ClinicalTrials.gov	Web search	All years	(i)6.9.19 (ii)14.2.20

Based on CS appendices[43]

(i) original search; (ii) update search

ASH = American Society of Hematology; BSH = British Society for Haematology; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Central Register of Controlled Trials; CRD = Centre for Reviews and Dissemination; CS = company submission; DARE = Database of Abstract Reviews of Effects; EHA = European Haematology Association

ERG comment:

- A single set of searches was undertaken to identify clinical effectiveness and adverse events data. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were searched, as well as a trials register search and reference checking. Both the original and the update searches were well conducted and documented, making them transparent and reproducible.
- No date or language limits were unnecessarily applied to the database searches. The date limit applied to conference searches was considered justifiable.
- Study design filters were appropriately used and based on those designed by the Scottish Intercollegiate Guidelines Network (SIGN).
- Additional synonyms could have been incorporated into the strategy, such as all trade names and the CAS registry number for the intervention, and the abbreviation 'VOC' for the condition, however this is unlikely to have greatly affected recall.

4.1.2 Inclusion criteria

The selection of relevant studies was performed in two stages, i.e. the selection of potentially relevant abstracts followed by the selection of potentially relevant full text publications. This process was conducted by two independent reviewers with intervention of a third reviewer in case of discrepancies.

Those full text publications which were judged to contain insufficient information to determine its eligibility were excluded, i.e. *"in cases where the article did not give enough information to be sure that it met the inclusion criteria, the article was excluded to ensure that only relevant articles were ultimately included in the SLR* [systematic literature review]*"*.[43]

The eligibility criteria used in the systematic literature research are given in appendix D of the CS (Table 4.2).[43]

Table 4.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Category	Inclusion criteria	Exclusion criteria
Population	Human. Patients ≥16 years with sickle cell disease.	Animal. Population did not include patients ≥16 years with sickle cell disease.
Intervention	The following interventions for the prevention of vaso-occlusive crises: • Crizanlizumab with or without hydroxycarbamide/hydroxyurea • The following interventions reflecting supportive care or established clinical management without crizanlizumab: hydroxycarbamide/hydroxyurea, blood transfusions and HSCT	Studies not investigating a relevant intervention specifically for the prevention of vaso-occlusive crises
Comparators	Any or none (i.e. no restrictions regarding comparators for the eligible interventions were applied)	Not applicable
Outcomes	• Clinical and safety outcomes including but not limited to: o Sickle cell crises (number of events/rate of events/time to event)	• Studies not reporting any listed outcomes of relevance • Studies reporting relevant outcomes, but

Category	Inclusion criteria	Exclusion criteria
	○ Hospitalisation (number of events/rate of events/days spent) ○ Annual rate of acute chest syndrome ○ Non-fatal stroke ○ Mortality ○ Safety/adverse events of treatment • Any HRQoL scales, including but not limited to SF-36, Haemo-QoL-A, EQ-5D, or BPI	in groups of a mixed population, without reporting data specifically for the patient group of interest
Study Design	• For all interventions including crizanlizumab: ○ RCTs ○ Interventional non-RCTs (to include non-randomised and uncontrolled clinical studies) • In addition, for crizanlizumab only: ○ Observational studies • SLRs and (network) meta-analyses: These were considered relevant at the title/abstract review stage and hand searched for relevant primary studies, but were excluded during the full-text review stage unless they themselves presented primary research	Any other study design, including: • Observational studies for interventions other than crizanlizumab • Economic evaluations • Non-systematic or narrative reviews • Editorials, notes or comments • Case reports/case studies
Publication	• Peer-reviewed journal articles • Conference abstracts published in or after 2017	Conference abstracts published prior to 2017

Based on Table 8 of the CS appendices[43]
BPI = brief pain inventory; CS = company submission; EQ-5D = EuroQol 5 dimensions questionnaire; Haemo-QoL-A = Haemophilia-specific Quality of Life Questionnaire; HRQoL = health-related quality of life; HSCT = haematopoietic stem cell transplantation; RCT = randomised controlled trial; SF-36 = 36-Item Short Form Health Survey; SLR = systematic literature review

ERG comment: The selection of relevant studies followed standard methodology. However, the exclusion criteria defining interventions appeared to pivot on the type of outcome analysed rather than the intervention under evaluation. The CS stated that *"studies not investigating a relevant intervention specifically for the prevention of vaso-occlusive crises"*.[43] Therefore, this appears discrepant with the definition of the criteria of relevant outcomes which includes other outcomes such as mortality, safety and HRQoL.

The exclusion of full text publications which eligibility was judged to be unclear appears questionable. However, according to Table 12 of the CS appendices, no records were excluded because of insufficient information.[43] The population characteristics were not restricted other than by age which is a demographic commonly reported in clinical studies.

4.1.3 Critique of data extraction

According to the CS, relevant details of the included studies were extracted in a template form by a single individual who was followed by the check of a second reviewer. Resulting discrepancies were settled by the intervention of a third individual.[1, 43]

ERG comment: The Cochrane Handbook for Systematic Reviews recommends that *"as a minimum, information that involves subjective interpretation and information that is critical to the interpretation*

of results (e.g. outcome data) should be extracted independently by at least two people".[44] Due to one reviewer completing data extraction and one person checking, there is a higher risk for errors.

4.1.4 Quality assessment

The quality of the included randomised controlled trials (RCTs) was assessed by the company using the checklist for RCTs developed by the Centre for Reviews and Dissemination (CRD).[45] This followed a similar process to the data extraction where the assessment by one reviewer was later checked by a second reviewer. Resulting discrepancies were settled with the intervention of a third reviewer.

ERG comment: RCTs were assessed based on the criteria described in box 1.5 of the CRD guidance and a reported in Table 13 of the CS appendices:[43, 45]

- *Was randomisation carried out appropriately?*
- *Was the concealment of the treatment allocation adequate?*
- *Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?*
- *Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?*
- *Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?*
- *Is there any evidence to suggest that the authors measured more outcomes than they reported?*
- *Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?*
- *Also consider whether the authors of the study publication declared any conflicts of interest/study funding.*

In contrast to methods described in the CS, version 2 of the Cochrane risk of bias tool for randomised trials is the current standard for risk of bias assessment of randomised trials.[46] This tool is structured as series of domains to aid an overall assessment and includes a domain dedicated to the analysis of potential bias resulting from the how the outcome is measured.

4.1.5 Evidence synthesis

No meta-analysis was performed as only one study (SUSTAIN) was identified, see section 4.2 of the report as well as chapter B.2.8 of the CS.[1]

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The primary evidence used in this submission came from the SUSTAIN trial.[27, 47] This was a double-blind, placebo-controlled, randomised controlled, phase II trial evaluating the efficacy and safety of crizanlizumab compared to placebo for the prevention of VOC in patients aged 16 to 65 years with SCD. The systematic review also identified the SUCCESSOR trial which was a retrospective study of patients from the US sites of SUSTAIN.[48, 49] This was not used as a source of data for the economic model as no patients received crizanlizumab during the study follow-up period. There was also a publication reporting a pooled analysis of safety data from SUSTAIN and the SOLACE study which is an ongoing, open label pharmacokinetic/dynamic study of crizanlizumab in patients aged 16 to 70 years with SCD.[50] Results for SOLACE alone are not yet available and these were not included in the economic model.

SUSTAIN compared two doses of crizanlizumab (2.5 mg/kg and 5 mg/kg) administered intravenously 14 times over 52 weeks with placebo. Patients were randomised on a 1:1:1 basis by a central interactive voice/web response system (IXRS) and the randomisation was stratified by concomitant use of HU and the number of sickle cell-related pain crises (SCPC) in the previous 12 months (two to four or five to 10). The primary endpoint was the annual rate of SCPC, defined as acute episodes of pain with no medically defined cause other than a vaso-occlusive event which resulted in a medical facility visit and treatment with oral or parenteral narcotics or a parenteral non-steroidal anti-inflammatory drugs (NSAIDs). ACS, hepatic sequestration, splenic sequestration, and priapism were also considered to be crisis events. Further details of other outcomes and the study methods are provided in Table 4.3.

Table 4.3: Study design and methods of SUSTAIN

Trial name	SUSTAIN (NCT01895361)
Location	International: 60 study centres in three countries (USA, Brazil, and Jamaica) conducted at study centres in the USA (51), Brazil (8) and Jamaica (1)
Design	Double-blind, randomised, placebo-controlled, multi-centre phase II trial. The trial consisted of a 30-day screening phase, a 52-week treatment phase, and a 6-week follow-up evaluation phase. The patients, care providers, and outcome assessors were unaware of the group assignments. Randomisation was stratified according to the number of SCPC in the previous year (2–4 or 5–10) and by concomitant HC/HU use (yes or no).
Eligibility criteria	Main inclusion and exclusion criteria: Inclusion criteria • 16 to 65 years of age • Confirmed medical history or diagnosis of SCD (including HbSS, HbSC, HbSβ^0-thalassemia or HbSβ+-thalassemia patients) • 2–10 SCPC within the 12 months before enrolment • Patients receiving HC/HU must have been prescribed HC/HU for the preceding six months and be dose-stabilised for at least three months Exclusion criteria • Patients who were undergoing long-term red-cell transfusion therapy
Method of study drug administration	Treatment arms: • Low-dose crizanlizumab (2.5 mg/kg; N=66) • High-dose crizanlizumab (5 mg/kg; N=67) • Placebo (N=65) Patients received two doses of either crizanlizumab or placebo two weeks apart (loading dose) and then one dose every four weeks. A total of 14 doses were administered over the 52-week study duration. Each dose was administered intravenously over a period of 30 minutes.
Permitted and disallowed concomitant medication	General medication consistent with the standard care for patients with SCD was allowed. Aspirin was permitted but any other chronic anticoagulant therapy (e.g. warfarin, heparin) was disallowed. HC/HU was permitted in any treatment arm provided patients were prescribed HC/HU for at least six months and were dose-stable for at least three months prior to the beginning of the study. HC/HU dosing was not to be altered or terminated throughout the 52-week study treatment period, other than for safety reasons. Patients not on HC/HU at the start of the study were not permitted to initiate treatment with HC/HU during the 52-week study period.

	Erythropoietin was permitted in any treatment arm provided patients were prescribed erythropoietin for at least six months and were dose-stable for at least three months. Emergent and occasional blood transfusions were permitted.
Primary endpoint	The annual rate of SCPC, which was calculated as follows: total number of crises x 365 ÷ (end date − date of randomisation + 1). SCPC were defined as acute episodes of pain, with no medically determined cause other than a vaso-occlusive event that resulted in a visit to a medical facility and treatment oral/parenteral narcotic agents or parenteral NSAIDs. ACS, hepatic sequestration, splenic sequestration, and priapism were also considered to be crisis events. All crises that were identified by trial investigators were adjudicated by a blinded independent crisis-review committee, of three independent haematologists.
Secondary endpoints	These included: • The annual rate of days hospitalised • The times to first and second crises • The annual rate of uncomplicated crises (defined as crises other than ACS, hepatic sequestration, splenic sequestration, or priapism) • The annual rate of ACS • BPI questionnaire • SF-36 v2 questionnaire • Changes in clinical laboratory parameters; biomarker analyses; pharmacokinetic and pharmacodynamic analyses (not reported here) • Safety – frequency and severity of adverse events During the treatment phase, assessments were completed on the day of receipt of the initial dose, two weeks later, every four weeks through week 50, and at week 52, for a total of 15 visits.
Pre-planned subgroup analyses	Pre-specified subgroup analyses for the annual rate of SCPC were performed according to concomitant HC/HU use (yes or no), history of SCPC (2–4 or 5–10 crises in the year prior to the study) and SCD genotype (HbS or non-HbS).[26, 51] Post-hoc analysis of other selected efficacy and safety outcomes were also performed for these sub-groups.[51]
Duration of study and follow-up	The study was ongoing from July 2013 to March 2016 and consisted of a 30-day screening phase, a 52-week treatment phase and a 6-week follow-up phase.

Based on Table 4 of the CS[1]
ACS = acute chest syndrome; BPI = Brief Pain Inventory; CS = company submission; HbSβ+ = haemoglobin S-beta plus; HbSβ0 = haemoglobin S-beta zero; HbSC = sickle cell–hemoglobin C; HbS = Homozygous haemoglobin S; HC = hydroxycarbamide; HU = hydroxyurea; kg = kilogram; mg = milligram; NSAID = non-steroidal anti-inflammatory drug; SCD = sickle cell disease; SCPC = sickle cell-related pain crises; SF-36 v2 = 36-Item Short Form Health Survey version 2; USA = United States of America

4.2.1 SUSTAIN statistical methods

The planned sample size of the SUSTAIN trial was 174 participants (50 per treatment arm with an additional 15% to allow for dropout). A total of 198 participants were randomised. The primary analysis was performed on the intention-to-treat (ITT) population which comprised all randomised patients, analysed according to their randomised treatment arm. The per-protocol (PP) population comprised all ITT patients who received at least 12 of the planned 14 study doses, completed a visit ≥14 days after the final dose and had no major protocol violations, this was also analysed according to randomised treatment arm. The safety population comprised all patients who received at least one dose of study

drug and was analysed according to treatment received. The ITT population contained all 198 randomised participants, the PP population contained 125 participants and the safety population contained 192 participants. Further details of the statistical methods are provided in Table 4.4.

Table 4.4: SUSTAIN statistical methods

Hypothesis	The primary analysis tested the null hypothesis that the distribution of annual rates of SCPC in patients treated with crizanlizumab and placebo are identical against the alternative hypothesis that the distribution of annual rates of SCPC are not identical.
Statistical analysis	Treatments were compared using a stratified Wilcoxon rank sum test, with randomisation stratification factors of HC/HU therapy and SCPC history as strata. Medians, median differences, and 95% CIs for the median differences were estimated using Hodges-Lehmann method, and the following hierarchical testing procedure was followed: $\alpha = 0.05$ was utilised to test high-dose crizanlizumab (5 mg/kg) versus placebo, and if significant, to test low dose (2.5 mg/kg) versus placebo. This controlled the overall alpha level for the study at 0.05 for the primary endpoint.
Sample size calculation	Sample size calculations were performed based upon the following assumptions: a 40% relative reduction (versus placebo) in the number of SCPC with a mean placebo event rate of 3.0 and standard deviation of 1.7; and, patients were randomized in 1:1:1 ratio into placebo: high dose: low dose, stratified by concomitant usage of HC/HU (yes; no) as well as by number of prior SCPC (2–4; 5–10) per year. Based on these assumptions, a total of 50 patients per arm were required for the study to have approximately 90% power to detect a 40% reduction in SCPC, using Wilcoxon's rank sum test ($\alpha = 0.05$). Assuming a 15% dropout rate, approximately 174 total patients were to be randomised into the study.
Data management, patient withdrawals	The primary analysis utilised the ITT principle and included all randomised patients. The SCPC rate for every patient was annualised to 12 months and the annual rate was imputed for patients who did not complete the trial. For patients who never received a dose, the end date used to calculate the annualised rate was the date of the last site contact.

Based on Table 7 of the CS[1]
CI = confidence interval; CS = company submission; HC = hydroxycarbamide; HU = hydroxyurea; ITT = intention-to-treat; kg = kilogram; mg = milligram; SCPC = sickle cell-related pain crises

4.2.2 SUSTAIN baseline data

A total of 198 participants were randomised and included in the ITT population and 43/67 (64.2%) of high-dose crizanlizumab, 45/66 (68.2%) of low-dose crizanlizumab and 41/65 (63.1%) of placebo patients completed the study. One patient in the high-dose group, two in the low-dose group and three in the placebo group did not receive any study treatment and were excluded from the safety population. Overall, the median age was [redacted], the most common genotype was HbSS [redacted] of patients were receiving concomitant HC/HU and [redacted] had between two and four SCPC in the previous 12 months. Most participants described their race as "black" ([redacted]) and none of the trial centres were in the UK or Europe. Baseline patient characteristics were well-balanced between the three treatment groups. Baseline data for the three treatment groups are shown in Table 4.5.

Table 4.5: SUSTAIN baseline patient characteristics

	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab, (2.5 mg/kg), N=66	Placebo, N=65
Age – years			
Median	29	29	26
Range	16–63	17–57	16–56
Gender – N (%)			
Male	32 (48)	30 (45)	27 (42)
Female	35 (52)	36 (55)	38 (58)
Race – N (%)			
Black	60 (90)	62 (94)	60 (92)
White	4 (6)	2 (3)	3 (5)
Other	3 (4)	2 (3)	2(3)
SCD genotype – N (%)			
HbSS	47 (70)	47 (71)	47 (72)
Other	20 (30)	19 (29)	18 (28)
Concomitant HC/HU use – N (%)			
Yes	42 (63)	41 (62)	40 (62)
No	25 (37)	25 (38)	25 (38)
SCPC during previous 12 months – N (%)			
2–4 crises	42 (63)	41 (62)	41 (63)
5–10 crises	25 (37)	25 (38)	24 (37)

Based on Table 5 of the CS[1]
CS = company submission; HC = hydroxycarbamide; HU = hydroxyurea; kg = kilogram; mg = milligram; SCD = sickle cell disease; SCPC = sickle cell-related pain crises

Details of concomitant medications used by ≥ 20% of participants within any treatment group are shown in Table 4.6. The most commonly used medications, [redacted] Participants on a chronic transfusion program or planning an exchange transfusion during the trial, were excluded from SUSTAIN so transfusions were infrequent. The median annual rate of packed red blood cell (RBC) units transfused was [redacted]

Table 4.6: Concomitant medications used by ≥20% of participants

Concomitant medication	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab, (2.5 mg/kg), N=66	Placebo, N=65
Number of patients with ≥1 concomitant medication[a,b] – N (%)	[redacted]	[redacted]	[redacted]
Acetaminophen (paracetamol)	[redacted]	[redacted]	[redacted]
Azithromycin	[redacted]	[redacted]	[redacted]
Benadryl	[redacted]	[redacted]	[redacted]
Dilaudid	[redacted]	[redacted]	[redacted]
Diphenhydramine	[redacted]	[redacted]	[redacted]
Folic acid	[redacted]	[redacted]	[redacted]
Heparin	[redacted]	[redacted]	[redacted]
Hydromorphone	[redacted]	[redacted]	[redacted]
HC/HU[c]	[redacted]	[redacted]	[redacted]
Ibuprofen	[redacted]	[redacted]	[redacted]
Ketorolac	[redacted]	[redacted]	[redacted]
Miralax	[redacted]	[redacted]	[redacted]
Morphine	[redacted]	[redacted]	[redacted]
Ondansetron	[redacted]	[redacted]	[redacted]
Oxycodone	[redacted]	[redacted]	[redacted]
Percocet	[redacted]	[redacted]	[redacted]
Phenergan	[redacted]	[redacted]	[redacted]
Potassium chloride	[redacted]	[redacted]	[redacted]
Sodium chloride	[redacted]	[redacted]	[redacted]
Toradol	[redacted]	[redacted]	[redacted]
Zofran	[redacted]	[redacted]	[redacted]

Based on Table 8 of the CS[1]

[a] Medications were coded using World Health Organization drug dictionary Version 01DEC2013E; [b] Concomitant medications were medications received at or after the first dosing of study drug through the last safety follow-up visit, or medication that was received prior to the first dosing with study drug and continued after dosing of study drug; [c] Hydrea and hidroxiurea (sic!) were also listed as being taken by [redacted] patients, respectively, in the high-dose crizanlizumab arm, [redacted] patients, respectively, in the low-dose crizanlizumab arm and [redacted], respectively, in the placebo arm

CS = company submission; HC = hydroxycarbamide; HU = hydroxyurea; ITT = intention-to-treat; kg = kilogram; mg = milligram;

4.2.3 SUSTAIN clinical effectiveness results

At the end of the 52-week treatment period (no results of longer follow-up available), the median annual SCPC rate in the high-dose crizanlizumab group (1.63, inter-quartile range (IQR) 0 to 3.97) was significantly lower than placebo (median 2.98, IQR 1.25 to 5.87, P =0.01 for difference vs. placebo). Results for the analysis of the annual SCPC rate for the ITT and PP populations are shown in Table 4.7.

Table 4.7: SUSTAIN primary endpoint annual rate of SCPC

	High-dose crizanlizumab (5 mg/kg)	Low-dose crizanlizumab (2.5 mg/kg)	Placebo
ITT population, N	**67**	**66**	**65**
Median annual rate (IQR)	1.63 (0.00 to 3.97)	2.01 (1.00 to 3.98)	2.98 (1.25 to 5.87)
P-value (difference vs. placebo)	0.01	0.18	-
Number with zero rate at trial end	24	12	11
PP population, N	**40**	**44**	**41**
Median annual rate (IQR)	1.04 (0.00 to 3.42)	2.00 (1.00 to 3.02)	2.18 (1.96 to 4.96)
P-value (difference vs. placebo)	0.018	0.13	-
Number with zero rate at trial end	15	7	5

Based on Table 9 of the CS[1] as well as Tables 7 and 8 of the CSR[27]
P-value from stratified Wilcoxon rank sum test
CI = confidence interval; CS = company submission; CSR = clinical study report; IQR = inter-quartile range; ITT = intention-to-treat; kg = kilogram; mg = milligram; PP = per-protocol; SCPC = sickle cell-related pain crises

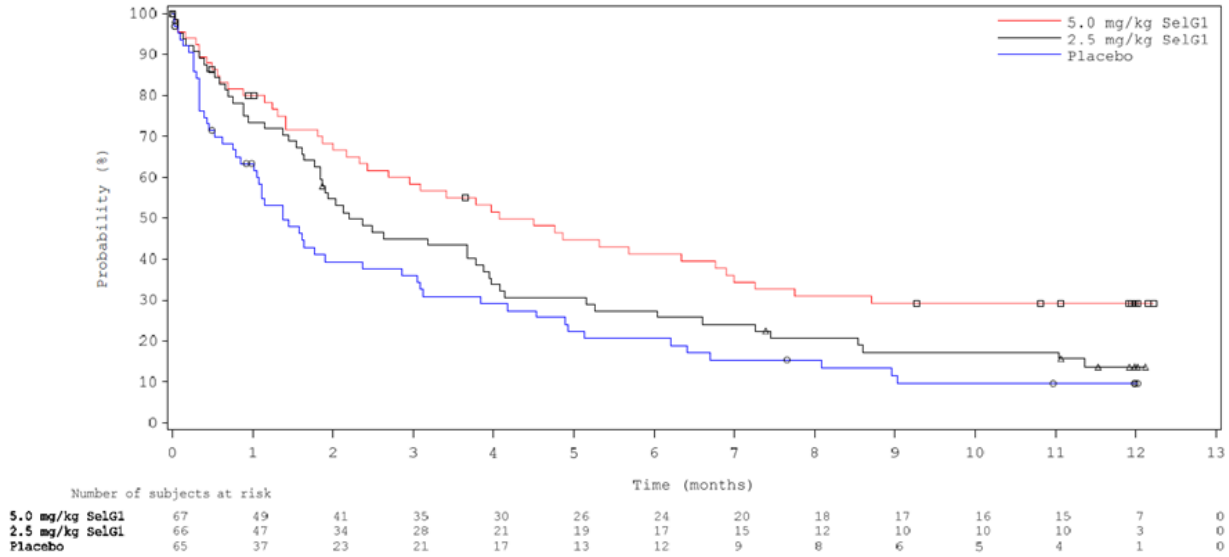
4.2.3.1 Time to first and second SCPC

Kaplan-Meier plots of the time to the first and second SCPC are shown in Figures 4.1 and 4.2, respectively. Time to the first SCPC was significantly longer with high-dose crizanlizumab compared to placebo (hazard ratio (HR) 0.50, 95% confidence interval (CI) 0.33 to 0.74, P=0.001) but not with low-dose crizanlizumab (HR 0.75, 95% CI 0.52 to 1.10, P=0.136). Median times to the first crisis were: high-dose 4.07 months (IQR 1.31 to upper limit not reached), low-dose 2.2 months (IQR 0.95 to 6.6 months) and placebo 1.38 months (IQR 0.39 to 4.90 months).

Similarly, the time to the second SCPC was also longer with high-dose crizanlizumab compared to placebo (HR 0.53, 95% CI 0.33 to 0.87, P=0.022) but not with low-dose crizanlizumab (HR 0.69, 95% CI 0.44 to 1.09, P=0.10). Median times to the second crisis were: high-dose 10.32 months (IQR 4.47 to upper limit not reached), low-dose 9.2 months (IQR 3.94 to 12.16 months) and placebo 5.09 months (IQR 2.96 to 11.01 months).

These results are also included in Table 4.8.

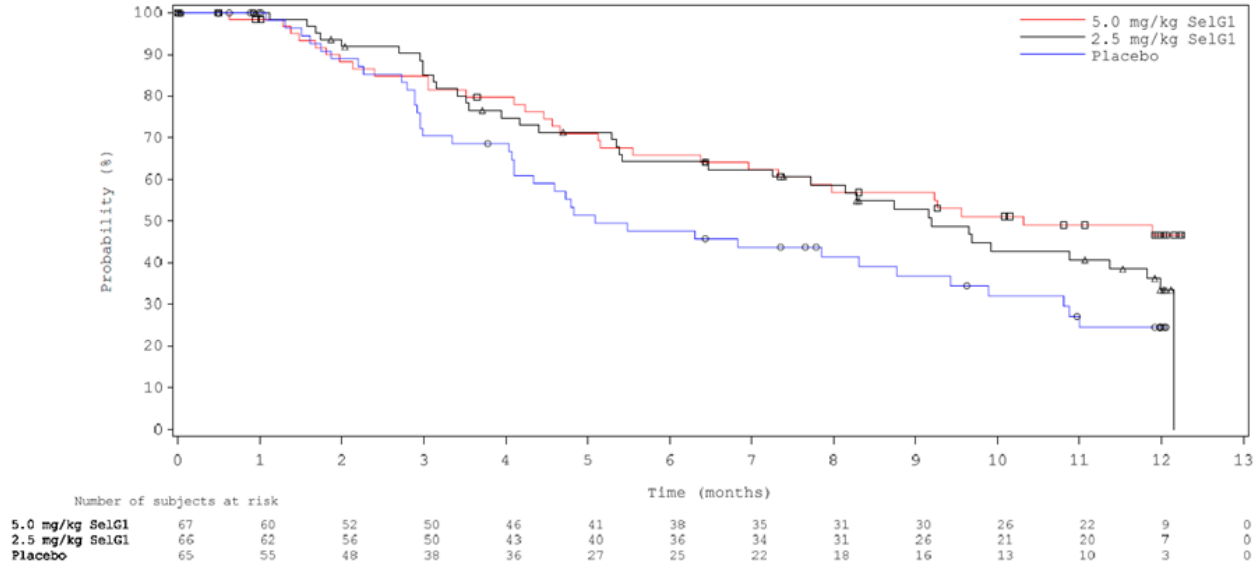
Figure 4.1: Kaplan-Meier plot of time to first SCPC



Based on Figure 3 of the CS[1]

CS = company submission; kg = kilogram; mg = milligram; SCPC = sickle cell-related pain crises

Figure 4.2: Kaplan-Meier plot of time to second SCPC



Based on Figure 4 of the CS[1]

CS = company submission; kg = kilogram; mg = milligram; SCPC = sickle cell-related pain crises

4.2.3.2 Secondary endpoints

Details of secondary endpoints of the SUSTAIN trial for the ITT population are provided in Table 4.8. There were no significant differences in the annual rate of days hospitalised between high-dose crizanlizumab (median 4.0, IQR 0.0 to 25.72) and placebo (median 6.87, IQR 0.0 to 28.3, P=0.45) or between low-dose crizanlizumab (median 6.87, IQR 0.0 to 18.0) and placebo (median 6.87, IQR 0.0 to 28.3, P=0.84). [redacted] This numerical reduction in the annualised rate of hospitalisation is however considered to be clinically relevant and the lack of statistical significance between the treatment arms for this endpoint is likely due to the variability and skewed nature of the data.

The analysis of annual rate of days hospitalised included all hospitalisations and not just those for SCPC so post-hoc analyses were performed to explore admissions due to SCPC. High-dose crizanlizumab significantly reduced the rate of SCPCs leading to a medical facility visit compared to placebo (2.3 versus 3.67 events per person year; incident rate ratio [IRR], 0.63 (95% CI, 0.5 to 0.79), P<0.0001).[34] This reduction in SCPCs leading to medical facility visits with was largely driven by a reduction in visits to emergency care units (IRR 0.55, 95% CI 0.35 to 0.87, P=0.01), and specialised SCD crisis centres (IRR 0.34, 95% CI 0.18 to 0.62, P=0.0005), as well as a trend towards a decrease in hospital inpatient admissions (IRR 0.76, 95% CI 0.56 to 1.05, P=0.094).

Table 4.8: SUSTAIN secondary endpoints (ITT population)

Outcome	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab (2.5 mg/kg), N=66	Placebo, N=65
Annual rate of days hospitalised			
Median rate (IQR)	4.00 (0.00–25.72)	6.87 (0.00–18.00)	6.87 (0.00–28.30)
Difference from placebo, %	-41.8	0.00	-
P-value[a]	0.45	0.84	-
Time to first SCPC			
Median time to first crisis (IQR), months	4.07 (1.31–NR)[b]	2.20 (0.95–6.60)	1.38 (0.39–4.90)
HR (95% CI)	0.50 (0.33–0.74)	0.75 (0.52–1.10)	-
P-value[c]	0.001	0.14	-
Time to second SCPC			
Median time to second crisis (IQR), months	10.32 (4.47–NR)[b]	9.20 (3.94–12.16)	5.09 (2.96–11.01)
HR (95% CI)	0.53 (0.33–0.87)	0.69 (0.44–1.09)	-
P-value[c]	0.02	0.10	-
Annual rate of uncomplicated SCPC[d]			
Median rate per year (IQR)	1.08 (0.00–3.96)	2.00 (0.00–3.02)	2.91 (1.00–5.00)
Difference from placebo, %	-62.9	-31.3	-
P-value[a]	0.02	0.12	-
Annual rate of ACS			
Median rate per year (IQR)	0 (0.00–0.00)	0 (0.00–0.00)	0 (0.00–0.00)
Difference from placebo, %	0.0	0.0	-
P-value[a]	0.78	0.87	-

Based on Table 10 of the CS[1]
[a] P-values are for the comparison between the active-treatment group and the placebo group and were calculated with the use of a stratified Wilcoxon rank-sum test; [b] The 75% value for the interquartile range was not observed within the 52-week trial and was considered to be not reported (NR). [c] P-values are for the comparison between the active-treatment group and the placebo group during the treatment phase and were calculated with the use

Outcome	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab (2.5 mg/kg), N=66	Placebo, N=65
of the log-rank test; [d] Uncomplicated SCPC are defined as crises other than ACS, hepatic sequestration, splenic sequestration, or priapism. ACS = acute chest syndrome; CI = confidence interval; CS = company submission; HR = hazard ratio; IQR = inter-quartile range; ITT = intention-to-treat; kg = kilogram; mg = milligram; NR = not reported; SCPC = sickle cell-related pain crises			

4.2.3.3 Uncomplicated crises and ACS

Uncomplicated crises were defined as SCPC other than ACS, hepatic sequestration, splenic sequestration, or priapism. The median rates per year of uncomplicated crises were 1.08 for high-dose crizanlizumab and 2.91 for placebo (reduction of 62.9%, P=0.02). [redacted] There was also no significant difference between groups in the median annual rate of ACS (zero for all groups). Further details of other complications are provided in Table 4.9.

Table 4.9: Treatment-emergent SCPC (safety population)

SCPC event	High-dose crizanlizumab (5 mg/kg), N=66		Low-dose crizanlizumab (2.5 mg/kg), N=64		Placebo, N=62	
	Patients, N (%)[a]	Events, N[a]	Patients, N (%)[a]	Events, N[a]	Patients, N (%)[a]	Events, N[a]
Any SCPC	[redacted]					
Uncomplicated SCPC	[redacted]					
ACS	[redacted]					
Hepatic sequestration						
Splenic sequestration						
Priapism						
Death[b]						
Based on Table 11 of the CS[1] Note: Treatment-emergent SCPC are defined as all SCPC which start (or increase in severity) after the date of first dose of study medication. All treatment-emergent SCPC were adjudicated by the CRC. [a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Multiple events for a patient that are in the same event category are counted multiple times in that event category. Multiple events belonging to more than one event category are counted multiple times in each of those event categories; [b] While death was removed as an SCPC event category by Amendment 2 to the Protocol, the CRC subsequently indicated that four events which met the criteria for SCPC should be given the event classification of "death". ACS = acute chest syndrome; CRC = Crisis Review Committee; CS = company submission; kg = kilogram; mg = milligram; SCPC = sickle cell-related pain crises						

4.2.3.4 Patient-reported outcomes

Patient-reported outcomes (PROs) were measured using the Brief Pain Inventory (BPI) and short-form 36 (SF-36) tools. Questionnaires were administered to patients at every treatment visit (days 1 and 15, every four weeks from week 6 and at weeks 52 (end of trial) and 58 (follow-up)). Results for the pain severity and interference domains of the BPI are shown in Table 4.10.

[redacted] The mean differences in change in pain severity at 52 weeks (end of the treatment period) compared to placebo were: [redacted]. The mean differences in change in pain interference at 52 weeks (end of the treatment period) compared to placebo were: [redacted].

Table 4.10: BPI pain severity and interference (ITT population)

	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab (2.5 mg/kg), N=66	Placebo, N=65
Pain severity			
Baseline, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 52 CfB, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Treatment difference	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	
Week 58 follow-up[b] CfB, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Treatment difference	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	
Pain interference			
Baseline, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab (2.5 mg/kg), N=66	Placebo, N=65
Week 52 CfB, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Treatment difference	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	
Week 58 follow-up[b] CfB, N	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	
LS mean (95% CI)	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	
Treatment difference	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	

Based on Tables 14 and 15 of the CS[1]
Note: BPI outcomes are calculated as the average of non-missing responses
[a] For patients who discontinue crizanlizumab or placebo, assessments six weeks or more after final dose are considered in the week 58 follow-up windowed visit
BPI = Brief Pain Inventory; CfB = change from baseline; CI = confidence interval; CS = company submission; ITT = intention-to-treat; kg = kilogram; LS = least squares; mg = milligram; SD = standard deviation

Results for the physical and mental health domains of SF-36 are shown in Table 4.11. [redacted] The mean differences in change in the physical health domain at 52 weeks (end of the treatment period) compared to placebo were: [redacted]. The mean differences in change in the mental health domain at 52 weeks (end of trial) compared to placebo were: [redacted]

Table 4.11: SF-36 physical and mental health domains (ITT population)

	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab (2.5 mg/kg), N=66	Placebo, N=65
Physical health			
Baseline, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab (2.5 mg/kg), N=66	Placebo, N=65
Week 52 CfB, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Treatment difference	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	
Week 58 follow-up[b] CfB, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Treatment difference	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	
Mental health			
Baseline, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 52 CfB, N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P- value	[redacted]	[redacted]	[redacted]
Treatment difference	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	
Week 58 follow-up[b] CfB, N	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	
LS mean (95% CI)	[redacted]	[redacted]	
P- value	[redacted]	[redacted]	
Treatment difference	[redacted]	[redacted]	
P-value	[redacted]	[redacted]	
Based on Tables 12 and 13 of the CS[1]			

	High-dose crizanlizumab (5 mg/kg), N=67	Low-dose crizanlizumab (2.5 mg/kg), N=66	Placebo, N=65
[a] For patients who discontinue crizanlizumab or placebo, assessments six weeks or more after final dose are considered in the week 58 follow-up windowed visit. CfB = change from baseline; CI = confidence interval; CS = company submission; ITT = intention-to-treat; kg = kilogram; LS = least squares; mg = milligram; SD = standard deviation			

4.2.3.5 Subgroup analyses

According to the CS, *"pre-specified subgroup analyses of the annual rates of SCPC in the ITT population were performed according to concomitant HC/HU use (yes or no), history of SCPC (2–4 or 5–10 crises in the 12 months prior to the study) and SCD genotype (HbSS or non-HbSS)"*.[1] It was further noted that *"across all subgroups, crizanlizumab 5 mg/kg was associated with a lower median annual SCPC rate compared to placebo. The subgroup analyses did not often meet statistical significance (P < 0.05), however the study was not powered to detect differences between treatment arms in these subgroups"*.[1] Detailed results are reported in Table 4.12.

Table 4.12: Subgroup analyses from the SUSTAIN trial (ITT population)

	High-dose crizanlizumab (5 mg/kg)	Low-dose crizanlizumab (2.5 mg/kg)	Placebo
According to concomitant HC use			
Yes	**n=42**	**n=41**	**n=40**
Median annual rate of SCPC (IQR)	2.43 (0.00–4.01)	2.00 (1.00–3.93)	3.58 (1.31–6.23)
Difference from placebo – %	-32.1	-44.1	-
Hodges-Lehmann median annual rate of SCPC[a]	[redacted]	[redacted]	[redacted]
Difference from placebo (95% CI; P-value)[b]	[redacted]	[redacted]	-
No	**n=25**	**n=25**	**n=25**
Median annual rate of SCPC (IQR)	1.00 (0.00–2.00)	2.16 (1.89–3.98)	2.00 (1.63–3.90)
Difference from placebo – %	-50.0	8.0	-
Hodges-Lehmann median annual rate of SCPC[a]	[redacted]	[redacted]	[redacted]
Difference from placebo	[redacted]	[redacted]	-

	High-dose crizanlizumab (5 mg/kg)	Low-dose crizanlizumab (2.5 mg/kg)	Placebo
(95% CI; P-value)[b]			
According to number of SCPC in previous 12 months			
2–4 SCPC	**n=42**	**n=41**	**n=41**
Median annual rate of SCPC (IQR)	1.14 (0.00–2.00)	2.00 (1.00–3.02)	2.00 (2.00–3.90)
Difference from placebo – %	-43.0	0.0	-
Hodges-Lehmann median annual rate of SCPC[a]	[redacted]	[redacted]	[redacted]
Difference from placebo (95% CI; P-value)[b]	[redacted]	[redacted]	-
5–10 SCPC	**n=25**	**n=25**	**n=24**
Median annual rate of SCPC (IQR)	1.97 (0.00–3.98)	3.02 (2.00–5.19)	5.32 (2.01–11.05)
Difference from placebo – %	-63.0	-43.2	-
Hodges-Lehmann median annual rate of SCPC[a]	[redacted]	[redacted]	[redacted]
Difference from placebo (95% CI; P-value)[b]	[redacted]	[redacted]	-
According the SCD genotype			
HbS	**n=47**	**n=47**	**n=47**
Median annual rate of SCPC (IQR)	1.97 (0.00–3.96)	2.05 (1.00–4.96)	3.01 (1.01–6.00)
Difference from placebo – %	-34.6	-31.9	-
Hodges-Lehmann median annual rate of SCPC[a]	[redacted]	[redacted]	[redacted]

	High-dose crizanlizumab (5 mg/kg)	Low-dose crizanlizumab (2.5 mg/kg)	Placebo
Difference from placebo (95% CI; P-value)[b]	[redacted]	[redacted]	-
Non-HbS	**n=20**	**n=19**	**n=18**
Median annual rate of SCPC (IQR)	0.99 (0.00–4.01)	2.00 (1.00–3.03)	2.00 (1.86–5.00)
Difference from placebo – %	-50.5	0.0	-
Hodges-Lehmann median annual rate of SCPC[a]	[redacted]	[redacted]	[redacted]
Difference from placebo (95% CI; P-value)[b]	[redacted]	[redacted]	-

Based on Table 19 of Appendix E of the CS[43]

[a] The Hodges-Lehmann median is a non-parametric estimator of the location parameter; [b] Median differences and confidence intervals were estimated using Hodges-Lehmann method. P-values were from a Stratified Wilcoxon Rank Sum Test, with HC/HU therapy (yes, no) and categorised crises history (2 to 4, 5 to 10) as reported in the Integrated Interactive Voice/Web Response System as the strata.

CI = confidence interval; CS = company submission; HbS = homozygous haemoglobin S; HC = hydroxycarbamide; HU = hydroxyurea; IQR = interquartile range; ITT = intention-to-treat; kg = kilogram; mg = milligram; SCD = sickle cell disease; SCPC = sickle cell-related pain crises

4.2.4 Safety outcomes

Section B.2.10 of the CS reported on the analysis of adverse events (AEs) in the SUSTAIN trial.[1] The population for this analysis included all participants who had received at least one dose of the study drug (n=192). The median duration of exposure to the study drug was [redacted] days for the high-dose crizanlizumab; [redacted] days for the low-dose and [redacted] days for the placebo arm. In terms of adherence, the percentage of infusions that the participants received relative to the expected number was [redacted] in both crizanlizumab arms and [redacted] for placebo. Discontinuation because of AE was reported in [redacted] receiving the 5 mg/kg of crizanlizumab, [redacted] on 2.5 mg/kg and [redacted] in the placebo arm, respectively.

The incidence of overall AE and serious adverse events (SAEs) was comparable across the three arms. In contrast, [redacted] (Table 4.13).

Five participants deaths occurred in the trial [redacted]. Two deaths happened in participants receiving 5 mg/kg crizanlizumab, one participant from ACS and one participant from endocarditis and sepsis. In the lower dose arm, one death occurred involving ACS, aspiration, respiratory failure, and progressive vascular congestion arm. Two participants also died in the placebo arm, one from right

ventricular failure and one from a confluence of VOC, ischaemic stroke, coma, sepsis, and venous thrombosis of the right lower limb.

Specific adverse events with an incidence of 10% or higher and serious adverse events reported by at least two participants in either crizanlizumab arm are presented in Table 4.14. The most frequent adverse events in the high-dose crizanlizumab included headache (17%), back pain (15%), nausea (18%) and arthralgia (18%).

In addition to these, the following adverse events considered to be both serious and life-threatening (but did not result in death) were documented in the CS: [redacted][1]

The CS states how the draft Summary of Product Characteristics (SmPC) for crizanlizumab incorporates results from the SOLACE trial of crizanlizumab 5 mg/kg in adults (n=45).[1, 25] In the 111 participants across both trials receiving 5 mg/kg a total of two participants suffering from infusion-related reactions were reported. Thus, the SmPC recommends monitoring patients after administration of crizanlizumab.[25]

Table 4.13: Overview of adverse events, n (%)

	Crizanlizumab 5 mg/kg (n=66)		Crizanlizumab 2.5 mg/kg (n=64)		Placebo (n=62)	
	Patients n (%)	**Events n**	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**
Any AE	57 (86.4)	459	56 (87.5)	434	55 (88.7)	358
Any drug-related AE	[redacted]	83	[redacted]	73	[redacted]	26
Any SAE	17 (25.8)	25	21 (32.8)	34	17 (27.4)	33
Any drug-related SAE	[redacted]	10	[redacted]	9	[redacted]	3
Any discontinuation due to AE	[redacted]	2	[redacted]	1	[redacted]	7
Death	2 (3.0)	3	1 (1.6)	4	2 (2.3)	6

Based on Table 17 of the CS[1] and Table 14.3.1.1 of the CSR[27]
AE = adverse events; CS = company submission; CSR = clinical study report; kg = kilogram; mg = milligram; SAE = serious adverse events

Table 4.14: Most common adverse events and serious adverse events, n (%)

	Crizanlizumab 5 mg/kg (n=66)	Crizanlizumab 2.5 mg/kg (n=64)	Placebo (n=62)
Serious adverse events[a]			
Influenza	0	3 (5)	0
Pneumonia	3 (5)	2 (3)	3 (5)
Pyrexia	2 (3)	0	1 (2)
Adverse events[b]			
Arthralgia	12 (18)	9 (14)	5 (8)
Back pain	10 (15)	13 (20)	7 (11)
Chest pain	1 (2)	7 (11)	1 (2)
Diarrhoea	7 (11	5 (8)	2 (3)
Headache	11 (17)	14 (22)	10 (16)

	Crizanlizumab 5 mg/kg (n=66)	Crizanlizumab 2.5 mg/kg (n=64)	Placebo (n=62)
Musculoskeletal pain	8 (12)	4 (6)	6 (10)
Nausea	12 (18)	11 (17)	7 (11)
Pain in extremity	11 (17)	8 (12)	10 (16)
Pruritus	5 (8)	7 (11)	3 (5)
Pyrexia	7 (11)	6 (9)	4 (6)
Upper respiratory tract infection	7 (11)	7 (11)	6 (10)
Urinary tract infection	9 (14)	7 (11)	7 (11)
Vomiting	5 (8)	7 (11)	3 (5)

Based on Table 18 of the CS[1]
[a] SAEs reported by at least two participants in either crizanlizumab arm; b Incidence of 10% or higher
CS = company submission; kg = kilogram; mg = milligram; SAE = serious adverse events

ERG comment: The safety of crizanlizumab compared to placebo presents no concerns. However, it should be noted that potential rare adverse events might have been missed due to the small sample size.

A number of observations need to be made:

1. Neither the CS nor the CSR provide a list of drug-related serious (or severe) adverse events by system organ class and preferred term.
2. The plausibility of AEs as related to the study drug was described by the investigator as *"not related; unlikely related; possibly related; probably related or definitively related"*.[27] The criteria for the determination of this plausibility have not been provided in the CS or the CSR.[1, 27]
3. According to the CS, sepsis affected just one participant in the placebo arm.[1] However, according to Table 14.3.1.9 of the CSR, [redacted].[27]
4. The interpretation of pyrexia as a severe AE appears unclear. The participant figures for this AE cannot be inferred from the numbers reported in Table 14.3.1.6 of the CSR which describes the proportion of participants suffering from mild, moderate, or severe pyrexia.[27]

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison was performed.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

SUSTAIN was the only included trial which compared crizanlizumab 5 mg/kg and 2.5 mg/kg plus standard care to placebo plus standard care. The CS stated that no other trials were identified from the SLR *"that were considered to represent a more relevant source of data for established clinical management compared to the placebo arm of SUSTAIN, and therefore no indirect treatment comparison has been conducted"*.[1]

ERG comment: The ERG agrees that SUSTAIN is the primary source of evidence and no indirect treatment comparisons were required.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness has been undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

A single set of searches was undertaken to identify clinical effectiveness and adverse events data. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were searched, including additional grey literature resources and reference checking. Searches were well conducted and documented, making them transparent and reproducible.

The primary evidence used in the CS came from the SUSTAIN trial, a double-blind, placebo-controlled, randomised controlled, phase II trial evaluating the efficacy and safety of crizanlizumab compared to placebo for the prevention of VOC in patients aged 16 to 65 years with SCD. SUSTAIN compared two doses of crizanlizumab (2.5 mg/kg and 5 mg/kg) administered intravenously 14 times over 52 weeks with placebo (results after longer follow-up not available). Most participants included in SUSTAIN described their race as "black" ([redacted]). None of the trial centres were in the UK or Europe.

Randomisation was stratified by concomitant use of HU and the number of SCPC in the previous 12 months (two to four or five to 10). The primary endpoint was the annual rate of SCPC, defined as acute episodes of pain with no medically defined cause other than a vaso-occlusive event which resulted in a medical facility visit and treatment with oral or parenteral narcotics or a parenteral NSAIDs.

At the end of the 52-week treatment period the median annual SCPC rate in the high-dose crizanlizumab group (1.63, inter-quartile range (IQR) 0 to 3.97) was significantly lower than placebo (median 2.98, IQR 1.25 to 5.87, P =0.01 for difference vs. placebo), see Table 4.7.

Time to the first SCPC was significantly longer with high-dose crizanlizumab compared to placebo (hazard ratio (HR) 0.50, 95% confidence interval (CI) 0.33 to 0.74, P=0.001) but not with low-dose crizanlizumab (HR 0.75, 95% CI 0.52 to 1.10, P=0.136). Similarly, the time to the second SCPC was also longer with high-dose crizanlizumab compared to placebo (HR 0.53, 95% CI 0.33 to 0.87, P=0.022) but not with low-dose crizanlizumab (HR 0.69, 95% CI 0.44 to 1.09, P=0.10), see Table 4.8 for results of secondary endpoints.

Uncomplicated crises were defined as SCPC other than ACS, hepatic sequestration, splenic sequestration, or priapism. The median rates per year of uncomplicated crises were 1.08 for high-dose crizanlizumab and 2.91 for placebo (reduction of 62.9%, P=0.02). [redacted] There was also no significant difference between groups in the median annual rate of ACS (zero for all groups). Further details of other complications are provided in Table 4.9.

Results for the pain severity and interference domains of the Brief Pain Inventory (BPI) are shown in Table 4.10. There were no statistically significant differences between groups regarding mean change from baseline in BPI pain severity and interference during the trial.

The incidence of overall adverse events (AEs) and serious adverse events (SAEs) was comparable across the three arms. In contrast, [redacted] (Table 4.13).

Five participants deaths occurred in the trial [redacted]. Two deaths happened in participants receiving 5 mg/kg crizanlizumab, one participant from ACS and one participant from endocarditis and

sepsis. In the lower dose arm, one death occurred involving ACS, aspiration, respiratory failure, and progressive vascular congestion arm. Two participants also died in the placebo arm, one from right ventricular failure and one from a confluence of VOC, ischaemic stroke, coma, sepsis, and venous thrombosis of the right lower limb.

In line with the NICE final scope, *"pre-specified subgroup analyses of the annual rates of SCPC in the ITT population were performed according to concomitant HC/HU use (yes or no), history of SCPC (2–4 or 5–10 crises in the 12 months prior to the study) and SCD genotype (HbSS or non-HbSS)"*.[1] It was noted that *"across all subgroups, crizanlizumab 5 mg/kg was associated with a lower median annual SCPC rate compared to placebo. The subgroup analyses did not often meet statistical significance (P < 0.05), however the study was not powered to detect differences between treatment arms in these subgroups"*.[1] Detailed results are reported in Table 4.12.

No meta-analysis, indirect comparison and/or multiple treatment comparison was performed.

5. Cost effectiveness

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

Appendix G of the CS details a single SLR which was conducted to identify all literature published on economic evaluations of interventions for the prevention of VOC in SCD, health state utility values for patients experiencing VOC in SCD, or their caregivers, and cost and/or resource use studies reporting data for patients experiencing VOC in SCD.[43] Searches were conducted in August 2019, with a subsequent update in January 2020. No language or publication date limits were reported. Databases were searched from date of inception. A summary of the sources searched is provided in Table 5.1.

Table 5.1: Data sources for the cost effectiveness systematic review

Resource	Host/source	Date range	Date searched
Electronic databases			
MEDLINE, MEDLINE In-Process, MEDLINE Daily and MEDLINE EPub Ahead of Print	Ovid	(i)1946-16.8.19 (ii)1946-24.1.20	(i)19.8.19 (ii)27.1.20
Embase	Ovid	(i)1974-16.8.19 (ii)1974-24.1.20	(i)19.8.19 (ii)27.1.20
HTAD	CRD website	Issue 4/4 October 2016	(i)19.8.19 (ii)27.1.20
NHS EED		Issue 2/4 April 2015	
Conference proceedings			
ASH Annual Meeting	Handsearch of online proceedings	2017-2019	(i)September 2019 (ii)January 2020
Annual Congress of the EHA		2017-2019	
Annual Symposium of the Foundation for Sickle Cell Disease Research		2017, 2019	
BSH Annual Scientific Meeting		2017-2019	
ISPOR - Annual International and European Meetings		2017-2019	
Additional resources			
AWSMG	Web search	All years	(i)19.9.19 (ii)13.2.20
NCPE			
NICE			
SMC			
CEA Registry			(i)16.9.19

Resource	Host/source	Date range	Date searched
ScHARRHUD			(ii)13.2.20
EQ-5D Publications Database			

Based on CS appendices[43]

(i) original search; (ii) update search

ASH = American Society of Hematology; AWMSG = All Wales Medicines Strategy Group; BSH = British Society for Haematology; CEA = Cost effectiveness analysis; CRD = Centre for Reviews and Dissemination; CS = company submission; EED = Economic Evaluation Database; EHA = European Haematology Association; EQ-5D = EuroQol 5 dimensions questionnaire; HTAD = Health Technology Assessment database; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NCPE = National Centre for Pharmacoeconomics; NHS = National Health Service, NICE = National Institute for Health and Care Excellence, ScHARRHUD = School of Health and Related Research Health Utilities Database, University of Sheffield; SMC = Scottish Medicines Consortium

ERG comment:

- A single search was undertaken for economic evaluations, cost and resource use studies and health state utility values. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were searched, including additional grey literature resources and reference checking. Both the original and the update searches were well conducted and documented, making them transparent and reproducible.
- No date or language limits were unnecessarily applied to the database searches. The date limit applied to conference searches was considered justifiable.
- Study design filters were appropriately used and based on terms designed by the Scottish Intercollegiate Guidelines Network (SIGN), the School of Health and Related Research (ScHARR) at the University of Sheffield, and the York Health Economics Consortium (YHEC).
- Additional synonyms could have been incorporated into the strategy, such as the abbreviation 'VOC' for the condition, however this is unlikely to have greatly affected recall.

5.1.2 Inclusion/exclusion criteria used in the study selection

Studies were selected for inclusion in two stages: first, the abstracts of the search results were reviewed by two independent reviewers for relevance using the eligibility criteria; second, the full-texts of potentially relevant articles were screened by two independent reviewers in order to obtain the final list of included studies. The results of the two reviewers were compared and any disagreements were resolved by discussion until a consensus was met. If necessary, a third independent reviewer made the final decision.[43]

In both the original and updated SLR, the review of titles and abstracts was performed using pre-defined eligibility criteria for economic evaluations, health-related quality of life and cost and resource use. These eligibility criteria, Shown in Table 5.2, were based on the decision problem and developed using the Population, Intervention(s), Comparator(s), Outcomes, Study type (PICOS) framework.

Table 5.2: Eligibility criteria for the economic SLR

Domain	Inclusion criteria	Exclusion criteria
Population	Patients ≥16 years with sickle cell disease	Population does not include patients ≥16 years with sickle cell disease
Intervention(s)	**Economic evaluations** The following interventions for the prevention of vaso-occlusive crises:	**Economic evaluations** Studies not investigating a relevant intervention

Domain	Inclusion criteria	Exclusion criteria
	• Crizanlizumab with or without hydroxycarbamide/hydroxyurea • Any other intervention reflecting supportive care or established clinical management without crizanlizumab, including, but not limited to hydroxy-carbamide/hydroxyurea, blood transfusions, and HSCT **HSUV studies** Any or none **CRU studies** Any or none	**HSUV studies** Not applicable (no restrictions were applied to interventions) **CRU studies** Not applicable (no restrictions were applied to interventions)
Comparator(s)	**Economic evaluations** Any **HSUV studies** Any or none **CRU studies** Any or none	Not applicable (no restrictions were applied to comparators)
Outcomes	**Economic evaluations** • ICERs • Cost per clinical outcome • Total QALYs • Total LYGs • Total costs • Incremental costs and QALYs **HSUV studies** Health state utility values related to vaso-occlusive crises for patients or their caregivers, including (but not limited to) those measured using: • Direct elicitation methods (e.g. standard gamble or time trade-off) • Indirect elicitation methods (e.g. EQ-5D, SF-6D, VAS, 15D, HUI, HUI2 or HUI3) • Mapping from generic or disease-specific HRQoL measures (e.g. SF-36) **CRU studies** Direct costs and resource use related to vaso-occlusive crises and with the potential to be relevant to an economic model of crizanlizumab, including but not limited to: • Hospital admission (frequency, duration and costs) • Cost of care following stroke events	Studies not presenting relevant outcomes for the population of interest

Domain	Inclusion criteria	Exclusion criteria
	• Cost of adverse events • Monitoring costs • Number and cost of transfusions • Drug costs, including cost of administration • Complication costs relating to a new vaso-occlusive crisis, acute chest syndrome, avascular necrosis, cardiomegaly, sepsis, or gall stones	
Study type	**Economic evaluations** Any of the following study designs: • Cost utility • Cost effectiveness • Cost consequence • Cost benefit • Cost minimisation **HSUV studies** Any study design **CRU studies** Any study design	**Economic evaluations** Any other types of analysis **HSUV studies** Not applicable (no restrictions by study type) **CRU studies** Not applicable (no restrictions by study type)
Publication type	• Original research studies including economic evaluations • HTAs • Conference abstracts published in or after 2017	• Any other publication type, including studies not reporting any original research • Conference abstracts published before 2017
	SLRs and (network) meta-analyses were considered relevant at the title/abstract review stage and hand searched for relevant primary studies, but were excluded during the full-text review stage unless they themselves presented primary research	
Geographical region	**Economic evaluations** Any **HSUV studies** Any **CRU studies** Studies conducted in a European setting	**Economic evaluations** Not applicable (no restrictions by geographical region) **HSUV studies** Not applicable (no restrictions by geographical region) **CRU studies** Studies conducted in a setting other than Europe
Other considerations	Human subjects	Studies not on human subjects

Based on Table 29 Appendix G of the CS[43]

CRU = cost resource use; CS = company submission; EQ-5D = EuroQol-five dimensions; HRQoL = health-related quality of life; HSCT = haematopoietic stem cell transplantation; HSUV = health state utility value; HTA = health technology assessment; HUI = health utility index; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY =quality-adjusted life year; SF-6D = Short form-six dimensions; SF-36 = 36-Item Short Form Health Survey; SLR = systematic literature review; VAS = visual analogue scale

ERG comment: The inclusion and exclusion criteria appear reasonable. The exclusion of non-European cost and resource use studies may have led to some relevant studies being excluded.

5.1.3 Included/excluded studies in the cost effectiveness review

5.1.3.1 Economic evaluations

A PRISMA (Transparent reporting of systematic reviews and meta-analyses) diagram showing the flow of records through each stage of the review process for the economic evaluations stream of both, the original SLR and the SLR update, is presented in Figure 5 of Appendix G of the CS.[43] Overall, 730 unique records were retrieved by the electronic database searches in the original SLR. After title and abstract review, five records potentially relevant to the economic evaluation stream were reviewed at full-text. In the SLR update, an additional 81 unique records were suitable for review. After title and abstract review, two potentially relevant economic evaluation records were selected to be reviewed at full-text. Supplementary searches of conferences, SLR bibliographies and websites yielded 982 records in the original SLR, and 415 in the SLR update. In total, across the original SLR and the SLR update, no economic evaluations were included in the SLR.

As part of the supplementary search of HTA websites, the economic evaluations of patient-controlled analgesia and low-molecular weight heparin for patients presenting at hospital with VOC, described in NICE clinical guideline (CG) 143 (Appendix F) were identified.[43] However, these were excluded from the SLR as interventions were for the management of VOCs rather than prevention.[52] Given the relevance of this economic evaluation to the appraisal, some inputs from these evaluations were utilised in the de-novo cost effectiveness model presented by the company.[1] A list of electronic database records excluded at the full-text review stage of the SLR for the economic evaluations topic is presented in Table 30 of Appendix G, along with a brief rationale for exclusion.[43]

5.1.3.2 Health-related quality of life (HRQoL)

A PRISMA diagram showing the flow of records through each stage of the review process for the health state utility value (HSUV) topic is presented in Figure 6 of Appendix H of the CS.[43] The 730 unique records retrieved by the original SLR provided eight records potentially relevant to the HRQoL stream at title and abstract review and an additional four from the updated SLR were also screened at full-text.[43] In total, three publications reporting three unique health state utility value (HSUV) studies were included in the SLR. A summary of the results of the three included publications can be found in Table 31 of Appendix H of the CS.[43] A list of electronic database records excluded at the full-text review stage of the SLR for the HSUV studies topic stream is presented in Table 32 of Appendix H, along with a brief rationale for exclusion.[43]

5.1.3.3 Cost and resource use

A PRISMA diagram showing the flow of records through each stage of the review process for the cost and resource use topic is presented in Figure 7 of Appendix I of the CS.[43] The 730 unique records retrieved by the original SLR provided 38 records potentially relevant to the cost and resource use stream at title and abstract review and an additional nine from the updated SLR were also screened at full-text.[43] In total, 15 publications reporting 14 unique CRU studies were included in the review. A summary of the results of the three included publications can be found in Table 33 of Appendix I of the CS.[43] A list of electronic database records excluded at the full-text review stage of the SLR for the HSUV studies is presented in Table 32 of Appendix I, along with a brief rationale for exclusion.[43] A list of electronic database records excluded at the full-text review stage of the SLR for the cost and resource use topic is presented in Table 34 of Appendix I, along with a brief rationale for exclusion.[43]

5.1.4 Conclusions of the cost effectiveness review

Overall, the cost effectiveness review appears to have been well conducted. The exclusion of non-European cost and resource use studies may have led to some relevant studies being excluded, but 14 European studies were identified which should provide a good level of evidence in this area.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

A summary of the economic evaluation conducted by the company is presented in Table 5.3.

Table 5.3: Summary of the company submission economic evaluation

	Approach	Source/Justification	Signpost (location in ERG report)
Model	A Markov cohort model was used to assess the cost effectiveness of crizanlizumab. The model had a time horizon of 55 years (considered a lifetime horizon in this population given the mean starting age of 37.1)	The choice of the time horizon (55 years) seems appropriate since all patients in the simulation die before reaching the time horizon.	Section 5.2.2
States and events	The model health states were defined according to the average number of VOC that patients experienced in one year. The company selected the following health states: <1 VOC, ≥1–<3 VOC or ≥3 VOCs. At the beginning of each new model cycle, patients who were alive at the end of the previous cycle were "redistributed" into the three VOC health states. Patients who died transitioned to the absorbing death state. In each model cycle, patients could experience the following SCD-related complications: acute chest syndrome, sepsis, gall stones, cardiac arrhythmias, cellulitis, leg ulcers, osteomyelitis, priapism (only in males) and pulmonary hypertension	The structure of the model was designed to capture differences between treatments in terms of the effect on the rate of VOC as well as the impact that this has in terms of mortality and other SCD-related complications. The health states included within the model structure (<1 VOC, ≥1–<3 VOC or ≥3 VOC) are based on findings from Platt et al. (1991) which showed that patients who experienced ≥3 VOC per year had a significantly higher mortality rate than patients experiencing <3 VOC per year.[53] Furthermore, more recent analyses of the HES database and LEGACY registry found that the number of VOC experienced by SCD patients impacts the risk of SCD-related complications and HRQoL, as well as mortality.[28, 54, 55]	Section 5.2.2
Comparators	The comparator is standard of care, consisting of supportive care (e.g. hydration with intravenous fluids and keeping warm), HC/HU and blood transfusions.	The final scope also listed ASCT as a relevant comparator. However, the company argue in the CS that ASCT is a treatment option of last resort and therefore it is not expected that crizanlizumab would displace or alter the number of SCD patients that would ultimately receive ASCT.	Section 5.2.4
Natural history	The most common sickle-cell genotype, seen in 67% of UK SCD patients, is homozygous haemoglobin S (HbS).[2] Patients with homozygous HbS tend to experience the most clinically severe form of the disease.[1] VOC is a major component of SCD and include acute and severe painful		Section 2.1

	Approach	Source/Justification	Signpost (location in ERG report)
	episodes.[1] Due to the increased cell-cell interactions between affected erythrocytes, other blood cells, and endothelial cells lining the wall of the blood vessel, this results in the formation of a multi-cellular aggregate within the blood vessel lumen.[6] This impacts on the delivery of oxygen to surrounding tissues, resulting in ischaemic injuries, severe pain, the potential for multi-organ damage, and other acute and chronic complications.[7] The main severe outcome of VOC is ACS, which can be a potentially life-threatening component of SCD, responsible for up to a quarter of SCD-related deaths.[1] Other SCD complications can include gallstones, avascular necrosis, ischaemic stroke and silent infarcts, splenic sequestration, leg ulcers, priapism in males, and pulmonary hypertension.[1, 3, 8]		
Treatment effectiveness	Treatment effectiveness was primarily based on the SUSTAIN trial and data from the HES database. The SUSTAIN trial was used to determine health state occupancy between the three VOC health states and the mean number of VOCs per health state in each treatment group. The HES data was used to estimate the risk of mortality and other complications in each of the VOC health states.	The SUSTAIN trial did not allow for determination of differences in long-term outcomes such as mortality or relatively rare SCD-complication events, as the short duration (52 weeks) and relatively small sample size of the study meant that few deaths or complications occurred during the trial. Additional sources of data were therefore required to model the impact of VOC on the risk of death and other complications.[1]	Section 5.2.6
Adverse events	Adverse events beyond the included SCD-related complications were not included in the model	Given the similar occurrence of grade 3 and 4 AEs across treatment arms the inclusion of AEs was assumed to have minimal impact on results.	Section 5.2.7
Health-related QoL	HRQoL was measured in patients in the SUSTAIN trial but this data was not used in the CS. Instead health state utility values (HSUVs) for each of the three VOC health state were utilised from the literature and per event utility decrements for VOC events and other complications were applied to these HSUVs. Utilities were age adjusted.	HRQoL data from the SUSTAIN trial was not utilised in the model as [redacted] of SF-36 questionnaires completed in the SUSTAIN trial were administered outside of a 7-day recall period of a VOC. Therefore, HSUVs per VOC health state were obtained from an unpublished analysis of the LEGACY Registry which included the SF-36. Utility decrements for VOC	Section 5.2.8

	Approach	Source/Justification	Signpost (location in ERG report)
		events were obtained from EQ-5D data from Anie et al. 2012 and decrements for other SCD complications was taken from a range of published sources.[1, 56]	
Resource utilisation and costs	The CS included the costs of drug acquisition, administration costs for interventions and comparators (including blood transfusions), costs associated with monitoring, and costs associated with the management of VOC and acute complications.	According to NICE reference case.	Section 5.2.9
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case.	Section 5.2.5
Sensitivity analysis	Probabilistic and one-way sensitivity analysis.	According to NICE reference case.	Section 6.2

ACS = acute chest syndrome; AE = adverse event; ASCT = allogenic stem-cell transplant; HbS = homozygous haemoglobin S; HC = hydroxycarbamide; HES = Hospital Episode Statistics; HRQoL = health-related quality of life; HSUVs = health state utility values; HU = hydroxyurea; NICE = National Institute for Health and Care Excellence; QoL = quality of life; SCD = sickle cell disease; SF-36 = 36-Item Short Form Health Survey VOC = vaso-occlusive crises

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	According to NICE reference case
Perspective on costs	NHS and PSS	According to NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	According to NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The choice of the time horizon (55 years) appears to be appropriate in this population given the baseline age of 37.1 years and that all patients in the simulation die before reaching the time horizon.
Synthesis of evidence on health effects	Based on systematic review	Systematic literature reviews were conducted for relevant cost effectiveness studies, and studies on HRQoL, cost and resource utilisation for the target population.
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.	Health effects are expressed in QALYs. HSUVs are measured using the SF-36. VOC per event decrements are measured using EQ-5D.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	HRQoL measured in patients, but not in SUSTAIN
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	SF-36 data from HSUVs mapped to EQ-5D UK utility values, which were valued in a representative sample of the UK population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	According to NICE reference case
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	According to NICE reference case
Discounting	The same annual rate for both costs and health effects (3.5%)	According to NICE reference case

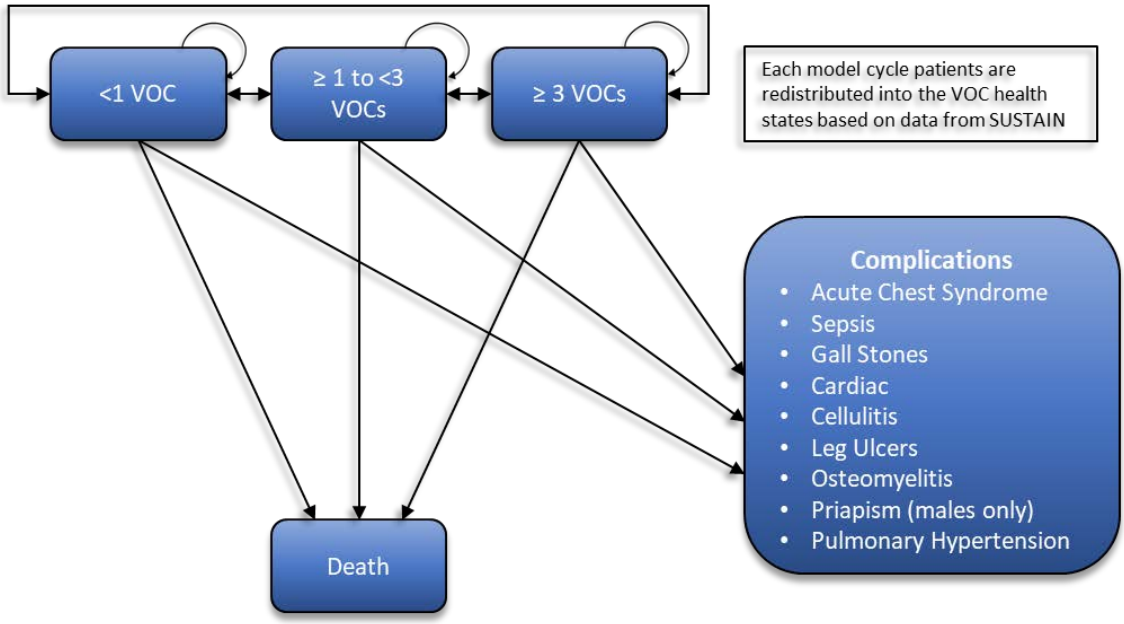
EQ-5D = European Quality of Life-5 Dimensions; ERG = Evidence Review Group; HRQoL = health-related quality of life; HSUVs = health state utility values; NHS = National Health Service; NICE = National Institute

Element of health technology assessment	Reference case	ERG comment on company's submission
for Health and Care Excellence; PSS = personal social services; QALY = quality-adjusted life year; SF-36 = 36-Item Short Form Health Survey; UK = United Kingdom		

5.2.2 Model structure

The company developed a de novo Markov model in Excel to assess the cost effectiveness of crizanlizumab versus established clinical management without crizanlizumab, further referred to as standard of care (SoC) as a treatment for the prevention of recurrent VOCs in patients with SCD.[1] The model health states were defined according to the average number of VOC that patients experienced in one year. In particular, the company selected the following categories: less than one, between one and three and more than three VOC to define the model health states. The distribution of patients per health state was estimated from SUSTAIN data.[1] The health state occupancy was determined by the mean annualised rate (calculated from the number of VOC events per year) from the high dose crizanlizumab arm and the placebo arm subdivided by those VOC categories in SUSTAIN. Furthermore, health state costs and utilities were calculated based on cost and utility decrements per VOC event, and combined with the mean number of VOC events that occurred in one year, as observed in SUSTAIN. An absorbing "death" health state is also included in the model. Additionally, in each model cycle, patients may experience the following SCD-related complications: acute chest syndrome, sepsis, gall stones, cardiac arrhythmias, cellulitis, leg ulcers, osteomyelitis, priapism (only in males) and pulmonary hypertension. A schematic representation of the model structure is shown in Figure 5.1. However, it should be noted that, as will be explained below, this representation is not completely accurate since transitions between each of the health states defined according to the VOC categories is not possible.

Figure 5.1: Model structure



Based on Figure 5 in CS[1]
CS = company submission; VOC = vaso-occlusive crisis

The annual probability of death and the annual probability of experiencing SCD-related complications was modelled to be dependent on age, gender and the VOC health state that was occupied within a simulation's year (i.e. the number of VOC experienced that year in the model).[1] These probabilities were modelled according to the results of an analysis of the HES database conducted by the company,

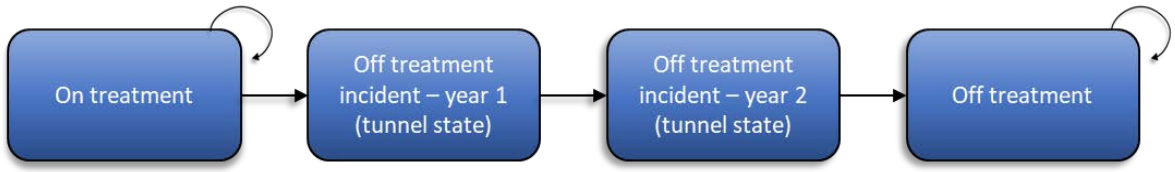
in which patients in the more than three and between one and three VOC health states were observed to have a higher probability of death and experiencing SCD-related complications, compared to patients in the less than one VOC health state. The company assumed in the model that SCD-related complications and death were independent, and in each model cycle, complications were assumed to occur first, before mortality was applied.[20]

At the beginning of each new model cycle, patients who were alive at the end of the previous cycle were "redistributed" into the three VOC health states.[1] The company considered that, in the absence of any other long-term data on the efficacy of crizanlizumab, the mean annualised rate of VOC from SUSTAIN was the most appropriate source to re-estimate the distribution of patients between the VOC health states in all cycles.

Furthermore, patients in the crizanlizumab arm of the model can discontinue treatment in any model cycle. From the next cycle after discontinuation these patients are assumed to receive SoC (with or without HC/HU).[1] The model distinguishes thus between patients who are still on treatment with crizanlizumab ('On treatment' health state: distribution of patients per VOC health states based on the crizanlizumab arm of SUSTAIN) and patients who have discontinued ('Off treatment' health state: distribution of patients per VOC health states based on the placebo arm of SUSTAIN).

Additionally, the company considered two tunnel health states ('Off treatment incident') in the model to account for extended treatment effectiveness which is applied in the two years following discontinuation with crizanlizumab.[1] In these tunnel health states, patients are assumed to receive the costs associated to SoC, but the treatment effectiveness from crizanlizumab or SoC can be applied, depending on the assumptions considered about the duration of the crizanlizumab treatment effect after discontinuation. Patients enter the first tunnel health state after discontinuation with crizanlizumab and spend one year in each tunnel state before moving to the 'Off treatment' health state. A representation of the division of the crizanlizumab VOC health states can be seen in Figure 5.2.

Figure 5.2: Additional health states in the crizanlizumab VOC health states of the model



Based on Figure 6 in CS[1]
CS = company submission; VOC = vaso-occlusive crisis

The model uses a cycle length of one year (reflecting the duration of the SUSTAIN trial) and half-cycle correction. Costs and utilities are applied to each health state of the model (except death) to calculate per-cycle costs and quality adjusted life-years (QALYs).

ERG comment: The ERG had several concerns regarding the model structure chosen by the company, which are summarised below:

- The VOC health states in the model (less than one VOC, between one and three VOC and more than three VOC) were based on Platt et al. 1991.[53] However, the inclusion criteria in SUSTAIN required experiencing 2-10 VOCs in the previous year. In clarification question B1.g,[20] the ERG asked the company to provide the number of patients at baseline with less than one VOC, between one and three VOC and more than three VOC in the 12 months prior, as well as a frequency distribution showing the number of VOCs experienced per patient in the 12 months prior to the SUSTAIN trial. The company response was: "*Entry criteria for the SUSTAIN trial*

required patients to have had 2–10 VOC in the previous year. This VOC rate was patient reported and used the same definition of VOC that was used for the primary endpoint of the SUSTAIN trial. Upon entry into SUSTAIN, patients were categorised based on VOC rate as either having experienced 2–4 or 5–10 VOC in the previous 12 months. Due to stratification of baseline VOC into these groups, the number of patients at baseline with <1, ≥1 to <3 and ≥3 VOC per year (as per the VOC categories used in the model, as described in response to Question B1 part a) cannot be accurately reported. Likewise, we also cannot report the frequency distribution of patients by VOC rate at baseline".[20] Based on this, the ERG conclusion is that transition probabilities in the model cannot be accurately estimated due to missing information (SUSTAIN data cannot inform transitions from the less than one VOC health state and can only partially inform transitions from the between one and three VOC, given that only patients with more than two VOC in the previous 12 months were included in the trial, which lasted for only 52 weeks).

- Furthermore, the initial distribution of patients over the VOC model health states does not correspond to the baseline distribution of patients in SUSTAIN. Since one of the inclusion criteria in SUSTAIN was experiencing 2-10 VOCs in the previous year, in particular, in SUSTAIN there were no patients with less than one VOC in the previous year at baseline. Thus, it is unclear why in the first cycle of the model the proportion of patients in this VOC health state is not equal to 0. In their response to clarification question B1.f,[20] the company indicated that since VOC rates in the model are annualised and represent the rate over a model cycle of one year, "*applying the initial baseline distribution of patients for the first model cycle would not accurately capture the treatment benefit received by patients in the first year of treatment*". Annualised rates "*should represent a patient's VOC rate for the entirety of the year*" and although "*patient entry criteria require a patient to have ≥2 VOC in the previous year, the VOC rate adjusts promptly as patients begin to respond to treatment with crizanlizumab*".[20] The ERG does not agree with this approach. The initial distribution (say cycle 0) should correspond to the distribution of patients at baseline. After one year the distribution should match that observed in SUSTAIN. Then, a half-cycle correction should be applied. This is the standard approach in Markov models.

- At the end of each model cycle, all alive patients are re-distributed between the VOC health states according to the proportions observed in SUSTAIN. Again, because the inclusion criteria in SUSTAIN was experiencing 2-10 VOCs in the previous year, this re-distribution also seems inappropriate. Therefore, the model is not using transition probabilities as in standard Markov models (e.g. transitions between VOC health states as depicted in Figure 5.1 are not directly modelled using transition probabilities).

- The company assumed in the model that there is no direct link between SCD-related complications and death (these were assumed to be independent, and in each model cycle, complications were assumed to occur first, before mortality was applied). For some complications, like acute chest syndrome, this assumption seems unrealistic. This was due to data limitations, as the company explained in their response to clarification question B2.[20] However, the company indicated that all-cause mortality (including death from acute chest syndrome) from the HES database was considered when estimating the baseline mortality hazard and the HRs for the VOC health states of the model. Additionally, the company indicated that "*in the HES database analysis the definition of VOC included both priapism and acute chest syndrome. Therefore, as the increased risk of death due to acute chest syndrome is already captured, applying a separate risk of death for acute chest syndrome would result in double*

counting of death".[20] As noted in Table 4 of the CS, "*VOC were defined as acute episodes of pain, with no medically determined cause other than vaso-occlusive event, that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral NSAID. ACS, hepatic sequestration, splenic sequestration, and priapism were also considered to be crisis events*".[1] Therefore, it is unclear to what extent the definitions of VOC in SUSTAIN and HES are equivalent and whether the impact of SCD-related complications on death are properly captured in the model.

With the available data, a time to event approach seems more logical since it does not require a definition of health state, transition probabilities and re-distribution of patients after each cycle. It can also accommodate complications as "events" in the model simulation and these can be linked directly to death.

5.2.3 Population

The patient population in the economic model was [redacted], in line with the decision problem and the anticipated licensed indication for crizanlizumab.[1] Patients included in the economic analysis had experienced [redacted], in line with the anticipated license (see section 3.1). Efficacy inputs for VOCs experienced in the model were based on data from the SUSTAIN trial, the population of which the company considered to be reflective of patients with SCD in the UK who are expected to be treated with crizanlizumab (in terms of age, ethnicity and genotype).[1]

The baseline characteristics used in the model for age and gender were taken from the HES database.[1] The company justified this choice as they used these characteristics as covariates in the models predicting the risk of mortality and complications from the HES data and therefore the use of baseline age and gender from HES maintained consistency with the natural history data used in the model, and also reflected the patient characteristics of individuals with SCD in the UK.[1] Patient weight was not available in the HES data and therefore the average body weight of adult SCD patients in the UK used in the NICE CG143 economic evaluation, adjusted for the proportion of females assumed from the HES data, was utilised for the base-case analysis.[1, 52] Baseline characteristics used in the model along with their source are displayed in Table 5.5 and compared to the mean values in SUSTAIN.

Table 5.5: Patient demographic inputs for base-case analysis compared to the values from SUSTAIN

Patient Characteristics	Value	Source	Value from SUSTAIN
Mean age, years (SD)	37.1 (15.4)	Company Data on File: HES database analysis[57]	[redacted]
% Female[a]	63%	HES database analysis, as reported in Morgan et al. 2019[55]	[redacted]
Body weight (kg)	55 kg (females) 65 kg (males) 58.7 kg	NICE CG143 (Appendix F) – Average weight of adults with SCD.[52] Assumptions following discussions with the Guideline Development Group	[redacted]

Based on Table 10 of the response to request for clarification[20]

[a] Of patients included in the HES analysis (N=15,076), 9,407 were female (62%), 5,491 were male (36%) and gender was missing for 178 patients (1%). For the purpose of the cost-effectiveness analysis, it was assumed that 62% of patients with missing gender were female and the remainder were male.

Patient Characteristics	Value	Source	Value from SUSTAIN
CG = clinical guideline; HES = Hospital Episode Statistics; NICE = National Institute for Health and Care Excellence; SCD = sickle cell disease; SD = standard deviation			

ERG comment: The company stated that they considered the SUSTAIN population to be reflective of UK patients with SCD who are expected to be treated with crizanlizumab.[1, 20] However, they chose to use baseline patient characteristics from other sources, as there were no UK patients in SUSTAIN and therefore these other sources may better reflect the UK population. Differences between the patient characteristics utilised in the model and the patient characteristics in the SUSTAIN trial are displayed in Table 5.5. As can be seen, patients from SUSTAIN were on average younger, more likely to be male and heavier than the UK data sources selected for use in the model.

Although the sources of patient characteristics adopted by the company come from UK sources, which is preferable in terms of geographical generalisability, it is unclear whether they represent the specific subgroup of UK patients with SCD who would be expected to receive crizanlizumab in clinical practice; namely those patients who experience recurrent VOCs. The weight estimate used in the company base-case is taken from NICE CG143 and described as the average weight of adults with SCD, suggesting it is not estimated from the subgroup of patients with recurrent VOCs.[52] The proportion of females used in the model is estimated from 15,076 patients with a recorded hospitalisation from SCD in the HES database between 2008 and 2018.[55] Table 8.1 of the HES database analysis report also shows that the mean age of 37.1 years utilised in the company base-case was in fact based on the same 15,076 patients and is therefore also taken from the entire SCD UK population in the HES data rather than patients experiencing recurrent VOCs.[57] In response to question B1b of the clarification letter the company provided data on the number of VOCs per year from 15,076 patients from the HES database (presumably the same patients given the equal sample size), which showed that [redacted] of patients in the HES database had no VOCs.[20] In their response to question B1b the company stated that "*a direct comparison cannot be made between datasets. This is because the HES data includes all SCD patients who have interacted with the HES database and the majority of SCD patients in this data set had very few or no VOC per year. Whereas, an inclusion criteria* [sic!] *for SUSTAIN was that patients were required to have ≥2 VOC in the previous 12 months (…) The SUSTAIN trial represents a subset of the HES cohort, i.e. those patients experiencing recurrent VOC. The characteristics of patients in this subset specifically have not been captured from the HES database analysis*".[20]

Firstly, this quote suggests that the company considered the two samples to be quite distinct and not comparable, since the SUSTAIN trial represents only a subset of patients in the HES data: namely patients experiencing ≥2 VOCs per year. While it is true that the HES database analysis report does not provide patient characteristics specific to the subgroup experiencing ≥2 VOCs per year, Table 8.5 of the HES database analysis report does provide baseline characteristics of patients admitted for VOCs and ACS and priapism by annual average rate of VOC (for which the proportion of patients split between <1, ≥1 to <3 and ≥3 VOC+ACS+priapism exactly matched the data provided by the company in Table 6 of the clarification response on the proportion of patients in each corresponding VOC health state from the HES database (suggesting they assumed these to be equivalent))[20]. These data from the HES database analysis report, provided below in Table 5.6, can provide an idea of the characteristics of patients experiencing regular VOCs versus the entire SCD population in the HES database. These suggest that while the population experiencing no VOCs are more likely to be male than female, the population experiencing recurrent VOCs+ACS+priapism is more evenly split between genders. The mean age also decreases with increasing rates of VOCs+ACS+priapism. The mean age in SUSTAIN is lower than the HES overall SCD sample and the split of females and males is more equal in SUSTAIN

than in the overall HES sample. This suggests that the sample characteristics in the SUSTAIN trial may be generalisable to the characteristics of the UK SCD population experiencing recurrent VOCs. Therefore, the ERG would prefer to use the patient characteristics from SUSTAIN to ensure that the patient characteristics in the model represent the correct subgroup of patients who will receive crizanlizumab in clinical practice. However, given the use of patient characteristics in the estimation of mortality and complications in the model, the ERG felt that changing these characteristics would create further issues in other areas of the model and therefore the age and gender distribution could not be changed in the base-case. However, the weight from SUSTAIN could be used.

Table 5.6: Baseline characteristics of HES patients admitted for VOCs and ACS and priapism by annual average rate of VOC

	Average annual rate of VOC+ACS+priapism		
	<1	**≥1 to <3**	**≥3**
N (%)	[redacted]	[redacted]	[redacted]
Gender, n(%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Ethnicity, n(%)			
Black	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Mixed	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]	[redacted]

Based on Table 8.5 of the HES database analysis report[57]
ACS = acute chest syndrome; HES = Hospital Episode Statistics; SD = standard deviation; VOC = vaso-occlusive crises

5.2.4 Interventions and comparators

The intervention in the economic model is crizanlizumab, administered as an intravenous infusion over a period of 30 minutes at a dose of 5 mg/kg, in line with the anticipated license. In the model, crizanlizumab is given continuously up to the point of treatment discontinuation, in line with the suggested posology in the draft Summary of Product Characteristics (SmPC).[25] [redacted]. Crizanlizumab is given in addition to established clinical management, with and without HC/HU, as described below.

The comparator in the economic analysis is established clinical management (SoC) in the UK without crizanlizumab. SoC consists of supportive care (e.g. hydration with intravenous fluids and keeping warm), HC/HU, and blood transfusions, as per the final scope.[42] Given that supportive care (hydration and keeping warm) are associated with low costs (if any) to the healthcare system, only HC/HU and blood transfusions are explicitly included in the model. The company did not include HSCT as SoC, as this is only considered for adults with severe SCD who have failed to respond to currently available

treatment and who have no other therapeutic options.[58] Treatment with crizanlizumab, as an add-on therapy to established clinical management, is not expected to displace HSCT as a treatment option of last resort or necessarily alter the number of patients who would ultimately receive HSCT.[1]

The CS states that in the UK not all patients receive HC/HU and so a proportion of patients in the crizanlizumab and SoC arms are modelled to receive HC/HU. This proportion was based on the information from all SCD patients in the National Haemoglobinopathy Registry annual report 2018/2019 and it was assumed that 14.2% of all SCD patients would receive HC/HU in the SoC arm, with the same proportion also applied to the crizanlizumab arm.[40] The company stated in the submission that the majority of HC/HU use is expected to be in patients with recurrent VOC, as per British Society for Haematology (BSH) treatment guideline recommendations. However, in the absence of a specific estimate for the recurrent VOC population, the value from all SCD patients in the National Haemoglobinopathy Registry was used.[22, 40] This assumed HC/HU usage was supported by a Consultant Haematologist who specialises in the treatment of SCD at a large London hospital who reported a HC/HU usage in approximately 16% of SCD patients. The company acknowledged that the proportion assumed to receive HC/HU in the model is lower than the use of concomitant HC/HU at baseline in the SUSTAIN trial ([redacted]).[27] Given that the model uses efficacy data from SUSTAIN, the company attempted to account for this difference in their base-case by utilising the relevant subgroup data available from SUSTAIN. Specifically, data from the concomitant HC/HU subgroups of SUSTAIN (yes and no) were weighted by the proportion of patients in the model assumed to receive HC/HU (14.2%) and used to model VOC rates in the crizanlizumab and SoC arms.

In their base-case the company assumed that [redacted] of patients in the SoC arm would be receiving chronic blood transfusion, based on data from the HES database.[39] The majority of patients receiving blood transfusions are expected to receive transfusions for the prevention of stroke, rather than to prevent recurrent VOC.[15, 18] To exclude patients who may be receiving transfusions for stroke prevention, only patients without a previous diagnosis of stroke were included in the analysis of blood transfusion data from the HES database. Over the last two years of the study period, [redacted] of patients included in the analysis were coded as receiving a blood transfusion and this value was used to inform the proportion of patients receiving blood transfusions in SoC arm of the model. Additional sources of data were available for this assumption. Transfusion data in the National Haemoglobinopathy Registry annual report 2018/2019 estimate that 6.6% of SCD patients receive transfusions, but details on reason for use are not provided. Data from an audit of transfusion services in the UK and Republic of Ireland suggest that 17% of elective transfusions in adults are for the prevention of recurrent VOC.[18, 40] The experience of one centre in London in 2008/2009 was that less than 1% of SCD patients (3/490) received a planned transfusion for the control of acute pain.[17] Finally, a Consultant Haematologist in the UK who specialises in SCD reported that as many as 20% of adult patients with SCD could be receiving regular blood transfusions, of which approximately half will be receiving transfusions for the prevention of recurrent VOC.[59]

The proportion of patients receiving chronic blood transfusions was assumed to be 0% in the crizanlizumab arm. This was justified as reflecting the eligibility criteria for the SUSTAIN trial, in which these patients were not eligible.[26] The company argued that, in practice, chronic blood transfusions for the purpose of reducing VOC are not expected to be used in patients receiving crizanlizumab. This is similar to the recommended use of blood transfusions in patients receiving HC/HU, where chronic blood transfusions should only be considered for patients for whom HC/HU is ineffective or contraindicated.[15] In addition to patients receiving chronic transfusions for the prevention of VOC, patients in both treatment arms were assumed to receive acute transfusions for the management of certain complications included in the model (i.e. ACS, sepsis and priapism), based on guidelines

from the BSH and feedback from a Consultant Haematologist in the UK who specialises in SCD.[15, 16, 59]

For adults, exchange transfusions account for the majority of blood transfusions in patients receiving chronic transfusions, and so it was assumed that all transfusions in the model would be exchange transfusions rather than top-up transfusions.[1, 39] According to feedback from a Consultant Haematologist in the UK who specialises in SCD, top-up transfusions are typically used in children for stroke prevention when exchange transfusion is difficult to perform, and for adults who are severely anaemic.[59] This is consistent with the guidelines from the BSH on the use of transfusions, which states that simple (top-up) transfusions are typically preferred when the primary reason for transfusion is to prevent or reverse the effects of severe anaemia.[60] The clinical expert also noted that manual exchange is rarely used for chronic transfusions and so all transfusions were assumed to be done via automated exchange transfusion.[59] This again reflects the guidelines produced by the BSH which describes automated exchange as the preferred technique for exchange transfusions and provides a clear recommendation that all patients should have access to automated exchange transfusions.[60]

In the model HC/HU usage affects both efficacy and costs, as data from SUSTAIN on VOC health state occupancy is available depending on whether or not HC/HU is taken in each treatment arm.[1] The use of chronic transfusions however only impacts costs in the model as patients receiving chronic transfusions were not eligible for inclusion in the SUSTAIN trial and so the impact of transfusions on annual VOC rates is not captured in the model. The company stated that very limited evidence is available from RCTs on the efficacy of chronic transfusions for the prevention of VOC in adults. The SLR described in Appendix D identified the two studies that included adult patients, but these were limited in their relevance or usefulness for the cost effectiveness analysis as one included only pregnant women with SCD, and the other only reported very limited details on VOC.[23, 43, 61]

ERG comment: The company stated in their submission that, [redacted].[1] In the economic model, separate efficacy data were provided according to whether crizanlizumab was given alongside HC/HU or without HC/HU. These efficacy data were then combined into a weighted average according to the proportion of SCD patients who currently receive HC/HU in clinical practice (14.2%), assuming the current proportion in clinical practice would also apply to patients receiving crizanlizumab. However, the NICE scope stated that if the evidence allows, subgroups defined by combination treatment with/without hydroxycarbamide should be considered, see section 4.2.3.5.[42] Therefore the ERG will present results for crizanlizumab as a combination therapy and as a monotherapy.

There are also additional uncertainties regarding the proportion of SCD patients experiencing recurrent VOCs who receive HC/HU in clinical practice. The company base-case assumed that 14.2% patients in the UK are expected to receive HC/HU. This assumption is based on data from the National Haemoglobinopathy Registry which shows that 14.2% of all patients with SCD (17.8% of patients aged ≥18 years) received treatment with HC/HU in 2016 in the UK.[40] This assumption was validated by a Consultant Haematologist specialised in the treatment of SCD at a large London hospital, who reported that approximately 16% of patients in their clinic receive HC/HU.[59] However, these proportions are very different to the proportion of patients who received HC/HU in the SUSTAIN trial ([redacted]).[27] Again this difference could be due to the fact that the data sources used by the company when making their assumption referred to the proportion of the entire SCD population who are currently receiving HC/HU and not the proportion of those SCD patients who experience recurrent VOCs. This is supported by the

company submission which stated that the majority of HC/HU use is expected to be in patients with recurrent VOC, as per BSH treatment guideline recommendations, but in the absence of a specific estimate for the recurrent VOC population, the value from the National Haemoglobinopathy Registry was used in the cost effectiveness analysis.[20] The ERG therefore considers that the proportion of patients receiving HC/HU in the SUSTAIN trial should be used in the model as this population reflects the population who would be expected to receive crizanlizumab in clinical practice. The company also assumed that the proportion of patients taking HC/HU will be unchanged whether they receive crizanlizumab or SoC only. This is another source of uncertainty for clinical practice.

The company also assumed that patients receiving crizanlizumab will not receive chronic blood transfusions, while [redacted] of patients receiving SoC will receive such treatment. This assumption was justified by the fact that patients receiving chronic blood transfusions were not eligible for inclusion in the SUSTAIN trial.[26] The company argued that in practice, chronic blood transfusions for the purpose of reducing VOC are not expected to be used in patients receiving crizanlizumab, in line with the recommended use of blood transfusions in patients receiving HC/HU, where chronic blood transfusions should only be considered for patients for whom HC/HU is ineffective or contraindicated.[15] However, the ERG noted that the SUSTAIN CSR and the Appendices to the CS show that some patients in the crizanlizumab arm did receive blood transfusions.[27, 43] In their response to request for clarification, the company noted that emergent and occasional blood transfusions were permitted in the SUSTAIN trial for the management of acute complications, such as VOC or severe anaemia, as part of SoC. [redacted] transfusions in [redacted] patients were performed in the crizanlizumab 5 mg/kg and [redacted] transfusions in [redacted] in the placebo arm. But these data were not representative of chronic blood transfusions. In the model, patients in both treatment arms were assumed to receive acute transfusions for the management of certain complications included in the model (i.e. ACS, sepsis and priapism), based on guidelines from the BSH and feedback from a Consultant Haematologist in the UK who specialises in SCD and therefore this use of blood transfusions is captured in both treatment groups.[20] The ERG is not sure that the exclusion of patients receiving chronic blood transfusions in the trial means that patients receiving crizanlizumab in practice will not also receive chronic transfusions, however given a lack of data no change was made in the base-case.

The percentage of patients receiving chronic blood transfusion for the percentage of VOC in the SoC group was assumed to be [redacted], based on the percentage of patients in the last two years of the HES study period who were coded as receiving a blood transfusion. In order to exclude patients who may be receiving transfusions for stroke prevention and therefore better estimate the proportion of patients receiving transfusions for recurrent VOC, only patients without a previous diagnosis of stroke were included in the analysis of blood transfusion data from the HES database. The HES database analysis included all SCD patients, not only those who experience recurrent VOCs and it was not clear whether or not patients not experiencing recurrent VOCs were excluded in the calculation of this percentage. Therefore, the percentage of patients experiencing recurrent VOCs who receive chronic blood transfusions may in fact be higher.

The final NICE scope included allogeneic stem cell transplants (ASCT) as a relevant comparator to crizanlizumab, however ASCT was not included in the model.[42] When asked about this at clarification, the company responded that ASCT presents a viable treatment option for a very small proportion of patients, namely those with clinically severe disease but without irreversible organ damage, and thus tends to be mainly considered for children with SCD, who are outside of the anticipated licence for crizanlizumab.[22, 62] They stated that ASCT is only considered for adults with severe SCD or existing comorbidities (e.g. stroke or pulmonary hypertension) who have failed to respond to current treatments.[58] ASCT was not therefore been considered as a relevant comparator to crizanlizumab for

the treatment of SCD as it is not expected that crizanlizumab would displace ASCT as a treatment option of last resort, or necessarily alter the number of patients with SCD that would ultimately receive ASCT (see section 3.3).[20] No data were available to the ERG on the likelihood that the availability of crizanlizumab would alter the number of patients receiving ASCT and therefore it is difficult to validate the assumption that it should not be included in the model.

5.2.5 Perspective, time horizon and discounting

The model takes the perspective of the National Health Service (NHS) and Personal Social Services (PSS) and costs and benefits are discounted at a rate of 3.5% as per the NICE reference case.[1] The model has a time horizon of 55 years, which can be considered lifetime given the baseline age of 37.1 years and the fact that all patients are in the dead state well before the end of the 55-year time horizon.

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Calculating annual VOC rates and patient distribution across health states

Treatment effectiveness was incorporated in the economic model by determining the patient distribution across the three VOC health states (<1, ≥1-<3, ≥3) and linking the mean annualised VOC rate within each health state to mortality and SCD-related complications. Annualised VOC rates were obtained from the SUSTAIN trial,[26] while the estimated association between VOC rates and mortality and complications resulted from statistical analysis on the HES database.[57] Some additional data were obtained through the National Haemoglobinopathy Registry.[40]

Annualised VOC rates were calculated for each patient in the SUSTAIN trial, using the total number of VOCs experienced during the trial period (which was a maximum of 52 weeks, though less if patients discontinued earlier). The per-patient annualised VOC rates were used to allocate patients to the three health states and subsequently to calculate the mean annualised VOC rate within each VOC health state.

Calculations were done separately for two subgroups in SUSTAIN; patients who received crizanlizumab or SoC in combination with HC/HU and patients who did not receive HC/HU, as shown in Table 5.7. A weighted average for the two subgroups was then calculated, based on what the company deemed to be the expected use of HC/HU in clinical practice. The company justified the need for weighting by stating that the proportion of patients receiving concomitant HC/HU in the SUSTAIN trial ([redacted] across all treatment arms) is not reflective of what has been observed in clinical practice (14.2% HC/HU use according to the National Haemoglobinopathy Registry).[40] In the company base-case, in both the crizanlizumab and SoC arms, 14.2% of patients were assumed to receive concomitant HC/HU. The weighted distributions of patients and mean VOC rate within each health state shown in Table 5.8 were kept constant over time for both the crizanlizumab and SoC arms, implying that as long as patients continue receiving treatment, treatment effectiveness stays constant over time.

Table 5.7: Efficacy model inputs (distribution to health states and annualised mean number of VOC for each health state, by treatment arm)

HC/HU use	VOC health state	Distribution (%)	Annualised mean number of VOC	Standard error
Efficacy by HC/HU use (base-case)				
Crizanlizumab				
With HC/HU	Patients with <1 VOC	[redacted]	[redacted]	[redacted]
	Patients with ≥1 to <3 VOC	[redacted]	[redacted]	[redacted]
	Patients with ≥3 VOC	[redacted]	[redacted]	[redacted]
No HC/HU	Patients with <1 VOC	[redacted]	[redacted]	[redacted]
	Patients with ≥1 to <3 VOC	[redacted]	[redacted]	[redacted]
	Patients with ≥3 VOC	[redacted]	[redacted]	[redacted]
SoC				
With HC/HU	Patients with <1 VOC	[redacted]	[redacted]	[redacted]
	Patients with ≥1 to <3 VOC	[redacted]	[redacted]	[redacted]
	Patients with ≥3 VOC	[redacted]	[redacted]	[redacted]
No HC/HU	Patients with <1 VOC	[redacted]	[redacted]	[redacted]
	Patients with ≥1 to <3 VOC	[redacted]	[redacted]	[redacted]
	Patients with ≥3 VOC	[redacted]	[redacted]	[redacted]

Based on Table 23 in the CS[1]
CS = company submission; HC = hydroxycarbamide; HU = hydroxyurea; SoC = standard of care; VOC = vaso-occlusive crises

Table 5.8: Weighted efficacy model inputs based on HC/HU use in the company base-case (distribution to health states and annualised mean number of VOC, by treatment arm)

Treatment arm	VOC health state	Distribution (%)	Annualised mean number of VOC
Crizanlizumab	Patients with <1 VOC	[redacted]	[redacted]
	Patients with ≥1 to <3 VOCs	[redacted]	[redacted]
	Patients with ≥3 VOCs	[redacted]	[redacted]
SoC	Patients with <1 VOC	[redacted]	[redacted]
	Patients with ≥1 to <3 VOCs	[redacted]	[redacted]
	Patients with ≥3 VOCs	[redacted]	[redacted]

Based on Table 24 of the CS[1]
CS = company submission; HC = hydroxycarbamide; HU = hydroxyurea; SoC = standard of care; VOC = vaso-occlusive crises

ERG comment: For [redacted] of the population in the HES database, the annual VOC rate was <1 (i.e. zero). The patients recruited into SUSTAIN were required to have a history of 2-10 VOCs in the

previous 12 months. The patient population recruited into the SUSTAIN trial therefore experienced more severe morbidity than the broader SCD patient population. The higher rate of HC/HU use in the SUSTAIN population may be a result of the severity of disease in this population. If both crizanlizumab and HC/HU are more likely to be used in patients with recurrent VOC (which is likely given that the aim of HC/HU is to prevent VOCs), then the percentage of patients receiving crizanlizumab who concomitantly receive HC/HU is likely to be higher in the subgroup of SCD patients experiencing recurrent VOCs than the percentage receiving HC/HU in the entire SCD population. Assuming the proportion of HC/HU usage from the entire UK population of SCD patients and adjusting the estimation of treatment effect accordingly may therefore be inappropriate.

Within the crizanlizumab and SoC arms, the distribution of patients into the different health states is assumed to be constant over time in the economic model. This implicitly assumes a constant lifetime treatment effect for crizanlizumab while on treatment. No evidence of the efficacy of crizanlizumab in patients still on treatment after one year was provided in the company submission and therefore there is no data to support the distribution of patients between the three VOC health states beyond the first model cycle. In the clarification letter, the company was asked whether the assumption of constant lifetime treatment effect was discussed with clinical experts.[41] The company indicated the assumption had not been validated with clinical experts.[63] The company was also asked to include in the model the possibility of a pre-specified duration for the crizanlizumab treatment effect, as well as the possibility of a waning treatment effect.[41] The company did not do so.

The company was asked to provide confidence intervals and P-values (assessing difference from placebo) for all *"mean annualised rate of VOC"* figures.[41] The company provided Table 5.9 and replied that *"given the low patient numbers in each subgroup and VOC health state, it is not expected that meaningful conclusions about statistical significance could be made for the difference in annualised mean number of VOC between the crizanlizumab and SoC groups, and so statistical tests to derive p-values have not been conducted"*.[20] Given that the number of VOCs per health state are drivers of model outcomes, a larger sample of evidence where significance of results could be investigated would be beneficial to increase confidence in results. Despite the low patient numbers and lack of statistical significance, the outcome uncertainty regarding both the patient distribution across the three health states and the mean annualised VOC rates within the health states was not included in the company's probabilistic sensitivity analysis. The company created four variables to reflect these elements of uncertainty for both the treatment and SoC arms but left them turned off in the analysis. The variables were turned on in the probabilistic sensitivity analysis (PSA) of the ERG base-case, after the company's sampling assumptions had been corrected. More details of this correction will be provided in the PSA section 6.2.1.

The ERG noted that the standard errors and confidence intervals provided in Table 5.9 do not appear to align with one another. The standard formula to calculate the 95% CIs for normally distributed variables based on the standard errors and numbers of observations provided results in CI estimates that are wider than those provided in Table 5.9. The ERG was unable to verify the provided standard errors, as they were hardcoded into the economic model and no further detail was found in the CSR.[27] The standard errors were used in the model for the sampling of the mean annualised VOC rates in the PSA, therefore it is possible that the uncertainty around this variable will be miscalculated.

Table 5.9: Annualised mean number of VOC for each health state by treatment arm

HC/HU use	VOC health state	N	Annualised mean number of VOC	Standard error	95% CI
Efficacy by HC/HU use					
Crizanlizumab					
With HC/HU	<1 VOC	[redacted]	[redacted]	[redacted]	[redacted]
	≥1 to <3 VOC	[redacted]	[redacted]	[redacted]	[redacted]
	≥3 VOC	[redacted]	[redacted]	[redacted]	[redacted]
No HC/HU	<1 VOC	[redacted]	[redacted]	[redacted]	[redacted]
	≥1 to <3 VOC	[redacted]	[redacted]	[redacted]	[redacted]
	≥3 VOC	[redacted]	[redacted]	[redacted]	[redacted]
SoC					
With HC/HU	<1 VOC	[redacted]	[redacted]	[redacted]	[redacted]
	≥1 to <3 VOC	[redacted]	[redacted]	[redacted]	[redacted]
	≥3 VOC	[redacted]	[redacted]	[redacted]	[redacted]
No HC/HU	<1 VOC	[redacted]	[redacted]	[redacted]	[redacted]
	≥1 to <3 VOC	[redacted]	[redacted]	[redacted]	[redacted]
	≥3 VOC	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 9 of the response to request for clarification[20]
CI = confidence interval; HC = hydroxycarbamide; HU = hydroxyurea; ITT = intention-to-treat; SoC = standard of care; VOC = vaso-occlusive crises

5.2.6.2 Treatment discontinuation

In the economic model it was assumed that patients who discontinued crizanlizumab were subject to a continuing treatment effect for two additional years.[1] This was implemented through two "Off treatment incident" tunnel states. In these tunnel states, crizanlizumab efficacy was applied by assuming the same distribution of patients into the VOC health states as in the treatment arm, while costs were assumed to be the same as in the SoC arm. In the third year following discontinuation and for the remainder of the model time horizon, the efficacy of SoC was applied. The company justified this assumption by referring to the SUCCESSOR study, in which 15 patients that had completed the high-dose crizanlizumab treatment arm experienced a similar mean annualised VOC rate in the 52 weeks post trial completion, compared to in the SUSTAIN trial (2.7 versus 2.89).[26, 48]

The discontinuation rate was assumed to be 32.8% in the first model cycle, which was based on the proportion of patients that discontinued crizanlizumab for reasons other than death in the high-dose arm of the SUSTAIN trial.[26] In subsequent model cycles, the discontinuation rate was assumed to be 4.5%, based on the rates for discontinuation due to physician choice (3%), AEs (1.5%) and lack of efficacy (0%) in the high-dose crizanlizumab arm. Other reasons for discontinuation in the SUSTAIN trial were withdrawal by the patient, non-compliance, lost to follow-up, and 'other reasons'. Scenario analyses were conducted by the company assuming alternative discontinuation rates (0%, 15%, 25% and 32.8%).

ERG comment: In their response to the request for clarification, the company indicated two years of treatment effect post-discontinuation to be "the likely *maximum* periods to observe *any* benefits" (italics

added), according to expert judgement.[20] The ERG deemed that assuming the maximum assumption is inappropriate for the base-case analysis. The SUCCESSOR data provided one year of follow-up after trial completion and indicated a continued treatment effect during this one year (mean annualised VOC rate of 2.7 in SUCCESSOR, versus 2.89 in SUSTAIN).[26, 48] It is possible that this effect would last longer than one year, but this has not been investigated. The ERG considers that there is some uncertainty related to these data given the small patient number (n=15) it is based on and the fact that the sample is made up of 15 out of 67 patients who completed the SUSTAIN trial and consented to continue being monitored which means these could be the patients with the better outcomes from treatment. The ERG assumed a one-year additional treatment benefit, in line with the SUCCESSOR evidence, in its base-case and acknowledged that there could be uncertainty in either direction surrounding this assumption of continued treatment benefit.

In the company's base-case the additional two years of treatment effect was assumed for all patients who discontinue treatment, including the 32.8% of patients who discontinue treatment in the first model cycle, i.e. before finishing one year of treatment. However, the SUCCESSOR data that provided the basis for the assumption of continued treatment benefit only included patients who completed one year of treatment (14 doses of crizanlizumab).[43] No follow-up data were available on patients that discontinued the SUSTAIN trial before receiving a full year of treatment. The ERG therefore prefers the assumption that only patients who completed at least one year of treatment (i.e. the first model cycle) receive treatment benefit post-discontinuation.

Furthermore, the ERG noted that withdrawal by the patient, non-compliance, and potentially other reasons too, are likely to be relevant causes of discontinuation beyond the first model cycle. The assumed rate of 4.5% discontinuation after the first model cycle may be an underestimation.

5.2.6.3 Extrapolation of mortality and complications

The statistical analysis on the HES database that was performed to obtain estimates of mortality and complications comprised several steps.[1] Firstly, annualised VOC rates were estimated using the period of follow-up and the total number of VOC experienced in that period. Secondly, Cox proportional hazards regression models were used to estimate the baseline hazard of relevant events (death or first occurrence of each complication) among patients with an annualised VOC rate <1, as well as the hazard ratios (HRs) for the ≥1-<3 and ≥3 VOC groups, shown in Tables 5.10 and 5.11. Adjustments were made for age at baseline (centred around mean age of 37 years in the HES database) and gender. Thirdly, parametric survival models (exponential, Weibull, Gompertz, lognormal, loglogistic, and generalised gamma) were applied to extrapolate the observed data for the <1 VOC group across the entire model horizon, again accounting for age and gender. Note that only acute complications or those requiring acute management were included in the analysis, except for central nervous system complications, such as subarachnoid and intracerebral haemorrhage. The company stated that the prevalence of these complications was low in the HES database.

Table 5.10: HRs for mortality based on average annual rate of VOC

HR (SE) based on average annual rate of VOC	<1 VOC	≥1–<3 VOC	≥3 VOC
Mortality	Reference group	[redacted]	[redacted]

Based on Table 27 of the CS[1]
CS = company submission; HR = hazard ratio; SE = standard error; VOC = vaso-occlusive crisis

Table 5.11: HRs for SCD-related complications based on average annual rate of VOC

HR (SE) based average annual rate of VOC	<1 VOC	≥1–<3 VOC	≥3 VOC
ACS	Reference	[redacted]	[redacted]
Gallstones	Reference	[redacted]	[redacted]
Sepsis	Reference	[redacted]	[redacted]
Pulmonary hypertension	Reference	[redacted]	[redacted]
Cardiac	Reference	[redacted]	[redacted]
Cellulitis	Reference	[redacted]	[redacted]
Leg ulcer	Reference	[redacted]	[redacted]
Osteomyelitis	Reference	[redacted]	[redacted]
Priapism	Reference	[redacted]	[redacted]

Based on Table 31 of the CS[1]
ACS = acute chest syndrome; CS = company submission; HR = hazard ratio; SCD = sickle cell disease; SE = standard error; VOC = vaso-occlusive crisis

The company indicated that the choice of survival models for the extrapolation of complications were based on goodness-of-fit statistics (prioritising Bayesian information criterion (BIC) over Akaike information criterion (AIC)) and visual plausibility, stating in their response to the request for clarification that it was not possible to assess the clinical plausibility of the extrapolations due to data limitations.[20] For mortality, additional consideration was given to how well the model predicted survival, when compared to life expectancy of patients with SCD. The chosen Gompertz distribution estimates median age of death to be 52.1 years, which the company deemed reasonable, citing a UK-based study (67 years for HbSS/HbSβ patients, with HbSS being the genotype for the majority of patients in the SUSTAIN trial), a US-based study (48 years for HbSS/HbSβ/HbSD patients), as well as the estimates of two clinical experts (55-60 years for HbSS patients).[64, 65] To ensure that the probability of death in each cycle was never lower than that of the general population, the model selected the maximum probability of death from either the VOC-adjusted mortality estimates or age- and gender-matched mortality for the general population from UK life tables.[1]

Table 5.12: Parametric curves selected for the base-case analysis for SCD-related complications

SCD-related complication	Parametric curve selected for the base-case analysis
ACS	Exponential
Gallstones	Exponential
Sepsis	Gompertz
Pulmonary hypertension	Exponential
Cardiac	Gompertz
Cellulitis	Exponential
Leg ulcer	Exponential
Osteomyelitis	Exponential
Priapism (males only)	Exponential

Based on Table 29 of the CS[1]
ACS = acute chest syndrome; CS = company submission; SCD = sickle cell disease

ERG comment: The ERG questions the appropriateness of using the HES database to link VOC state outcomes from the SUSTAIN trial to mortality and complications, due to the difference in the two patient populations in terms of VOC state distribution (see Table 5.13).

The ERG would have liked to use the patient characteristics from the SUSTAIN trial (age, gender) in its base-case, in order to better reflect the patient population likely to receive crizanlizumab in clinical practice. However, the ERG did not feel confident that using the HRs estimated from the HES database (which were hardcoded into the model), alongside a different mean age and gender distribution in the model (see Table 5.5 in section 5.2.3), would be appropriate. Therefore, the ERG could not use the age and gender distribution from the SUSTAIN trial, despite feeling that these better reflect the population who will receive crizanlizumab in clinical practice.

Table 5.13: Proportion of patients in each health state in SUSTAIN and the HES database

Dataset	<1 VOC/year, n (%)	≥1 to <3 VOC/year, n (%)	≥3 VOC/year, n (%)
SUSTAIN trial (n=132)[a]	[redacted]	[redacted]	[redacted]
HES database (all patients)[b]	[redacted]	[redacted]	[redacted]

Based on Table 6 of the response to request for clarification[20]
[a] Distribution of patients in the 5 mg/kg crizanlizumab and placebo groups at trial end. Patients required to have ≥2 VOC in previous 12 months at beginning of trial; [b] Includes all patients in the HES database – data on those with ≥2 VOC/year at study inclusion are not available
HES = hospital episodes statistics; VOC = vaso-occlusive crisis

5.2.7 Adverse events

Other than the SCD-related complications included in the model, the company did not include any AEs in the model. The company noted that Grade ≥3 adverse events occurred in [redacted] in the high dose crizanlizumab (5 mg/kg) arm, and [redacted] in the placebo treatment arm of the SUSTAIN trial.[20]. They argued that due to the low incidence of events and the similar incidence of events between treatment arms, the inclusion of Grade ≥3 adverse events based on safety data from SUSTAIN was not expected to have a major impact on the results of the cost effectiveness analysis.

ERG comment: The ERG is not convinced that omitting the most severe adverse events was properly justified. The clinical study report indicated that there are some small differences in AEs between crizanlizumab and placebo, even though overall incidence rates of any AE occurring in the treatment arms was similar.[27] If different AEs have a substantially different impact on costs and outcomes, this could become important. As the patient population of the SUSTAIN trial was relatively small, these differences might have been simply due to chance. Hence, more robust data on SAE's would be beneficial to be able to definitively state that SAEs do not influence the cost effectiveness outcomes. The ERG requested that the company include Grade ≥3 treatment emergent AEs, and their impact on costs and QALYs, at clarification.[41] The company refused, stating that due to the low incidence of events and the similar incidence of events between treatment arms, the inclusion of Grade ≥3 AEs based on safety data from SUSTAIN was not expected to have a major impact on the results of the cost effectiveness analysis, and therefore AEs were not included in the model.[20] While the ERG feels that Grade ≥3 AEs should have been included in the model for completeness, as they could have an impact on costs and benefits, the ERG did not have sufficient time to include these and agreed that in this case AEs are unlikely to be the driver of model results.

5.2.8 Health-related quality of life

5.2.8.1 Identification and selection of utility values

In the SUSTAIN trial, HRQoL data were collected using the Brief Pain Inventory (BPI) and 36-item Short Form survey version 2.0 (SF-36 v2) questionnaires (both seven-day recall) at fixed time points; at each treatment visit (at days 1 and 15), at every four weeks from week 6, at week 52 and the week 58 follow-up visit.[1] The vast majority ([redacted] of SF-36 questionnaires were administered outside of a seven-day recall period that included a VOC. The company therefore noted that it was possible that the HRQoL data measured in SUSTAIN missed or did not fully capture the expected impact of VOC on patient HRQoL and assessments of pain, and that the HRQoL captured in SUSTAIN rather is more representative of the HRQoL of SCD patients between VOC events. Changes in HRQoL over time as well as differences between treatment arms were explored by the company, but the SUSTAIN trial [redacted]. The company stated that the 52-week duration of SUSTAIN was likely too short to demonstrate an overall change in HRQoL related to SCD-related complications and long-term organ damage.[23] Referring to these arguments, the company justified their decision to derive utility values from the published literature rather than from HRQoL data collected from the SUSTAIN trial.

A systematic literature review was conducted to identify studies reporting utility estimates in patients with SCD. This led to the identification of three studies that reported relevant utility data, two studies were described in full-text articles, Thom et al. 2019 and Anie et al. 2012, and one study was described in a conference abstract, Besser et al. 2019 (LEGACY registry study).[56, 66, 67]

In the CS, an unpublished analysis of the LEGACY registry data was used to derive the utility values for the model health states (<1 VOC, ≥1–<3 VOC, or ≥3 VOC) as shown in Table 5.14.[1] In the LEGACY registry study, HRQoL data were collected using the SF-36 at specific time intervals and not on the occurrence of specific events (such as VOCs events). Rather than the impact of individual VOC events, the company therefore considers LEGACY to capture the long-lasting impact of recurrent VOC on quality of life through chronic complications and the emotional impact of more frequent VOC events,[20] relevant for each of the VOC health states. With these arguments, the company justified the application of a "per event" decrement for each VOC event, in addition to the different VOC health state utility values. The health state values that were derived from the LEGACY registry data were treated as the baseline utility value in each cycle, to which additional decrements in utility related to individual VOC events are applied.

Both Thom et al. 2019 and Anie et al. 2012 provided utility decrements for individual VOC events based on EQ-5D health state descriptions.[56, 67] The decision to use the utility decrements derived by Anie et al. was justified by the company by indicating that in this study EQ-5D was data collected from UK patients, as opposed to US patients in the Thom set al. study. Using the utilities reported in Anie et al., a per event utility decrement was calculated that included both the loss of utility during the VOC (two days prior to and during hospitalisation) and during the one week following discharge from hospital, as shown in Table 5.15. The decrements in utility were applied per VOC event in each cycle (i.e. based on the mean number of VOC).

In the company's base-case analysis, the health state utility values were age-adjusted using the methods described by Brazier et al. 2019.[68]

Table 5.14: Health state utility values

Health state	Utility
Patients with <1 VOC	[redacted]
Patients with ≥1 and <3 VOCs	[redacted]
Patients with ≥3 VOCs	[redacted]

Based on Table 34 of the CS[1]
CS = company submission; VOC: vaso-occlusive crisis

Table5 .15: Utility decrements for individual VOC events

Model input	Utility decrement	Duration of impact
Days of Pain Prior to Hospitalisation (per VOC)	0.360	2 days
Days Hospitalised per VOC	0.360	3 days
Days Post-Hospitalisation	0.100	7 days
Calculated VOC Decrement (per event)	0.007	Calculated as annual utility decrement

Based on Table 32 of the CS[1]
CS = company submission; VOC = vaso-occlusive crisis

ERG comment: In the SUSTAIN trial, HRQoL data were collected at specific time intervals and not on the occurrence of specific events. This data might have missed or not fully captured the impact of the individual VOC events, and the low percentage of questionnaires completed within a seven-day window of a VOC event supported the company's assumption. As the company noted, the HRQoL captured in SUSTAIN will rather be representative of the HRQoL of SCD patients between VOC events. The ERG believes the HRQoL data from the SUSTAIN trial might therefore be suitable for deriving the health state utility values. Given the frequent intervals at which HRQoL data were collected in SUSTAIN along with the company's assumption that the results from the SUSTAIN trial can be considered generalisable to the UK setting, it was not clear to the ERG why the company favoured using the utilities derived from an unpublished analysis of the US-specific LEGACY registry data over data from their trial. At the clarification stage, the ERG therefore requested the company to provide the utility estimates from the SUSTAIN trial and include the option in the model to use these as health state utility values for the cost effectiveness analyses. The company was not willing to provide this option in the model nor to provide more details on the HRQoL data collected in the SUSTAIN trial.[20] Therefore, the ERG was not able to assess the impact of using the SUSTAIN utilities instead of the LEGACY utilities on the cost effectiveness results.

Furthermore, details on the LEGACY registry study were only reported in a conference abstract and in information provided by the company. In the absence of a full-text article, and in the absence of utility estimates from the SUSTAIN trial, the ability of the ERG to validate the appropriateness of using the LEGACY data instead of the SUSTAIN data for deriving health state utilities is limited. To illustrate, the company mentions that *"([redacted] of the SF-36 questionnaires that were administered in the SUSTAIN trial were not completed within a 7-day window of a VOC (…) meaning that the detrimental impact of VOC on HRQoL is unlikely to have been captured by the vast majority of completed SF-36 questionnaires"*.[1] The company hereby justified their decision to apply different utility values for the different VOC health states as well as a per event VOC utility decrement. However, it was not known whether within the LEGACY register study the HRQoL data were also collected for the vast majority outside a seven-day window of a VOC event. More importantly, a four-week recall period was used in the LEGACY registry study, which increased the likelihood that a VOC event occurred within the recall

period of the HRQoL instrument and its impact will have been captured in the health state utility values. The ERG notes that even in the least severe health state (<1 VOC) the utility estimate from the unpublished LEGACY data analysis is lower than the steady-state SCD utility estimate of 0.732 reported in the NICE clinical guideline CG143 (Appendix F), which was calculated as a weighted average of four sources that reported utility with good agreement between the studies (range 0.700 – 0.788).[52] Given that the utility estimates derived from the LEGACY registry data are lower than the estimates reported in the previously described sources, the ERG has concerns about the company's assumption that the impact of individual VOC events is not captured within the health state utility values derived from the LEGACY registry. The ERG will test the impact of using alternative assumptions on the utility impact of VOC events in scenario analyses. Finally, the ERG felt there was uncertainty in the assumption that patients experience the utility impact of a VOC event for two days before seeking medical support at hospital. The CS reported that this assumption was validated by only one clinician, while in their response to clarification the company cited one study conducted in children with SCD which showed that 23%, 38%, 12% and 26% of patients had 0, 1, 2, ≥3 days of pain prior to hospital admission for a VOC respectively.[1, 69] Therefore, the impact of this assumption will be tested in an additional scenario analysis.

5.2.8.2 Adverse event disutilities

The company also considered utility decrements associated with individual complications of SCD (Table 5.16). These were sourced from values and assumptions identified through targeted literature searches and those that have been used previously as part of NICE appraisals and guidelines, with proxy conditions used in absence of utility values for the specific complication of interest.[1] Decrements in utility for adverse events associated with treatment with crizanlizumab or SoC were not included in the model. The company stated that the incidence of serious adverse events was similar between the high dose crizanlizumab and placebo treatment arms. The company further noted that the utility decrements for sepsis and cardiac arrhythmia are likely to underestimate respectively the loss of utility during an acute sepsis event and the loss of utility associated with other cardiac complications such as cardiac arrest.[1] However, given the low frequency of these complications in the model and the limited impact that they have on cost effectiveness results, the company did not expect that the underestimation of the utility decrements associated with these complications will have a major impact on the cost effectiveness results.

Table 5.16: Utility decrements and duration of impact for adverse events

Adverse event	Utility decrement	Duration of impact
Acute Chest Syndrome	0.56	1 month
Gallstones	0.12	1 month
Sepsis	0.16	1 month
Pulmonary Hypertension	0.21	1 month
Cardiac	0.07	1 month
Cellulitis	0.29	1 month
Leg Ulcers	0.11	1 month
Osteomyelitis	0.46	1 month
Priapism (males only)	0	1 month
Based on Table 33 of the CS[1] CS = company submission		

ERG comment: As explained in section 5.2.7, the ERG noted that not all adverse event costs associated with crizanlizumab, HC/HU and blood transfusions are incorporated into the economic model. By omitting grade 3 and grade 4 adverse events, the impact of these events on utility are not accounted for in the cost effectiveness results. In addition, the company's base-case model did not include a utility decrement to account for the impact of the four-weekly intravenous infusions. The ERG could not identify any evidence regarding the utility impact of the injection and 30-minute intravenous infusions for the population of interest. However, the ERG considered that including a utility decrement for administration is expected to have a limited influence on the cost effectiveness due to the short duration of the utility decrement. Hence, the ERG decided not to include a utility decrement to account for the impact of the four-weekly intravenous infusions.

5.2.9 Resources and costs

The company analysis included costs that would be incurred by the NHS and PSS.[1] Appropriate sources of unit costs, such as NHS reference costs 2018–19, NHS Blood and Transplant price list 2019–20[70], and electronic Marketing Information Tool (eMIT) 2020[71], were used for cost inputs in the model.[1]

The following cost types were included in the model:

- drug acquisition and administration costs for interventions and comparators (including blood transfusions),
- costs associated with monitoring, and
- costs associated with the management of VOC and acute complications.

In line with the definition of VOC used in SUSTAIN and the use of HES to identify complications associated with SCD, the cost of events were derived assuming that patients would receive hospital care, and so the NHS reference cost schedule has primarily been used as a source of inputs for these events.[1]

Even though costs and resource use data were also identified via a SLR, also specifically for the UK, the studies were not used to derive inputs for the model. This was due to the use of data from SUSTAIN and the HES database to specifically model the number of VOC and acute complication events requiring hospitalisation.[1]

5.2.9.1 Intervention and comparators' costs and resource use

5.2.9.1.1 Treatment costs

An overview of relevant acquisition costs for treatment with crizanlizumab and supportive care (i.e. HC/HU and blood transfusion) is presented in Table 5.17.

The acquisition costs of crizanlizumab (5 mg/kg) and HC/HU (15 mg/kg), both of which are dosed according to body weight, were calculated using an average patient body weight of 58.69 kg given the estimated weight per gender in NICE CG143 and the gender distribution used in the model[52]. For crizanlizumab, the total drug acquisition cost per cycle was adjusted to account for compliance (via relative dose intensity (RDI) of [redacted]), based on data from the SUSTAIN trial.[26] For HC/HU, 100.0% compliance was assumed.

The recommended dose of crizanlizumab is 5 mg/kg administered over a period of 30 minutes by intravenous infusion at week 0, week 2, and every four weeks thereafter (resulting in 14 administration in year 1 and 13 administrations for the following years).[1] Drug wastage is assumed for each

administration (rounded up to the nearest whole number of vials). A scenario was also conducted in which vial sharing was assumed to occur.

For HC/HU it was assumed that patients would already be receiving a stable dose of HC/HU on entry into the model.[1] For HC/HU the company assumed that patients with SCD received the lowest recommended maintenance dose of 15 mg/kg.[72, 73]

Adult patients with SCD receiving chronic blood transfusions for the prevention of VOC were expected to mainly receive automated exchange transfusions.[1] Based on clinical expert opinion, the company assumed patients received one transfusion approximately once every six weeks (resulting in 8.7 transfusions per cycle), with one transfusion consisting of between 8–12 units of blood.[59] The company assumed that all patients would receive 10 units of blood per automated exchange transfusion. The cost per transfusion (£2,548.84) was based on the of cost per unit of blood for red cell exchange, as reported in the NHS Blood and Transplant price list 2019–20, assuming wastage equivalent of 1.5% the cost per unit of blood (as per the NICE NG24 costing statement), and other costs related to transfusions (i.e. staff time and disposables), as reported in the NICE NG24 costing statement for blood transfusions and costs were inflated from 2015/16 to 2018/19 using the NHSCII Pay and Prices inflation index.[70, 74, 75] Due to these assumptions, iron chelation therapy was not included in the model.

Table 5.17: Treatment acquisition costs included in the base-case analysis

Treatment	Recommended dosing/administration schedule	Dose per administration (mg)[b]	Unit size	Unit cost	Cost per administration[c]	Compliance	Sources
Crizanlizumab (Year 1)	5 mg/kg at Week 0, Week 2 and every four weeks thereafter (i.e. 14 administrations in Year 1)[a]	293.40	100 mg per vial	[redacted] per vial (list price) [redacted] per vial (with PAS)	[redacted] (list price) [redacted] (with PAS)	[redacted]	Crizanlizumab draft SmPC [posology];[25] Novartis data on file: SUSTAIN CSR [compliance][27]
Crizanlizumab (Year 2+)	5 mg/kg every four weeks (i.e. 13 administrations in Year 2 and following years)[a]						
HC/HU	15 mg/kg per day (i.e. 365.25 administrations per year)	880.3	500 mg per capsule (pack of 100)	£0.10 per capsule (£9.56 per pack)	£0.19	100.0%	Xromi® and Siklos® SmPCs[72, 73] [posology]; eMIT[71] [unit cost]; Assumption [compliance]
Blood transfusions	One automated exchange transfusion every six weeks (i.e. 8.7 administrations per year)	10 units	n/a	£49.10 and £40.51 cost of staff time and disposables for first and subsequent units of blood £210.36 per unit of blood (£213.52 with wastage)	£2,548.84	n/a	Expert opinion [frequency of transfusion]; NHS Blood and Transplant price list (2019–20)[70] [unit cost for blood]; NICE NG24: costing statement Appendix 1 (inflated to 2018/19 using the NHSCII Pay and Prices inflation index)[74, 75] [cost of staff time and disposables]

Based on Table 35 of the CS[1]

[a] The number of administrations per year in the model was calculated as (365.25/28 + 1) for Year 1 and (365.25/28) for Year 2 and following years; [b] The dose per administration for crizanlizumab and HC/HU was calculated based on an assumed average body weight of 58.69 kg; [c] It is assumed that unused drug is discarded for each administration, rounded-up whole units are therefore used for the cost calculation (e.g. 3 vials per administration of crizanlizumab and 2 capsules per administration of HC/HU)

CS = company submission; CSR = clinical study report; HC/HU = hydroxycarbamide/hydroxyurea; NHS = National Health Service = NICE: National Institute for Health and Care Excellence; RDI = relative dose intensity; SmPC = Summary of Product Characteristics

The total annual (per cycle) treatment acquisition costs, based on the recommended dosing schedules, cost per administration and compliance for each treatment are presented in Table 5.18. Crizanlizumab costs were calculated with and without the confidential Patient Access Scheme (PAS) discount of [redacted].[23]

Table 5.18: Treatment acquisition costs per model cycle

Treatment	Cost per model cycle[a]	Source
Crizanlizumab (cycle 1)	[redacted] (list price) [redacted] (with PAS)	Calculated
Crizanlizumab (cycle 2+)	[redacted] (list price) [redacted] (with PAS)	Calculated
HC/HU	£69.84	Calculated
Blood transfusions	£22,165.51	Calculated

Based on Table 36 of the CS[1]
[a] The cost per model cycle is calculated as the number of administrations per cycle (adjusted for compliance) multiplied by the cost per administration.
CS = company submission; HC = hydroxycarbamide; HU = hydroxyurea; PAS = Patient Access Scheme

5.2.9.1.2 Administration costs

Administration costs associated with the treatment with crizanlizumab (per administration and per year, including adjustments for compliance) are presented in Table 5.19. For the cost of administration, it was assumed that specialised nurse time would be required for up to one hour and 30 minutes. The cost per administration was calculated to be £169.50 based on a unit cost of £113.00 per hour of patient contact for a Band 6 hospital-based nurse, as reported in the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2019.[75] Administration costs were only applied for crizanlizumab as it is administered via intravenous infusion.

Table 5.19: Administration costs for crizanlizumab

Treatment	Cost per administration	Source
Crizanlizumab	£169.50	Assumed 1 hour and 30 minutes of Band 6 hospital-based nurse time per administration. Unit cost (£113.00) as reported in the PSSRU Unit Costs of Health and Social Care 2019.[75]

Based on Table 37 of the CS[1]
CS = company submission; PSSRU = Personal Social Services Research Unit

5.2.9.1.3 Monitoring costs

An overview of monitoring costs included in the base-case analysis is presented in Table 5.20. No additional monitoring was assumed to be required for treatment with crizanlizumab. Thus, only costs associated with monitoring for HC/HU were applied. Monitoring requirements for ongoing HC/HU use were based on recommendations from the Specialist Pharmacy Service (SPS) and British National Formulary (BNF) online.[76, 77] Taking into account that 14.2% of patients are expected to receive HC/HU in both treatment arms, the overall monitoring cost per cycle in each treatment arm was calculated to be £4.87.

Table 5.20: Monitoring costs for HC/HU

Type of monitoring	Recommended frequency (per year)	Unit cost	Source
Haematological (full blood count, including reticulocyte count)	Every 2 months	£2.79	NHS SPS and BNF online (accessed 16.01.2020)[76, 77] [type and frequency] NHS Reference Costs 2018–19 [DAPS05 - Haematology] [costs]
Renal (urea and electrolytes)	Every 3 months	£1.10	NHS SPS and BNF online (accessed 16.01.2020)[76, 77] [type and frequency] NHS Reference Costs 2018–19 [DAPS04 – Clinical biochemistry] [costs]
Hepatic (liver function test)	Every 3 months	£1.10	
Lactate dehydrogenase test	Every 3 months	£1.10	
Foetal haemoglobin %	Every 3 months	£1.10	

Based on Table 38 of the CS[1]
BNF = British National Formulary; CS = company submission; HC = hydroxycarbamide; HU = hydroxyurea; NHS = National Health Service; SPS = Specialised Pharmacy Services

5.2.9.2 Health-state unit costs and resource use

The absolute number of VOC per year was calculated for each VOC health state and each treatment arm. For each VOC event that occurred, the cost of hospitalisation due to VOC was applied in the model.[1] Costs associated with pain relief medication were not included in the model.

The cost per VOC (£1,300.64) was primarily based on a weighted average of the NHS reference costs 2018–19 for sickle-cell anaemia with crisis (weighted average of costs for SA36A-C: Sickle-Cell Anaemia with Crisis, with CC Score 0–6+ [non-elective short stay, non-elective long stay, Day Case]).[1] The BSH guidelines also note that blood transfusions may be considered for patients with complicated VOC. In addition to the NHS reference cost for sickle-cell anaemia with crisis, the cost of a single blood transfusion was also applied in the model for a proportion of VOC. The cost of transfusion was added for [redacted] of VOC in the model.[27] Including the cost of transfusion, the total cost per VOC in the base-case analysis was £1,619.24.

Based on feedback from a Consultant Haematologist in the UK, patients that experienced <1 or ≥1–<3 annualised VOC were assumed to receive one appointment per year, whereas patients with ≥3 annualised VOC were modelled to receive three appointments per year (see Table 5.21).[59]

Table 5.21: Cost per cycle of Consultant Haematologist visit

Annualised VOC rate	Cost	Source
<1	£168.02	Cost of one visit per year based on NHS reference costs 2018–19: WF01A non-admitted face-to-face attendance, follow-up, 303 – Clinical Haematology),
≥1–<3		
≥3	£504.06	Cost of three visits per year based on NHS reference costs 2018–19: WF01A non-admitted face-to-face attendance, follow-up, 303 – Clinical Haematology)

Based on Table 39 of the CS[1]
CS = company submission; NHS = National Health Service; VOC = vaso-occlusive crises

5.2.9.3 Adverse reaction unit costs and resource use

The company included several acute complications related to SCD in the model, identified from the analysis of the HES database. The per event costs used in the base-case analysis for each of these complications are presented in Table 5.22 and have primarily been sourced from relevant costs identified in the NHS reference costs schedule 2018–19.

For the cost of ACS, hospitalisation for asthma was used as a proxy condition, as per the approach used for utility decrements.[1] The company also assumed, based on feedback from a Consultant Haematologist in the UK who specialises in SCD and guidelines from the BSH, that patients experiencing ACS would require a single blood transfusion.[15, 59] The cost of an automated exchange blood transfusion was also applied for sepsis and priapism (for all events), as in severe cases, patients may also receive a blood transfusion for these events, as advised in the clinician feedback and described in the BSH guidelines for transfusion.[15, 59]

The cost for adverse events associated with crizanlizumab treatment, HC/HU and blood transfusion were not included in the model.

Table 5.22: Costs per event for acute complications of SCD

Complication	Cost per event	Source
ACS	£5,163.30	NHS Reference Costs 2018–19 [DZ15M (Asthma with Interventions) – Total HRG] (£2,614.49) Plus, cost of exchange transfusion for all patients (£2,548.81).
Gallstones	£5,635.33	Diagnosis: liver function test and ultrasound, as per NICE CG188[78] NHS Reference Costs 2018–19 [DAPS04 Clinical Biochemistry] NHS Reference Costs 2018–19 [weighted average across RD40Z (Ultrasound Scan with duration of less than 20 minutes, without Contrast – Total HRG) to RD43Z (Ultrasound Scan with duration of 20 minutes and over, with Contrast) – Total HRG] Management: cholecystectomy and endoscopic retrograde cholangiopancreatography, as per NICE CG188[78] NHS Reference Costs 2018–19 [weighted average across GA10H (Laparoscopic Cholecystectomy, with CC Score 4+) to GA10N (Open Cholecystectomy, with CC Score 0) – Total HRG] NHS Reference Costs 2018–19 [weighted average across GB05F (Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 5+) to GA09F (Complex Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 0-1) – Total HRG]
Sepsis	£4,754.46	NHS Reference Costs 2018–19 [weighted average across WJ06A (Sepsis with Multiple Interventions, with CC Score 9+) to WJ06J (Sepsis without Interventions, with CC Score 0-4) – Total HRG] (£2,205.65)

Complication	Cost per event	Source
		Plus, cost of exchange transfusion for all patients (£2,548.81).
Pulmonary hypertension	£1,486.34	NHS Reference Costs 2018–19 [weighted average across EB15A (Primary Pulmonary Hypertension with CC Score 9+) and EB15C (Primary Pulmonary Hypertension with CC Score 0-3) – Total HRG]
Cardiac	£929.24	Assumed all events are arrhythmias, as per the approach to utility decrements NHS Reference Costs 2018–19 [weighted average across EB07A to EB07E (Arrhythmia or Conduction Disorder, with CC score 0 to 13+) – Total HRG]
Cellulitis	£3,830.26	NHS Reference Costs 2018–19 [weighted average across JD07A (Skin Disorders with Interventions, with CC score 12+) to JD07H (Skin Disorders with Interventions, with CC score 0-3) – Total HRG]
Leg ulcer	£3,149.86	Guest et al. (2017). Mean annual cost of healthcare resource use associated with managing healed venous leg ulcer (inflated from 2015/16 to 2018/19 using the NHSCII Pay and Prices inflation index)[75, 79]
Osteomyelitis	£3,126.81	NHS Reference Costs 2018–19 [weighted average across HD25D (Infections of Bones or Joints, with CC Score 13+) to HD25H (Infections of Bones or Joints, with CC Score 0-1) – Total HRG]
Priapism (males only)	£3,592.50	NHS Reference Costs 2018–19 [weighted average across LB58C (Penile Disorder with Interventions) and LB58D (Penile Disorder without Interventions) – Total HRG] (£1,043.69) Plus cost of exchange transfusion for all patients (£2,548.81).

Based on Table 40 of the CS[1]
ACS = acute chest syndrome; CS = company submission; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; SCD = sickle cell disease

ERG comment: The ERG's main concern is the input for body weight in the calculation of the dose of crizanlizumab. As discussed in section 5.2.3, the company assumed a mean body weight of 58.69 kg, based on inputs used in the NICE CG143 economic evaluations of the average body weight of adult SCD patients in the UK.[52] NICE CG143 considers the entire SCD patient population in the UK, which is a broader patient population than the intended patient population for crizanlizumab. In comparison, the mean body weight in the SUSTAIN trial was significantly higher at [redacted].[27] This difference was attributed to differences in study sites (USA, Brazil, and Jamaica versus. the UK) and the male/female ratio (a higher female ratio in the NICE CG143). Given that the SUSTAIN trial represents the recurrent VOC population to be treated, it is expected that the body weight from the population in the SUSTAIN trial is a better fit for the model. The company confirmed in their response to the clarification letter that they consider the SUSTAIN population to be reflective of UK patients with SCD who are expected to be treated with crizanlizumab.[20] The ERG considers that the patient population in the SUSTAIN trial should be considered in the model, as this population more accurately fits the population that is expected to be treated with crizanlizumab (e.g. patients with recurrent VOCs). Hence, the ERG base-case includes the mean body weight as reported in the SUSTAIN trial.

The ERG asked the company for (minor) adjustments to the economic model with regards to the drug administration costs at clarification. For the administration of crizanlizumab, the company omitted resource costs required for the administration procedure such as costs for certain materials (e.g. syringe, sodium chloride/dextrose). The company argued that the additional material costs associated with the administration of crizanlizumab had not been included in the model as these costs are expected to be negligible compared to the costs for health care staff and drug acquisition.[20] The company did not expect that the inclusion of these additional costs would have a major impact on the cost effectiveness results. The ERG agrees that the impact of including these costs would be minimal. However, the ERG argues that these costs should have been included for the completeness.

Furthermore, in the electronic model, the yearly administration costs for crizanlizumab follow a different calculation than for the acquisition cost of crizanlizumab. The ERG asked the company for clarification as to why a different method of cost calculation was conducted in this case and why the compliance rate of [redacted] was omitted in the calculation of the administration cost. The company noted that the omission of the compliance rate to the calculation for administration costs was not intentional.[20] The company added an option to apply compliance rates to the administration costs to the economic model. The ERG will use this new option in the ERG base-case.

The ERG noted that the cost of the initial administration by a band-6 nurse in the first year of the cycle was not included in the economic model. The company confirmed that this administration cost for the additional dose of crizanlizumab in the first year of the model was not included in the original model that was submitted. This omission was not intentional.[20] An option to apply the administration cost to the additional crizanlizumab dose received in the first year has been added to the cost effectiveness model. The ERG will use this new option in the ERG base-case.

Overall, the ERG thinks the calculation of monitoring costs for crizanlizumab and HC/HU is plausible. The ERG noted that health care staff costs in addition to the cost for laboratory tests in the monitoring cost for HC/HU were not included in the model. The company confirmed that these costs were omitted, and argued that given that the same costs would be applied to the same proportion of patients in each treatment arm in the model, it is not expected that the introduction of these costs would have a major impact on the cost effectiveness results.[20] The ERG agrees that the impact of including these costs would be minimal. Nevertheless, the ERG argues these costs should be included for the completeness of the model.

The ERG noted that not all adverse event costs associated with crizanlizumab, HC/HU and blood transfusions were incorporated into the economic model. As discussed in section 5.2.7, the company omitted Grade 3 and Grade 4 adverse events arguing that the low incidence of events and the similar incidence of events between treatment arms in the SUSTAIN trial, was not expected to have a major impact on the results of the cost effectiveness analysis.[20] The ERG is not convinced that omitting the most severe adverse events was justified and argues that costs for AE should be included in the model for completeness. However, the ERG base-case will not include additional AEs, as the ERG agrees that in this case AEs are unlikely to be a driver of results.

6. Cost effectiveness results

6.1 Company's cost effectiveness results

The deterministic base-case results for crizanlizumab versus SoC are presented in Table 6.1 (list price for crizanlizumab) and Table 6.2 (with PAS for crizanlizumab). Compared to SoC, crizanlizumab was associated with an increased number of life years ([redacted]) and QALYs gained ([redacted]), but also higher total costs ([redacted] at list price and [redacted] with PAS for crizanlizumab). In the base-case analysis, the ICER for crizanlizumab versus SoC was [redacted] (list price) and £329,868.32 (with PAS for crizanlizumab). The company is intending to discuss a Managed Access Agreement with NICE and NHS England, in order to improve the cost effectiveness of crizanlizumab.[1]

In terms of discounted costs, the largest difference between treatment arms was due to the cost of crizanlizumab as an add-on to established clinical management in the crizanlizumab arm. The cost of complications overall was however lower in the crizanlizumab arm compared to the SoC arm. The greatest difference between treatment arms in terms of discounted QALYs, were the QALYs accrued in the <1 VOC health state, which were higher in the crizanlizumab arm ([redacted]) than in the SoC arm ([redacted]).

Table 6.1: Company base-case cost effectiveness results (discounted; list price)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Crizanlizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]				

Based on Table 43 of the CS[1]
CS = company submission; ICER = incremental cost-effectiveness ratio; incr. = incremental; LYG = life years gained; QALYs = quality-adjusted life years; SoC = standard of care

Table 6.2: Company base-case cost effectiveness results (discounted; includes PAS for crizanlizumab)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Crizanlizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£329,868.32
SoC	[redacted]	[redacted]	[redacted]				

Based on Table 44 of the CS[1]
CS = company submission; ICER = incremental cost-effectiveness ratio; incr. = incremental; LYG = life years gained; QALYs = quality-adjusted life years; SoC = standard of care

6.2 Company's sensitivity analyses

6.2.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted in order to assess the impact of parameter uncertainty on the results of the cost-effectiveness analysis. The PSA was run for 1,000 iterations and in each iteration model inputs for all parameters were randomly drawn from specified distributions, as outlined in Table 45 of the CS.[1] Where possible the standard error or standard deviation associated with the mean value was used to define the distribution, otherwise it was assumed that the standard error would be 20% of the mean value.

The results of the PSA are presented in Table 6.3 (list price) and Table 6.4 (with PAS for crizanlizumab). The average probabilistic ICERs from the PSA are higher than those in the deterministic base-case analysis. The company explains that this is partly expected to be a consequence of varying

weight in the probabilistic analyses, which results in some iterations requiring patients to receive four vials of crizanlizumab, rather than the three vials included in the base-case analysis.[1]

Table 6.3: Mean probabilistic results (list price)

Comparison	Incremental costs	Incremental QALYs	ICER (£/QALY)
Crizanlizumab versus SoC	[redacted]	[redacted]	[redacted]

Based on Table 46 of the CS[1]
CS = company submission; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years; SoC = standard of care

Table 6.4: Mean probabilistic results (including PAS for crizanlizumab)

Comparison	Incremental costs	Incremental QALYs	ICER (£/QALY)
Crizanlizumab versus SoC	[redacted]	[redacted]	£370,699

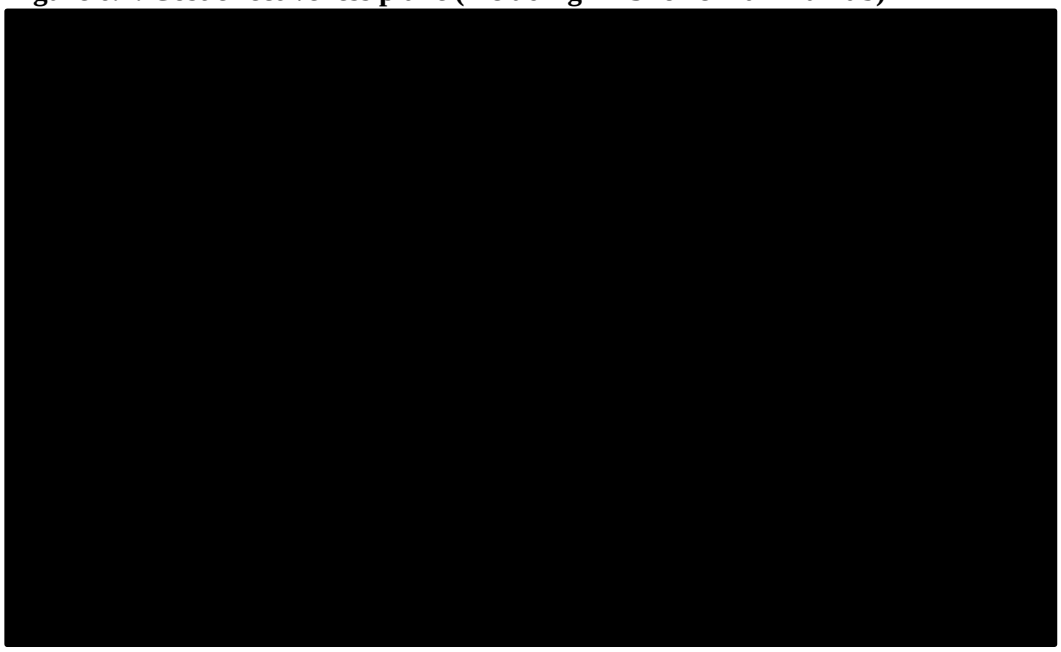
Based on Table 47 of the CS[1]
CS = company submission; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALYs = quality-adjusted life years; SoC = standard of care

Scatter plots showing the incremental costs and QALYs for crizanlizumab versus SoC across all iterations in the PSA are presented in Figure 6.1 (list price) and Figure 6.2 (including PAS for crizanlizumab). Both show all the simulations falling into the north-eastern quadrant where crizanlizumab is more costly and more effective than SoC. Figure 6.2 shows that, when including the PAS, only approximately 1 of the 1,000 simulations falls below the £30,000 per QALY gained threshold.

Figure 6.1: Cost effectiveness plane (list price)

Based on Figure 9 of the CS[1]
CS = company submission; QALY = quality adjusted life year

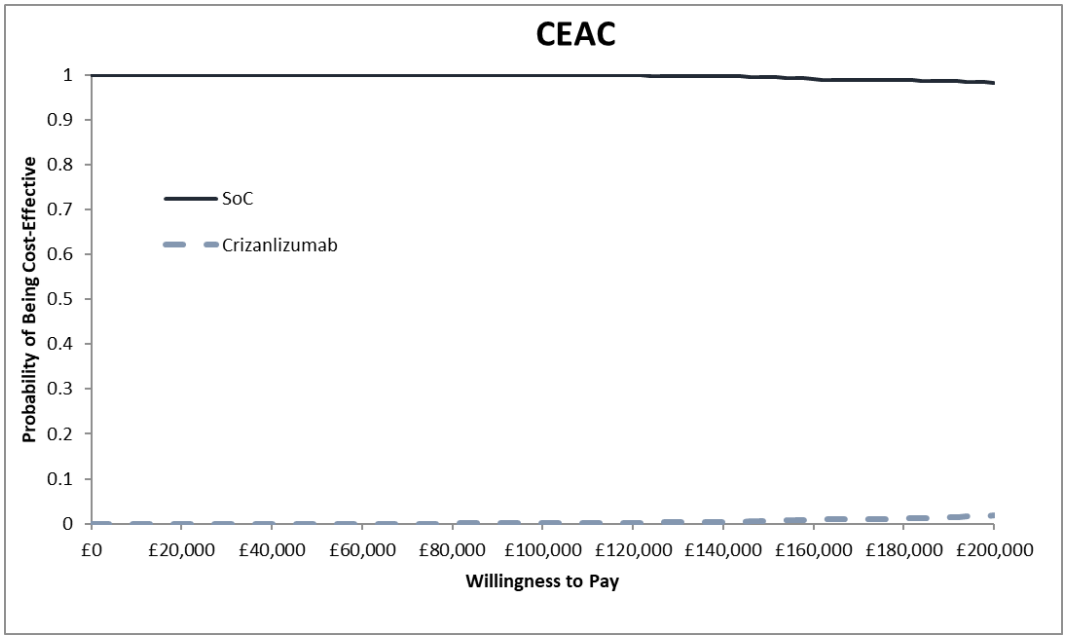
Figure 6.2: Cost effectiveness plane (including PAS for crizanlizumab)



Based on Figure 10 of the CS[1]
CS = company submission; PAS = Patient Access Scheme; QALY = quality adjusted life year

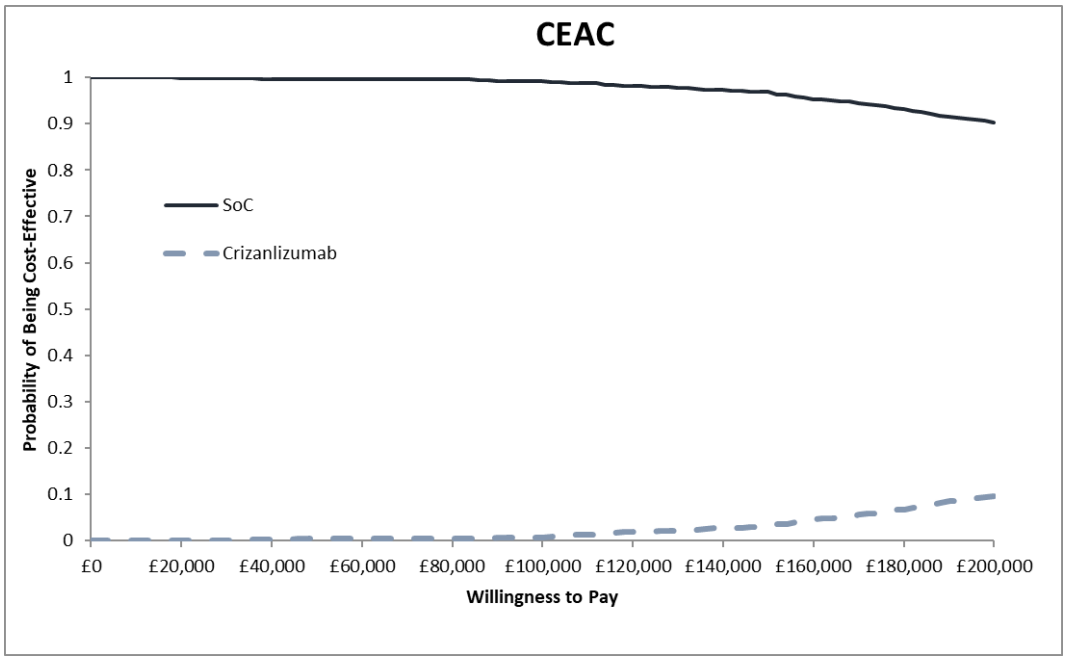
Cost effectiveness acceptability curves are presented in Figure 6.3 (list price) and Figure 6.4 (including PAS for crizanlizumab). Both show that has approximately 0% probability of being the cost effective option at the upper limit of the standard NICE STA threshold of £30,000 per QALY gained.

Figure 6.3: Cost effectiveness acceptability curve for crizanlizumab and SoC (list price)



Based on Figure 11 of the CS[1]
CEAC = cost effectiveness acceptability curve; CS = company submission; SoC = standard of care

Figure 6.4: Cost effectiveness acceptability curve (including PAS for crizanlizumab)



Based on Figure 12 of the CS[1]

CEAC = cost effectiveness acceptability curve; CS = company submission; PAS = Patient Access Scheme; SoC = standard of care

ERG comment: The proportion of patients in each VOC health state and the number of VOC events per health state were not included in the company's PSA as they were turned off in the PSA input sheet. These inputs represent important areas of parameter uncertainty and therefore should be included in the PSA. These are included in the ERG PSA.

The calculation of the Dirichlet distribution used to determine the proportion of patients in each of the three VOC states was also corrected by the ERG. The company assumed that the values for the proportions of patients in health states VOC <1 and VOC ≥1-<3 were drawn from beta distributions independently, with the proportion of patients in health state VOC >3 being calculated as one minus the previous two. This would imply that the uncertainty around the third probability, which is the largest (judged based on the standard errors for the VOC >3 groups), is not directly sampled in the PSA. The ERG corrected for this by using a Dirichlet distribution to sample the three values (proportions of patients in VOC<1, ≥1-<3, and >3) at the same time.

Additionally the company report that, where possible the standard error or standard deviation associated with the mean value was used to define the distribution in the PSA.[1] Given that estimates are sample means the standard error should always be used and therefore it is incorrect to use the standard deviation. It is not clear whether the standard deviation was ever used instead of the standard error.

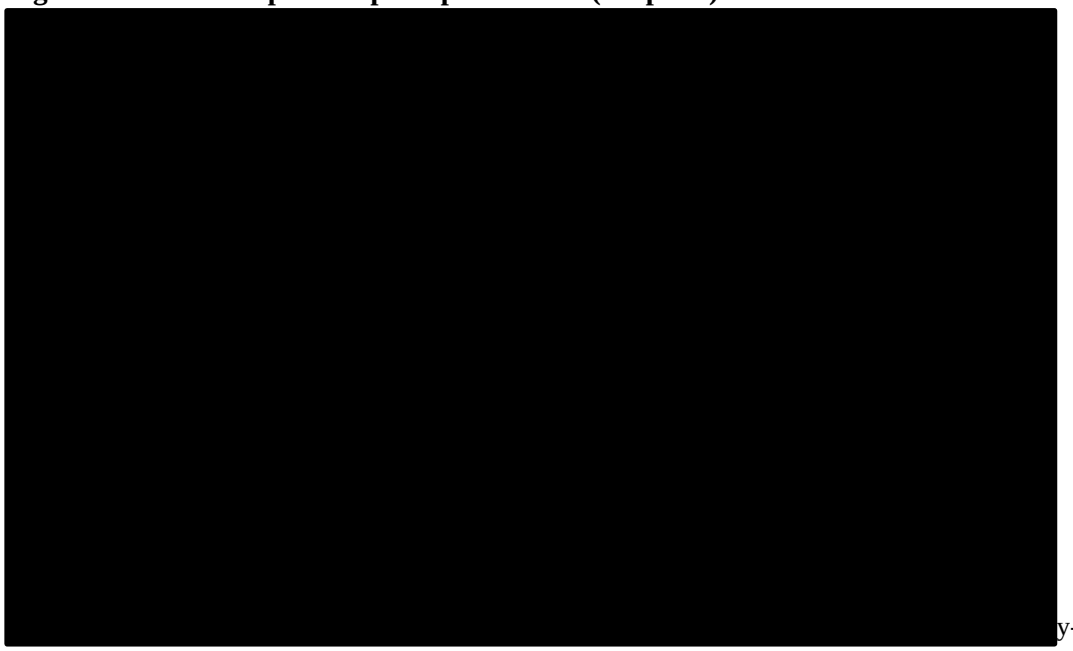
6.2.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted by varying the input for each parameter in the model by ±20% of their mean value, whilst keeping all other inputs the same.[1] For certain parameters where standard errors of the mean were available the bounds were defined by the upper and lower limits 95% CI.

As shown in Figure 6.5 (list price) and Figure 6.6 (with PAS for crizanlizumab), the parameters with the greatest impact on the ICER for crizanlizumab versus SoC were those related to drug costs (e.g. body weight and compliance) and the utility values used for VOC health states (and in particular for

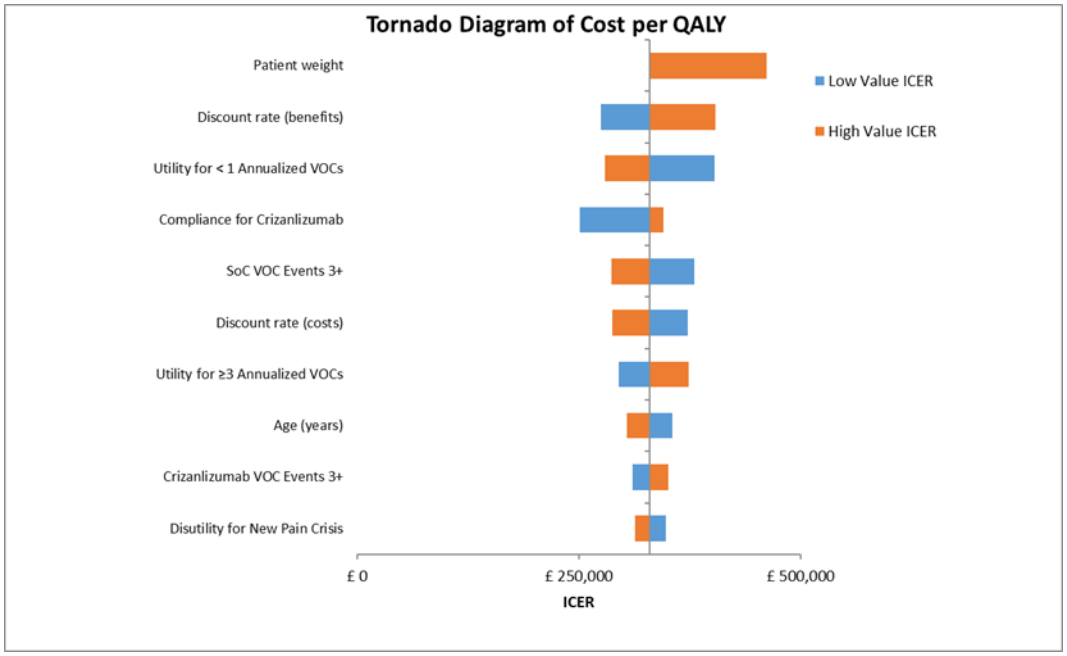
<1 VOC). Parameters associated with complications did not feature in the top 10 most influential parameters for the analysis, suggesting that individually these did not have a major impact on the cost effectiveness results. Of the complications included in the model, ACS had the greatest impact on the results.

Figure 6.5: Tornado plot – top ten parameters (list price)



y-adjusted life year; SoC = standard of care; VOC = vaso-occlusive crises

Figure 6.6: Tornado plot – top ten parameters (including PAS for crizanlizumab)



Based on Figure 14 of the CS[1]

CS = company submission; ICER = incremental cost effectiveness ratio; PAS = Patient Access Scheme; QALYs = QALYs: quality-adjusted life years; SoC = standard of care

ERG comment: The discount rate should not be included in the DSA as the discount rate is fixed by the NICE reference case and is therefore not an area of uncertainty. The ERG removed the discount rate from their ERG DSA.

The DSA was conducted by varying the input by ±20% of the mean value for many of the included parameters. However, the selection of a 20% range of uncertainty is arbitrary and this method will not necessarily represent an equally plausible range of values for each parameter.

6.2.3 Scenario analyses

The company conducted scenario analyses to explore the impact of certain assumptions and alternative inputs in the model on the results of the cost effectiveness model. The results of these scenario analyses are presented in Table 6.5.

For scenarios in which the rate of discontinuation for crizanlizumab in subsequent years was increased, both the incremental costs and incremental QALYs were reduced, with the overall impact of lowering the ICER compared to the base-case. Assuming no further discontinuation of crizanlizumab after year 1 (scenario 1a) resulted in an increase in the incremental costs and QALYs, and an overall increase in the ICER compared to the base-case.[80]

Assuming that treatment efficacy would be maintained one-year post-discontinuation resulted in an increase in the ICER. Removing this post-discontinuation efficacy completely from the model resulted in a further increase in the ICER. In addition, if vial sharing was included in the model, the ICER decreased. With crizanlizumab expected to be administered in a hospital-based setting, the compounding of services and potential vial sharing is a possible scenario in clinical practice.

Based on the results of the DSA, the complication with the greatest impact on the cost effectiveness results is ACS. In the scenario exploring an alternative distribution for the extrapolation of baseline hazards for ACS, the ICER for crizanlizumab remained relatively unchanged.

Reducing the time horizon to 20 years did not have a substantial impact on the results of the cost effectiveness model. At this point a high proportion of patients had died in the model already, and of those remaining alive in the crizanlizumab arm, more patients were in the ‘Off treatment’ health state receiving SoC than in the ‘On treatment’ health state. However, using a time horizon of 10 years resulted in a large increase in the ICER.

Table 6.5: Results from scenario analyses for crizanlizumab versus SoC

	Description	List price			Including PAS		
		Incr. costs	Incr. QALYs	ICER (£/QALY)	Incr. costs	Incr. QALYs	ICER (£/QALY)
	Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£329,868.32
1a	**Crizanlizumab discontinuation rate in subsequent years: 0%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£344,539.96
1b	**Crizanlizumab discontinuation rate in subsequent years: 15%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£293,208.20
1c	**Crizanlizumab discontinuation rate in subsequent years: 25%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£258,851.73
1d	**Crizanlizumab discontinuation rate in subsequent years: 32.8%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£234,933.64
2a	**1-year post-continuation efficacy for crizanlizumab**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£357,081.60
2b	**No post-discontinuation efficacy for crizanlizumab**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£389,062.07
3	**Extrapolation of mortality: Generalised gamma**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£285,806.54
4	**Extrapolation of ACS: Gompertz**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£329,650.37
5	**No age-adjustment for utility values**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£319,596.80
6	**With vial sharing**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£321,197.90
7	**Body weight based on SUSTAIN**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£461,903.32
8a	**Time horizon: 20 years**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£335,885.77
8b	**Time horizon: 10 years**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£453,988.26

Based on Table 49 of the CS[1]

ACS = acute chest syndrome; CS = company submission; ICER = incremental cost-effectiveness ratio; incr. = incremental; PAS = Patient Access Scheme; QALYs = quality-adjusted life years; SoC = standard of care

ERG comment: The results of the company's scenarios surrounding discontinuation seem counterintuitive, with crizanlizumab becoming more cost effective as discontinuation rates increase. The ERG also considered that some important areas of uncertainty in the model remain unexamined by the company, including the patient characteristics used in the model and assumptions surrounding HC/HU use and assumptions made by the company surrounding utilities. The ERG will explore these areas of uncertainty in their scenario analyses described in section 7.1.3.

6.3 Model validation and face validity check

The company sought clinical and health economic expert opinion as part of the model conceptualisation and development process to ensure that the model structure, and the key assumptions underpinning the model, were consistent with the clinical course of SCD and the experience of patients with the condition.[1]

To ensure that the model inputs and assumptions were relevant to UK clinical practice, feedback from a Consultant Haematologist in the UK who specialises in SCD was also sought by the company during the development of the cost effectiveness model. Clinician feedback was used to validate the cost and resource inputs described in the model, including inputs relating to the use of blood transfusions, and also to validate the assumptions regarding current clinical management of SCD (i.e. the proportion of patients being treated with HC/HU and those receiving blood transfusions for the prevention of recurrent VOC).[59] Where possible, UK sources were used for model inputs, and similar inputs and approaches to those used in the economic evaluations for NICE CG143 were adopted in the model.[52]

The company used published sources of literature to assess the plausibility of the clinical outcomes predicted by the model. A study published by Gardner et al. 2016, which reports survival outcomes for adult patients from a single centre in London (N=712; aged 16–80 years) over a 10-year period (2004–2013), was used.[64] The use of HC/HU and chronic blood transfusions during the study period (72/712 [10.1%] and 71/712 [9.97%], respectively) is largely consistent with the inputs used in the cost effectiveness analysis, and so the outcomes reported in this study are considered to be relevant for assessing survival in the SoC arm of the model.[64] Using the Gompertz distribution in the base-case, the median age of death (with all patients having died in the model) was predicted to be 52.1 years in the SoC arm, and so reflects the reduced life-expectancy of SCD patients with recurrent VOC.

The Gardner et al. 2016 estimated survival from age at birth, and so these estimates are subject to left-truncation bias and may overestimate the life-expectancy of patients with SCD.[64] In a retrospective analysis of adult patients with SCD across two centres in the USA, median survival was estimated from age at baseline and was reported to be 48.0 years.[65] With the possibility that survival in SCD patients with recurrent VOC could be considerably lower than those reported in Gardner et al. 2016, the use of the Gompertz distribution (median age of death, 52.1 years in the SoC arm) was considered to be the more clinically plausible when compared to alternative distributions.

The average annualised rate of VOC in the model was lower in the crizanlizumab arm (2.56) compared to the SoC arm (4.14), and the rates predicted by the model were similar to the mean annual rate of VOC reported in the SUSTAIN trial for the high-dose crizanlizumab arm [redacted] and placebo arm [redacted] respectively.[27]

ERG comment: While the company did attempt to validate the plausibility of the model outcomes in terms of survival, this was based on a study, the population of which did not match patients who would be expected to receive crizanlizumab in clinical practice (i.e. those experiencing recurrent VOC) and

therefore the survival in the study used may not be reflective of the population under consideration in this submission. This therefore remains an area of uncertainty.

The ERG requested further details of the model validation conducted by the company at clarification. The company responded that the model programming was checked by an analyst who was not involved in the original development of the model using a validation checklist. This involved a quality control check of the formulae used in the model and stress testing of the model to ensure that it behaved as expected when extreme values were used.[20] However, no further details were provided and therefore the ERG could not verify what was done or any results.

7. Evidence Review Group's additional analyses

7.1 Exploratory and sensitivity analyses undertaken by the ERG

7.1.1 Explanation of the company adjustments after the request for clarification

In their response to the request for clarification,[20] the company stated that while implementing the changes to the model in response to Question B.30 part c, two corrections were made to the model:

1. To apply the cost of crizanlizumab administration once every 28 days per cycle and not simply 12 times per cycle

2. To apply the cost of single dose of crizanlizumab as the additional cost in cycle 1 and not the annual cost of crizanlizumab

The company reported that together these corrections resulted in a change in the base-case ICER presented in the CS from £329,868.32 to £332,487.98 per QALY gained (with PAS).[20]

7.1.2 Explanation of the ERG adjustments

The changes made by the ERG (to the model received with the response to the clarification letter) were subdivided into the following three categories (according to Kaltenthaler et al. 2016)[81]:

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

After these changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

7.1.2.1 Fixing errors

1. Correcting the Dirichlet distributions used to sample the proportion of patients in each VOC health state in the PSA. This did not affect the ERG base-case.

7.1.2.2 Fixing violations

2. Including the VOC parameters (proportion of patients per VOC state and annualised number of VOCs per state) in the PSA. This did not affect the ERG base-case.

7.1.2.3 Matters of judgement

3. In the company model, administration costs were not applied for the additional administration of crizanlizumab in the first year. This was applied in the ERG base-case

4. The ERG felt it was correct to apply the compliance rate to crizanlizumab administration costs, as it was applied for drug costs.

5. The ERG prefers to use the patient weight from SUSTAIN rather than from CG143 as the SUSTAIN trial is claimed to be reflective of the population who will receive crizanlizumab in UK clinical practice and the estimate from CG143 is based on all SCD patients and not only those experiencing recurrent VOCs.[52]

6. The ERG prefers to assume the HC/HU usage from SUSTAIN, given that the population in SUSTAIN matches the intended use of crizanlizumab in UK clinical practice.

7. The ERG prefers to assume that post-discontinuation efficacy is only maintained for one year, in line with the data provided from SUCCESSOR.

8. The ERG prefers to assume that only patients who complete one year of crizanlizumab treatment receive the post-discontinuation efficacy, in line with the data provided from SUCCESSOR.

The main assumptions made by the company and the ERG for their preferred base-case analyses are summarised in Table 7.1.

Table 7.1: Company and ERG base-case preferred assumptions

Base-case preferred assumptions	Company	ERG	Justification for change
Correction of Dirichlet distributions used to sample the number of proportion of patients in each VOC health state	Assumed 1- other proportions for group with largest SE	Applied Dirichlet	Section 6.2.1
Inclusion of the VOC parameters in the PSA	Not included in company PSA	These parameters represent an important area of parameter uncertainty and should be included	Section 6.2.1
Administration costs applied for the additional administration of crizanlizumab in the first year	Did not apply cost of the additional administration of crizanlizumab in the first year	The cost of the additional administration should be applied	Section 5.2.9
Compliance rate applied to crizanlizumab administration costs	Assumed full administration costs, not weighted by compliance	If drug costs and corrected for compliance it is appropriate to also account for compliance in administration costs	Section 5.2.9
Patient weight assumed from SUSTAIN rather than from CG143	Assumed patient weight from CG143, weighted according to gender distribution from HES database as these represented UK specific estimates	ERG prefer to use values from the SUSTAIN trial as this represents the population expected to receive crizanlizumab in clinical practice (those with recurrent VOCs)	Section 5.2.3
HC/HU usage assumed from SUSTAIN	Company assumed HC/HU usage of 14.2%, based on data from the National	ERG prefer to use values from the SUSTAIN trial as this represents the population expected to	Section 5.2.4

Base-case preferred assumptions	Company	ERG	Justification for change
	Haemoglobinopathy Registry instead of [redacted] seen in the SUSTAIN trial.	receive crizanlizumab in clinical practice (those with recurrent VOCs)	
Post-discontinuation efficacy is only maintained for 1 year	Assumed 2 years of post-discontinuation efficacy	Assumed 1-year post-discontinuation efficacy, in line with available data from the SUCCESSOR trial	Section 5.2.6
Only patients who complete 1 year of crizanlizumab treatment receive the post-discontinuation efficacy	Assumed all patients receive post-discontinuation efficacy, even those discontinuing in first year	Assume only patients who complete 1 year of crizanlizumab treatment receive the post-discontinuation efficacy, in line with available data from the SUCCESSOR trial	Section 5.2.6

CG = clinical guideline; ERG = Evidence Review Group; PSA = probabilistic sensitivity analysis; SE = standard error; UK = United Kingdom; VOC = vaso-occlusive crises

7.1.3 Additional scenarios conducted by the ERG

The ERG conducted several additional scenario analyses in which the main sources of uncertainty identified by the ERG were explored. These were the uncertainties associated with the patient characteristics and HC/HU use which best reflect the population who will receive crizanlizumab in clinical practice, the expected use of chronic transfusion in clinical practice, the long-term efficacy of crizanlizumab, both while still on treatment and post-discontinuation and the assumptions made by the company surrounding utilities. A list of the scenario analyses conducted by the ERG is provided below.

7.1.3.1 Scenario set 1: Patient characteristics

The ERG prefers to use the patient characteristics (age, gender distribution and weight) from the SUSTAIN trial, as these were reported to be representative of the population who will receive crizanlizumab in UK clinical practice. The company chose to use UK specific estimates of patient characteristics but these were not specific to SCD patients who experience recurrent VOCs and instead represent the characteristics of all SCD patients. It is not clear to what extent the characteristics of the broader SCD population are representative of those patients experiencing recurrent VOCs. However, the company used the age and gender from HES in the calculation of HRs for mortality and complications and therefore the ERG did not change age and gender in their base-case. Only weight was changed in the base-case. Scenarios will be performed whereby the characteristics are all taken from the UK estimates and all taken from SUSTAIN to examine the impact on results. It should be noted that by changing the baseline age and gender distribution in the model to the values from SUSTAIN, it is assumed that the HRs for mortality and complications obtained from HES are valid for the SUSTAIN characteristics however this cannot be verified.

7.1.3.2 Scenario set 2: HC/HU use

The company assume HC/HU use of 14.2% from the National Haemoglobinopathy Registry, instead of [redacted], as seen in the SUSTAIN trial. The data from the National Haemoglobinopathy Registry includes all SCD patients, not just those experiencing recurrent VOCs. Given that HC/HU treatment is used to

reduce VOCs, it is likely that it is mostly used in patients experiencing recurrent VOCs and therefore its use will likely be higher than 14.2%. Therefore, the ERG base-case used the usage from SUSTAIN. The company also state in their submission that [redacted]. The ERG therefore performed scenarios considering 0% and 100% of HC/HU use as well as the company's base-case assumption of 14.2%.

7.1.3.3 Scenario set 3: Chronic transfusions

There is uncertainty in the model surrounding the proportion of patients in either arm who will receive treatment with chronic blood transfusions. The base-case (both company and ERG) assumed [redacted] of the SoC arm and 0% of the crizanlizumab arm will receive chronic transfusions. Again the [redacted] is estimated from all patients in the HES database, including patients not experiencing VOCs. Therefore, in a population experiencing recurrent VOCs, this proportion could be higher. The company assumed that none of the patients receiving crizanlizumab will also receive chronic blood transfusion, but this is uncertain, with a lack of clinical practice data. Therefore, different proportions of patients receiving chronic transfusions in each arm were tested to examine the impact on results.

7.1.3.4 Scenario set 4: Duration of treatment effect (while still on treatment)

The company assumed that the transition probabilities in the crizanlizumab and SoC arms stay the same over time. This implies a constant lifetime treatment effect, which is an assumption that has not been clinically validated by the company. The ERG performed a scenario analysis in which several options for a finite duration of treatment effect (five, 10, or 15 years) were considered. It was assumed that, once crizanlizumab is no longer effective, patients stop receiving crizanlizumab and move to the SoC arm instead. In another scenario set, it was assumed that patients continue to receive crizanlizumab, even as its effect wanes over time. It was not deemed feasible to implement in the model the assumption of a gradually decreasing treatment effect over time. Instead, patients were assumed to receive full treatment benefits for a pre-specified period (five, 10, or 15 years), after which they received no treatment benefit at all and were subject to the transition probabilities and mean annualised VOC rates per health state of the SoC arm.

7.1.3.5 Scenario set 5: Post-discontinuation efficacy

The company assumed two years of maintained post-discontinuation efficacy in all patients, including those who discontinued in the first year. The company had data from the SUCCESSOR trial which showed that efficacy was maintained one year after completion of crizanlizumab in patients who completed the SUSTAIN trial. Therefore, in the ERG base-case the post-discontinuation efficacy was reduced to one year, only in patients who finished the first year of treatment. These assumptions were altered in scenarios to test the impact on results.

7.1.3.6 Scenario set 6: changing HRQoL modelling assumptions and utility sources

The company base-case utilised health state utility values derived from an unpublished analysis of the LEGACY registry study.[1] These health state values were treated as the baseline utility value in each cycle to which additional decrements in utility related to individual VOC events were applied. Utility estimates from the SUSTAIN trial were not provided. Therefore, the ERG decided to rely on the LEGACY health state values for the base-case. The health state values of the unpublished analysis of the LEGACY registry study were lower than the estimates from published studies described in NICE CG143 (Appendix F), which might imply that the LEGACY health state values potentially capture (a part of) the HRQoL impact of individual VOC events alongside the HRQoL impact of SCD between

events.[52] The ERG therefore tested scenarios in which the impact of VOC events is solely captured within the health state value or is solely captured as per event decrement. The impact of these changes was provided, as well as the impact of assuming that patients experience a utility decrement two days prior to the hospitalisation for the VOC event.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

7.2.1 Results of the ERG preferred base-case scenario

The results of the ERG preferred base-case analysis (as outlined in section 7.1.2 of this report) are displayed in Table 7.2. The implementation of the ERG preferred assumptions resulted in an ICER of £693,689.30, which is slightly more than double the company's base-case ICER of £329,868.32.

Table 7.2: ERG base-case deterministic results for the (discounted, with PAS)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Crizanlizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£693,689.30
SoC	[redacted]	[redacted]	[redacted]				

Based on electronic model, updated in response to request for clarification[20]
ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; QALYs = quality adjusted life years

A PSA was also conducted using the ERG preferred base-case assumptions. The results of the ERG PSA are shown in Table 7.3. The probabilistic ICER was £524,226, which is substantially lower than the deterministic ICER. This is due to the inclusion and sampling of the proportion of patients in each of the VOC health states. This was also an issue in the company model provided in response to clarification and could not be fixed by the ERG in the time available.

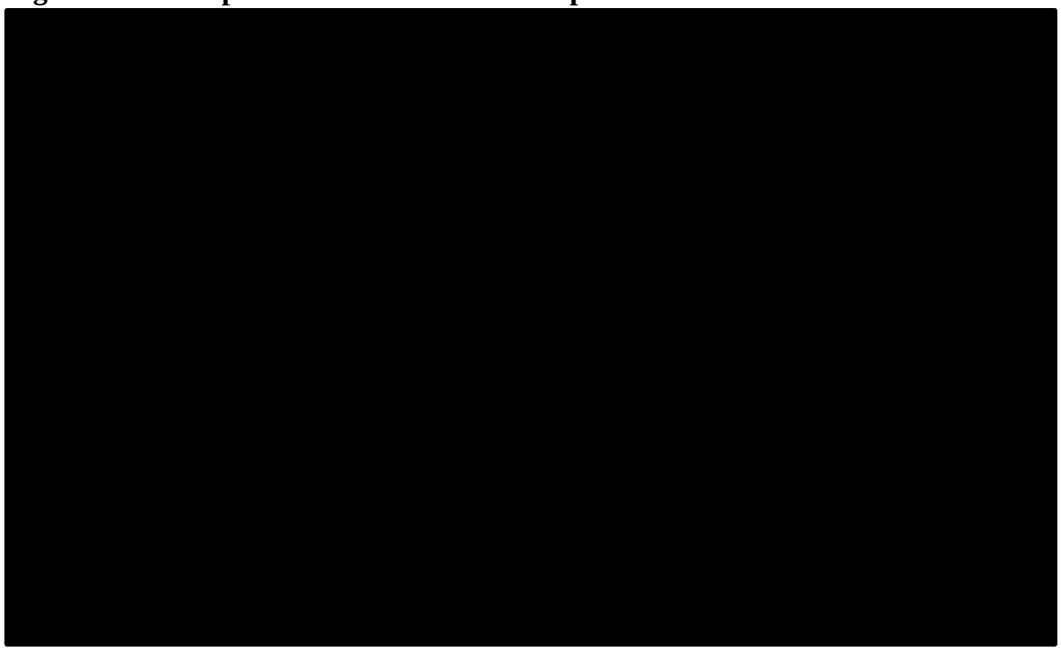
Table 7.3: ERG base-case probabilistic results for the (discounted, with PAS)

Technologies	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus SoC (£/QALY)
Crizanlizumab	[redacted]	[redacted]	[redacted]	£524,226

Based on electronic model, updated in response to request for clarification[20]
ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; QALYs = quality adjusted life years

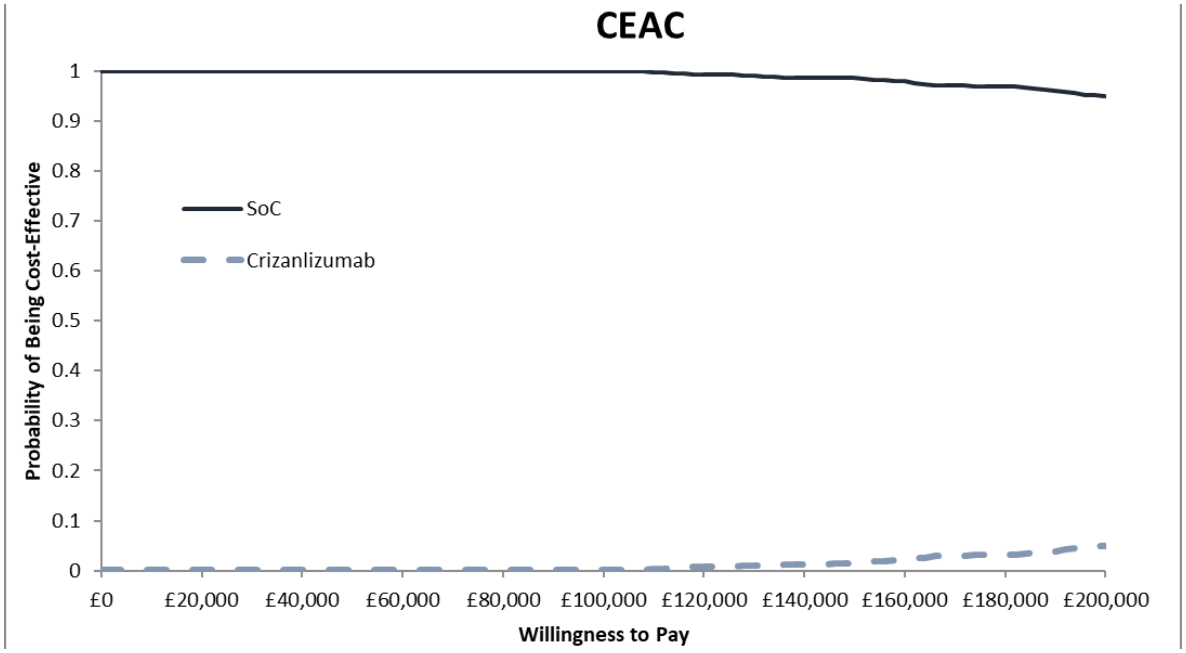
The incremental costs and incremental QALYs obtained from the ERG PSA were plotted in the cost effectiveness (CE)-plane and a cost effectiveness acceptability curve (CEAC) was calculated. These are shown in Figures 7.1 and 7.2, respectively. Most of the simulations ([redacted]) fell in the north-east quadrant of the CE-plane, where crizanlizumab provides additional QALYs to SoC, but at additional costs. However, none of these simulations in the north-west quadrant fell below the £30,000 per QALY gained threshold. SoC dominated crizanlizumab in the north-west quadrant of the CE-plane in [redacted] of simulations. Crizanlizumab dominated SoC in [redacted] of simulations in the south-east quadrant of the CE-plane. The CEAC indicated that at WTP thresholds of £20,000 and £30,000, the probability that crizanlizumab is cost effective remains at [redacted].

Figure 7.1: ERG preferred cost effectiveness plane



Based on electronic model, updated in response to request for clarification[20]
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

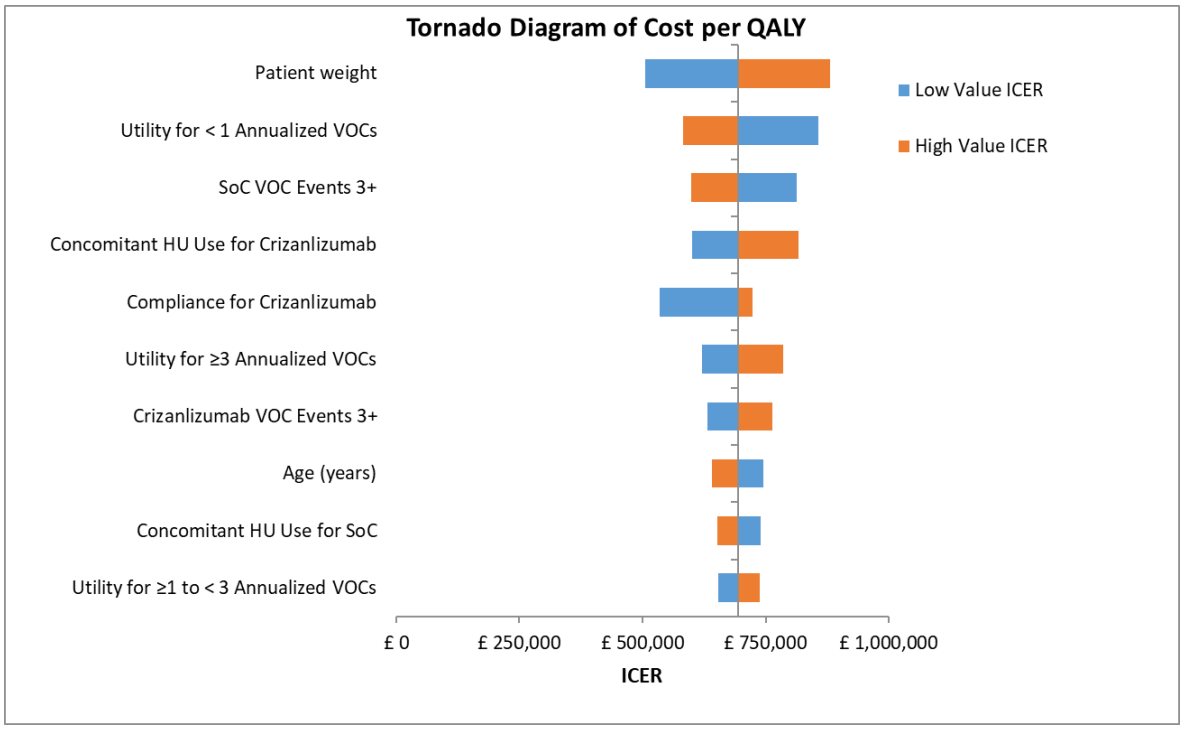
Figure 7.2: ERG preferred cost effectiveness acceptability curve



Based on electronic model, updated in response to request for clarification[20]
CEAC = cost effectiveness acceptability curve; ERG = Evidence Review Group; SoC = standard of care

The results of the ERG DSA are displayed in Figure 7.3. This shows that patient weight, utilities, number of VOC events in the most severe VOC health state, concomitant HC/HU use and compliance for crizanlizumab are the most influential parameters on the ICER.

Figure 7.3: ERG preferred one-way sensitivity analysis



Based on electronic model, updated in response to request for clarification[20]
ERG = Evidence Review Group; HU = hydroxyurea; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; VOC = vaso-occlusive crises

7.2.2 Results of the ERG additional exploratory scenario analyses

7.2.2.1 Scenario set 1: Patient characteristics

Assuming all patient characteristics from UK sources resulted in the lowest ICER of £505,666, while assuming all characteristics from SUSTAIN resulted in the largest ICER of £733,489 (Table 7.4). This range of results shows the importance of the patient characteristics in the analysis.

Table 7.4: Patient characteristic scenarios

Patient characteristics	Crizanlizumab		SoC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Age, gender, and weight UK (company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£505,666
Age, gender, and weight SUSTAIN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£733,489
Age and gender UK; weight SUSTAIN (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£693,689

Based on electronic model, updated in response to request for clarification[20]
BC = base-case; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY = quality adjusted life year; SoC = standard of care; UK = United Kingdom

7.2.2.2 Scenario set 2: HC/HU use

The lowest ICER in this scenario set (£484,103) was obtained when no patients in either arm were assumed to receive HC/HU, while the highest ICER of £953,475 was obtained when all patients were assumed to receive HC/HU (Table 7.5). Again, the range of results shows that the assumed HC/HU usage is a driver of results.

Table 7.5: HC/HU usage scenario analyses

HC/HU use	Crizanlizumab		SoC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
HC/HU use 14.2% (UK estimate) (company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£519,073
HC/HU use SUSTAIN (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£693,689
No HC/HU use in either arm (always monotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£484,103
Everyone HC/HU use in both arms (always combination therapy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£953,475

HC/HU use	Crizanlizumab		SoC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Based on electronic model, updated in response to request for clarification[20] BC = base-case; ERG = Evidence Review Group; HC = hydroxycarbamide; HU = hydroxyurea; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY = quality adjusted life year; SoC = standard of care; UK = United Kingdom							

7.2.2.3 Scenario set 3: Chronic transfusion assumptions

Some variation in results is also seen when assuming different proportions of chronic transfusion treatment in the different arms. The smallest ICER (£652,383) resulted from assuming proportions of 0|% and [redacted] in the crizanlizumab and SoC arms respectively while the largest (£736,619) resulted from assuming equal usage of [redacted] in both arms (Table 7.6). However, the range in results is smaller than the previous scenarios suggesting that this assumption is driving results less than patient characteristics and HC/HU use.

Table 7.6: Chronic transfusion scenario analyses

Chronic transfusion assumptions	Crizanlizumab		SoC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Criz = 0% SoC = [redacted] (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£693,689
Criz = [redacted] SoC = [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£736,619
Criz = 0% SoC = [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£652,383
Criz = [redacted] SoC = [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£715,154
Based on electronic model, updated in response to request for clarification[20] Criz = crizanlizumab; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY = quality adjusted life year; SoC = standard of care							

7.2.2.4 Scenario set 4: Assumed duration of treatment effect

The company assumed that the transition probabilities in the crizanlizumab arm stay the same over time. This implies a constant lifetime treatment effect, which is an assumption that has not been clinically validated by the company. Scenario analysis were conducted to account for the possibility that crizanlizumab is effective for a limited period. The first scenario set assumes that patients stop receiving crizanlizumab ones its effectiveness ceases, while the second set assumes continuing treatment despite ceased treatment effectiveness. While continuing to give crizanlizumab once it is no longer effective may not be a realistic scenario, the second scenario set serves to proxy a waning treatment effect over time. In the case of a gradually decreasing treatment effect, crizanlizumab may continue to be given to the patient. The most optimistic scenario (15 years of full treatment effect, treatment discontinued once it is no longer effective) raises the base-case ICER to £701,525, while the most pessimistic scenario (five years of full treatment effect, continued treatment) raises the base-case ICER to £1,439,905 (Table 7.7).

Table 7.7: ERG Long-term treatment effectiveness scenario analyses

	Crizanlizumab		SoC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
5-year treatment effectiveness, discontinued treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£748,970
10-year treatment effectiveness, discontinued treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£738,055
15-year treatment effectiveness, discontinued treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£701,525
5-year treatment effectiveness, continued treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,439,905
10-year treatment effectiveness, continued treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£871,452
15-year treatment effectiveness, continued treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£754,456

Based on electronic model, updated in response to request for clarification[20]
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY = quality adjusted life year; SoC = standard of care

7.2.2.5 Scenario set 5: Post-discontinuation treatment effectiveness

Changes in the assumptions surrounding post-discontinuation treatment effectiveness had a smaller impact on results, with ICERs ranging from £693,689 for the ERG base-case assumption to £621,678 for the company assumption (Table 7.8).

Table 7.8: ERG Post-discontinuation treatment effectiveness scenario analyses

Post-discontinuation treatment effectiveness	Crizanlizumab		SoC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
2 years all patients (company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£621,678
2 years in patients completing 1 year of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£667,550
1 year in patients completing 1 year of treatment (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£693,689
1 year in all patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£668,370

Based on electronic model, updated in response to request for clarification[20]
BC = base-case; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY = quality adjusted life year; SoC = standard of care

7.2.2.6 Scenario set 6: changing HRQoL modelling assumptions and utility sources

For their base-case, the ERG utilised health state utility values derived from an unpublished analysis of the LEGACY registry study, on which addition per event decrements were applied for individual VOC events. However, based on the values of the LEGACY utility estimates and the four-week recall period of the SF-36 that was used to derive these estimates, the ERG felt that applying the additional per event decrement might lead to an overestimation of the impact of individual VOC events. The assumption that the impact of VOC events is captured solely within the health state values increases the ICER by approximately £218,000 (Table 7.9). The assumption that the impact of VOC events is solely captured in per event decrements increases the ICER by approximately £156,000 when using the LEGACY <1 VOC health state value as baseline utility value for all patients. In the scenario that a per event VOC utility decrement is applied when using the steady-state utility from NICE CG143 as baseline utility value for all patients, the ICER increases by approximately £124,000.[52] Finally, the assumption that patients experience a utility decrement from the moment of hospitalisation instead of two days priors increases the ICER by approximately £51,000.

Table 7.9: ERG HRQoL scenario analyses

Utility scenario's	Crizanlizumab		SoC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Impact VOC through health state and per-event decrement, with VOC impact starting two days prior to hospitalisation (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£693,689
Impact individual VOC events captured in health state utility value only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£911,405
Impact VOC events captured as per-event decrement only, using the <1 VOC health state utility as steady-state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£849,796
Impact VOC events captured as per-event decrement only, using the steady-state utility from NICE CG143	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£818,111
VOC utility decrement starts at hospitalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£744,939

Based on electronic model, updated in response to request for clarification[20]

BC = base-case; CG = clinical guideline; ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; Incr. = incremental; NICE = National Institute for Health and Care Excellence; QALY = quality adjusted life year; SoC = standard of care; VOC = vaso-occlusive crises

7.3 ERG's preferred assumptions

The ERG preferred changes to the updated company base-case were described in section 7.1.2. The cost effectiveness results of the ERG preferred base-case are presented in Table 7.10 in eight steps, where, in each step, the cumulative impact on the model results is shown. The assumption with the largest impact on the ICER was assuming the HC/HU usage from SUSTAIN followed by assuming the patient weight from SUSTAIN. These results emphasise the importance of clarifying whether the SUSTAIN trial is indeed generalisable to UK clinical practice in terms of population and treatment.

Table 7.10: ERG's preferred model assumptions (with PAS)

Preferred assumption	Section in ERG report	Crizanlizumab		SoC		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case CS	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£329,868
Company base-case post-clarification	7.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£332,488
ERG change 1 - Correct Dirichlet in PSA	6.2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£332,488
ERG change 2 - Include VOC state distributions and number of VOCs per health state in PSA	6.2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£332,488
ERG change 3 - Cost additional administration of crizanlizumab in the first year	5.2.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£332,488
ERG change 4 - Applied compliance to administration costs	5.2.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£331,252
ERG change 5 - Patient weight from SUSTAIN	5.2.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£463,269
ERG change 6 - HC/HU usage from SUSTAIN	5.2.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£621,678
ERG change 7 - Post-discontinuation efficacy maintained for 1 year.	5.2.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£668,370
ERG change 8 - Only patients completing first year of treatment get extended post-discontinuation efficacy	5.2.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£693,689

Based on electronic model, updated in response to request for clarification[20]

ERG = Evidence Review Group; HC = hydroxycarbamide; HU = hydroxyurea; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY = quality adjusted life year; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; SoC = standard of care; VOC = vaso-occlusive crises

7.4 Conclusions of the cost effectiveness section

The company submitted a de-novo Markov cohort model to assess the cost effectiveness of crizanlizumab versus SoC as a treatment for the prevention of recurrent VOCs in patients with SCD. The model health states were defined according to the average number of VOC that patients experienced in one year. The company selected the following health states: <1 VOC, ≥1–<3 VOC or ≥3 VOCs. At the beginning of each new model cycle, patients who were alive at the end of the previous cycle were "redistributed" into the three VOC health states. Patients who died transitioned to the absorbing death state. In each model cycle, patients could experience the following SCD-related complications: acute chest syndrome, sepsis, gall stones, cardiac arrhythmias, cellulitis, leg ulcers, osteomyelitis, priapism (only in males) and pulmonary hypertension

The ERG has concerns about whether the current model is fit for purpose. The main issue is that the definition of health states in terms of VOC per year (less than one, between one and three, and more than three VOC) does not match with the way it was recorded in SUSTAIN (between two and four, and between five and 10). Consequently, transition probabilities for the model cannot be derived using data from the 52-week SUSTAIN trial. To overcome this limitation, and in the absence of any longer-term data on the use of crizanlizumab, the company re-distributed all alive patients between the VOC health states at the end of every model cycle according to the proportions observed in SUSTAIN. However, this also seems inappropriate since SUSTAIN only provides information about patients with more than two VOC at baseline (how patients with less than two VOC would transition after the first year in the model and following treatment with crizanlizumab is unknown given the 52-week duration of the trial). Furthermore, the company assumed in the model that there is no direct link between SCD-related complications and death. For some complications, like acute chest syndrome, this assumption seems unrealistic. Even though the company indicated that since all-cause mortality (including death from acute chest syndrome) from the HES database was considered when estimating the baseline mortality hazard and the HRs for the VOC health states of the model, applying a separate risk of death for acute chest syndrome would result in double counting of death; it remains unclear to what extent the definitions of VOC in SUSTAIN and HES are equivalent and whether the impact of SCD-related complications on death are properly captured in the model. With the available data, a time to event approach seems more logical and would overcome the concerns raised by the ERG.

The main source of efficacy data in the model comes from the SUSTAIN trial, which is used to distribute patients in each treatment group between the three VOC health states and determines the mean number of VOCs per treatment group per health state in each cycle. The company argued that patients in SUSTAIN were representative of the population who would be expected to receive crizanlizumab in UK clinical practice i.e. those patients experiencing recurrent VOCs. However, in their base-case the company assumed baseline patient characteristics of age and gender distribution from the HES database and weight from the NICE CG143 guideline, arguing that the use of UK based estimates was more appropriate.[52] However, the vast majority of SCD patients in the HES database analysis did not experience recurrent VOC and therefore represented a much broader, and possibly less severe, group of patients than would receive crizanlizumab in practice. The estimated weight from the NICE guideline was also intended to be representative of all SCD patients. Therefore, the ERG would argue that patient characteristics should be have taken from the SUSTAIN trial in the base-case, especially as this source represents the main source of treatment efficacy in the submission as it determined patients' health state occupancy and number of VOC events and therefore was a driver of their risk of complications, mortality and their costs and HRQoL.

There were also uncertainties relating to treatment usage in both arms. In their base-case, the company also assumed that the proportion of patients receiving HC/HU in each treatment group was better represented by estimates from UK data than from the SUSTAIN trial. Therefore, in their base-case they assumed 14.2% of patients received HC/HU in each treatment arm, based on information from the National Haemoglobinopathy Registry annual report 2018/2019 which included all SCD patients, rather than [redacted] of patients as seen in the SUSTAIN trial. Given that the aim of HC/HU treatment is to prevent recurrent VOC, it can be assumed that its use would be higher in a population experiencing recurrent VOC. This was supported by the company submission which stated that the majority of HC/HU use was expected to be in patients with recurrent VOC, as per BSH treatment guideline recommendations, but in the absence of a specific estimate for the recurrent VOC population, the value from the National Haemoglobinopathy Registry was used in the cost effectiveness analysis.[20] The ERG therefore considered that the proportion of patients receiving HC/HU in the SUSTAIN trial should be used in the model as this population reflects the population expected to receive crizanlizumab in clinical practice. The company also assumed that no patients receiving crizanlizumab would receive chronic blood transfusions, while [redacted] of SoC patients would. Again, the assumption of [redacted] was taken from all SCD patients in the HES analysis who did not have a prior diagnosis of stroke (in order to exclude patients receiving transfusions for the prevention of stroke) and not only those experiencing recurrent VOCs who did not have a prior diagnosis of stroke. Therefore, in a recurrent population the usage is likely to be higher. There is no data with which to validate the assumption that no patients treated with crizanlizumab will receive chronic blood transfusion in clinical practice. Therefore, these assumptions were explored in ERG scenarios.

The company incorporated treatment effectiveness in the economic model by considering the patient distribution across the three VOC health states (<1, ≥1-<3, ≥3) and linking the mean annualised VOC rate within each health state to mortality and complications. Annualised VOC rates were obtained through the SUSTAIN trial, while the estimated association between VOC rates and mortality and complications resulted from statistical analysis on the HES database. In the company's base-case, the distribution of patients into the different health states and the rate of VOCs in each state were assumed to be constant over time within the crizanlizumab and SoC arms. This implicitly assumed a constant lifetime treatment effect for crizanlizumab while on treatment.

The company assumed that patients who discontinued crizanlizumab were subject to a continuing treatment effect for two additional years. This was based on data from the follow-up trial SUCCESSOR, in which 15 patients that had completed the high-dose crizanlizumab treatment arm experienced a mean annualised VOC rate in the year post trial completion, similar to the SUSTAIN trial (2.7 versus 2.89). In the company's base-case it was assumed that the additional two years of treatment effect applied to all patients who discontinued treatment, including the 32.8% of patients who discontinued treatment in the first model cycle.

The ERG is concerned that no data was available on the long-term efficacy of crizanlizumab beyond one year of treatment and yet the base-case assumed a lifetime treatment effect. The company indicated in their response to the clarification letter that this assumption has also not been clinically validated.[20] In the absence of data the ERG has not changed this in the base-case but the impact on results, as observed in the ERG scenarios, is large when assuming shorter durations of treatment efficacy.

In their response to the clarification letter, the company indicated two years of treatment effect post-discontinuation to be "the likely *maximum* periods to observe *any* benefits" (italics added).[20] The ERG therefore suspected that assuming two years of post-discontinuation treatment effect would overestimate the actual treatment benefit and reduced the post-discontinuation benefit to one year in the

ERG base-case, to reflect the data available from SUCCESSOR. Given that the SUCCESSOR study provided data only for patients who finished one year of treatment, the ERG deemed it more appropriate to allocate the additional post-discontinuation treatment effect only to patients who finished the first cycle.

The ERG questions the appropriateness of using the patient characteristics in the HES database to link VOC state outcomes for the population in the SUSTAIN trial to mortality and complications, due to the large differences between the two patient populations in terms of VOC state distribution. The ERG would have liked to use the patient characteristics from the SUSTAIN trial (age, gender) in its base-case, in order to better reflect the patient population likely to receive crizanlizumab in clinical practice. However, the ERG did not feel confident that using the HRs (used to estimate mortality and complications based on mean annualised VOC rate) that were estimated from the HES data set, with a different mean age and gender distribution, would be appropriate to apply.

The company declined to include grade 3 and 4 AEs observed in the SUSTAIN trial in the model as they assumed that given the similar overall incidence of AEs across the treatment arms, this would not have a large impact on costs. The ERG would argue that different AEs can have very different impacts on costs and QALYs and therefore AEs should have been included for completeness. However, they do agree that in this case they are unlikely to be the driver of results.

The company did not provide utility estimates from the SUSTAIN trial, arguing that limitations of the SUSTAIN trial with regards to the collection of HRQoL data (e.g. HRQoL collected at fixed timepoints which may or may not have corresponded to the occurrence of a VOC) and the limited duration of the trial, led to their decision to derive utility values from published studies. The impact of frequent VOC events is captured within the health state utility values used for each VOC state, onto which an additional per event utility decrement is applied for each individual VOC event. The company utilised health state utility values derived from an unpublished analysis of the LEGACY registry data. The per event utility decrements were derived from the published study by Anie et al. 2012.[56] The ERG raised their concerns regarding choice of applying the LEGACY health state utility values which differ per VOC health state in addition to the per event decrement for individual VOC events and conducted several additional scenario analyses to explore the influence of changing modelling assumptions for utilities on the cost-effectiveness results. These scenarios showed that the utilities values used have a substantial effect on the ICER and are a driver of results.

Costs were generally implemented appropriately in the model, although the ERG did request several small corrections at clarification. For the yearly administration cost for crizanlizumab and for the acquisition cost of crizanlizumab, the company provided an adapted version of the electronic model aligning the two calculations, which deviated in the original submission. Further, the company provided on option in the model to include administration cost for the additional dose of crizanlizumab in the first year, which was originally omitted. This option was included in the base-case analysis by the ERG. The company did not include costs for materials such as syringe and sodium chloride/dextrose used for the administration of crizanlizumab arguing that these costs would be negligible and not impact cost effectiveness outcomes. The ERG concludes that for completeness all material cost should be included. Furthermore, the company did not include staff cost for the monitoring for HC/HU arguing that the same costs would be applied to the same proportion of patients in each treatment arm in the model. Considering the same argument could be made for the other monitoring resources included in the electronic model, the ERG concludes that for completeness all monitoring cost should be included. The ERG did not include these in their ERG given time constraints and the likely small impact on results.

The company base-case results indicated that, compared to SoC, crizanlizumab generates an additional [redacted] QALYs, at an additional cost of [redacted] when including the agreed PAS for crizanlizumab. This results in an ICER of £329,868.32 per QALY gained which is substantially higher than the standard STA NICE threshold range of £20,000-30,000 per QALY gained. The probabilistic base-case resulted in an ICER of £370,699 and indicated that at a threshold of £30,000, crizanlizumab has less than [redacted]%. probability of being cost effective. The company DSA and scenario analyses showed that assumptions surrounding patient weight, utilities and post-discontinuation compliance had the largest impact on results, out of those parameters and assumptions tested.

The ERG made several changes to the company base-case including assuming the patient weight and HC/HU usage from the SUSTAIN trial, assuming only one year post-discontinuation efficacy for crizanlizumab only in patients who completed one year of treatment, applying the compliance rates to crizanlizumab administration costs, costing the additional dose of crizanlizumab in the first year and including VOC state proportions and mean number of VOCs in the PSA while correcting the Dirichlet calculation for the distribution of patients. These changes indicated that crizanlizumab generated an additional [redacted] QALYs at an additional cost of [redacted], resulting in an ERG base-case ICER of £693,689 per QALY gained. The ERG probabilistic analysis suggested that a WTP thresholds of £20,000 and £30,000, the probability that crizanlizumab is cost effective remains at [redacted]%. The ERG changes which had the largest impact on results were assuming the HC/HU usage and patient weight from the SUSTAIN trial. The ERG scenarios showed that the assumptions which had the largest impact on results were assumptions surrounding the long-term efficacy of crizanlizumab, HC/HU usage, utilities and patient characteristics. These represent substantial areas of uncertainty in the submission which should be further addressed before any firm conclusions on cost effectiveness can be made.

8. End of life

In the CS, the company did not include any statement regarding crizanlizumab meeting the end of life criteria defined by NICE.[1, 43]

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