EUnetHTA Joint Action 3 WP4

Relative effectiveness assessment of pharmaceutical technologies

CRIZANLIZUMAB FOR THE PREVENTION OF RECURRENT VASO-OCCLUSIVE CRISES IN SICKLE CELL DISEASE PATIENTS AGED 16 YEARS AND OLDER

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Conflicts of interest

All authors, co-authors, dedicated reviewers, observers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflicts of interest were evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse event
ACS	Acute chest syndrome
ARR	Absolute risk reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
BPI	Brief Pain Inventory
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CRC	Central review committee
CSR	Clinical study report
CTD	Common technical document
DOI	Declaration of interest
ECA	EUnetHTA Confidentiality Arrangement
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUnetHTA	European Network of Health Technology Assessment
GCP	Good clinical practice
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
Hb	Haemoglobin
HbF	Foetal haemoglobin
HbS	Haemoglobin S (sickle haemoglobin)
HbSC	Heterozygous sickle cell/haemoglobin C disease
HbSS	Homozygous sickle cell disease (sickle cell anaemia)
HbSβ0	Heterozygous sickle cell/β^0-thalassemia disease
HbSβ+	Heterozygous sickle cell/β^+-thalassemia disease
HL	Hodges-Lehmann
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
HTAi	Health Technology Assessment international
HU/HC	Hydroxyurea/hydroxycarbamide
ICD	International Classification of Diseases
ITT	Intention-to-treat
MAH	Market Authorisation Holder
MD	Mean difference
MeSH	Medical Subject Headings
Mg/kg	Milligrams per kilogram
NA	Not applicable
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PK/PD	Pharmacokinetics/pharmacodynamics
PP	Per protocol
QoL	Quality of life
RCT	Randomised controlled trial
REA	Relative effectiveness assessment
RR	Relative risk/risk ratio

SAE	Serious adverse event
SCD	Sickle cell disease
SD	Standard deviation
SF-36	36-Item Short Form Health Survey
SLR	Systematic literature review
SMD	Standardised mean difference
SmPC	Summary of product characteristics
SOP	Standard operating procedure
VOC	Vaso-occlusive crisis
WP4	Work Package 4

EXECUTIVE SUMMARY OF THE ASSESSMENT OF CRIZANLIZUMAB

Introduction

Sickle cell disease (SCD) describes a group of inherited blood disorders that affect the structure of haemoglobin in red blood cells. The main clinical features of SCD include painful vaso-occlusive crises (VOCs), organ damage, and varying degrees of anaemia and related symptoms. SCD genotypes include HbSS, HbSC, HbSβ^0-thalassemia, HbSβ^+-thalassemia, and others.

The clinical manifestations of SCD are heterogeneous, with unpredictable frequency and severity of vaso-occlusive pain episodes. Given this clinical heterogeneity, the management of SCD can be complex and includes preventing and treating its acute and/or chronic complications. The only approved therapy in Europe for the prevention of (recurrent) VOCs is hydroxyurea, also called hydroxycarbamide (abbreviated to HU/HC). Chronic blood transfusions are indicated and administered in more exceptional circumstances, such as when the frequency of VOCs is extremely high despite the use of HU/HC or for the (secondary) prevention of severe complications such as acute chest syndrome (ACS) or stroke.

Crizanlizumab (Adakveo®) is a selective humanised IgG2 kappa monoclonal antibody that binds to its target P-selectin with high affinity, thereby blocking interactions between P-selectin and its ligands. The binding of crizanlizumab to P-selectin inhibits the P-selectin-mediated cellular adhesive interactions that play a key role in the pathogenesis of vaso-occlusion and subsequent VOCs.

On 23rd July 2020, the Committee for Medicinal Products for Human Use (CHMP) gave a positive opinion recommending a conditional marketing authorisation for crizanlizumab for the following indication: "Adakveo® is indicated for the prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and older. It can be given as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate."

Objective and scope

The aim of this assessment is to compare the clinical effectiveness and safety of crizanlizumab in SCD patients with relevant comparator(s). The scope of the assessment is presented in Table 0.1. Scope of the assessmentTable 0.1.

Table 0.1. Scope of the assessment

Description	Assessment scope
PICO	Research question: What is the relative effectiveness and safety of crizanlizumab, added to standard of care with or without HU/HC, in SCD patients aged 16 years and older?
Population	Patients aged 16 years and over with SCD and recurrent VOCs
Intervention	Crizanlizumab (added to standard care, including HU/HC and/or best supportive care)
Comparison	1. HU/HC plus best supportive care 2. Best supportive care
Outcomes	**Clinical effectiveness** • Mortality • Annualised rate of VOCs leading to a healthcare visit or hospitalisation* • Time to first VOC* • Percentage of patients without VOC events* • Health-related quality of life* • Annualised rate of days hospitalised* **Safety** • Overall adverse events • Treatment-related severe adverse events* • Discontinuations due to treatment-related adverse events* • Fatal adverse events*

* Outcomes with an asterisk (*) were directly or indirectly mentioned by patient organisations to be of particular importance for SCD patients.
Abbreviations: HU/HC=hydroxyurea/hydroxycarbamide; VOC=vaso-occlusive crisis.

Methods

The present assessment was primarily based on the data and analyses included in the Submission Dossier prepared by the Marketing Authorisation Holder (MAH; Novartis). As part of the assessment, the completeness of the data and analyses in the Submission Dossier was verified. Additionally, the data analysis and synthesis methods applied by the MAH were checked against the requirements for the Submission Dossier and applicable EUnetHTA guidelines (https://www.eunethta.eu/methodologyguidelines/) and assessed with regard to scientific validity.

The Submission Dossier submitted by the MAH included a systematic literature review (SLR) to identify studies on crizanlizumab in four bibliographic databases: Embase, MEDLINE, Cochrane [Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL)], and the Database of Abstracts of Reviews of Effects (DARE). The original search was performed on the 13th August 2019 and was updated on the 27th January 2020. The search was complemented with searches of the ClinicalTrials.gov registry of clinical trials and manual searches of the abstracts from prominent haematology conferences that took place between 2017 and 2019. Search terms related to crizanlizumab and SCD were used, and these were combined with validated study design search filters to identify randomised controlled trials (RCTs) and observational studies. Exclusion criteria were age below 16 years, studies of non-human subjects, and study designs other than RCTs and observational studies. The information specialist critically assessed the methodology and replicability of the submitted information retrieval and verified completeness of the search in study registries.

Information used to assess the clinical effectiveness and safety of crizanlizumab was extracted from the core Submission Dossier and verified against the Common Technical Document (CTD) and other original documentation provided in the Submission Dossier (NB: the MAH did not submit the full Clinical Study Report, only the CTD). Supplementary analyses requested by the CHMP and presented in the European Public Assessment Report were used to evaluate the clinical effectiveness and safety of crizanlizumab[1].

The revised Cochrane risk-of-bias tool for randomised trials (RoB 2) quality rating tool was used to assess the risk of bias in randomised trials for each relevant endpoint. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework was used to rate the certainty of evidence for each outcome.

An open call for patient input was published on 27th September 2019. The French Federation for Sickle Cell Disease and Thalassemia (France) and Sickle Cell and Thalassaemia Ireland (Republic of Ireland) provided their perspectives on the impact of SCD, patient-relevant outcomes, and current treatment options. The outcomes used in the PICO were all mentioned directly or indirectly by the two patient organisations, underscoring the clinical relevance of the outcomes included.

Results

SLR

The information specialist concluded that the SLR was overall well constructed and complete, such that the risk of missing relevant studies was low. Since the final search conducted by the MAH was in January 2020, the information specialist conducted a supplementary search on crizanlizumab, which revealed no additional studies.

Study selection

The MAH deemed two studies relevant for the assessment of crizanlizumab: the SUSTAIN study and the SOLACE-adults study. The SUSTAIN trial was the primary source of evidence for this assessment since it complied with the entire PICO. The SOLACE-adults study is an ongoing, open-label pharmacokinetics/pharmacodynamics (PK/PD) study evaluating the safety of crizanlizumab. Since SOLACE-adults makes no comparison with standard of care, this study could not inform the relative effectiveness assessment of crizanlizumab. Nevertheless, since the SOLACE-adults study collected data on safety outcomes and investigated the to-be commercialised formulation of crizanlizumab (SEG101 rather than SelG1, which was used in SUSTAIN), the safety results from SOLACE-adults are

included in Appendix 5: Safety pool analysis including SOLACE-adults (supportive evidence) to assess comparability of the two crizanlizumab formulations.

SUSTAIN study

SUSTAIN (A2201) was a randomised, double-blind, placebo-controlled, multi-centre phase II trial to determine the efficacy and safety of crizanlizumab in patients with SCD aged 16 to 65 years experiencing recurrent VOCs. Patients were randomised in a 1:1:1 ratio to 5 mg/kg crizanlizumab (high dose), 2.5 mg/kg crizanlizumab (low dose), or placebo. Patients were stratified by concomitant HU/HC use (yes vs no) and by the number of VOCs in the last year (2-4 vs 5-10). Patients receiving HU/HC must have been prescribed HU/HC for the preceding six months and be dose-stabilised for at least three months. The primary outcome was the annualised rate of VOCs, and the key secondary outcome was the annualised rate of days hospitalised. Other pre-specified outcomes included time to first VOC, health-related quality of life (HRQoL), and adverse events (AEs). The total study duration was 58 weeks (treatment duration 52 weeks).

Statistical analysis of SUSTAIN

The (pre-specified) analyses of the primary outcome (annualised VOC rate) were conducted using Central Review Committee (CRC)-adjudicated data, Wilcoxon's rank-sum test, and simple annualisation for imputation of missing data. The following effect estimates were produced: standard median as well as one- or two-sample Hodges-Lehmann (HL) estimates (with 95% confidence intervals (CI) for the two-sample HL estimate).

The main comparison was the treatment difference between crizanlizumab 5.0 mg/kg, the recommended crizanlizumab dose, versus placebo in addition to standard care with or without HU/HC. The results of crizanlizumab 2.5 mg/kg are not presented in this assessment.

Study results

Three-hundred and twenty-nine patients were screened for eligibility, of whom 198 were included in the study. Of 131 excluded patients, 118 did not meet the eligibility criteria and 13 declined to participate. The median age of the entire study population was 28.0 years (range 16-63 years), and 55.1% were female. The vast majority of patients were black (91.9%) followed by white (4.5%) and other (3.5%). HbSS was the most prevalent genotype (71.2%). Most patients were on HU/HC (62.1%) and had experienced 2-4 VOCs in the previous 12 months (62.6%). Baseline characteristics between patients randomised to crizanlizumab 5.0 mg/kg (n=67) and placebo (n=65) were well balanced. Approximately one-third (69 of 198; 34.8%) of patients discontinued the study prematurely.

Efficacy

Pre-specified analyses

The results of the pre-specified efficacy analyses are shown in Table 0.2.

Table 0.2. Results of the pre-specified analyses of efficacy outcomes

SUSTAIN (A2201)	Crizanlizumab 5.0 mg/kg N=67	Placebo N=65	Treatment difference	*p*-value
Annualised rate of VOCs	Standard median (range): 1.63 (0.0, 24.3)	Standard median (range): 2.98 (0.0, 24.3)	Difference between medians: -45.3% HL median estimate difference (95% CI): -1.01 (-2.00, 0.00), corresponding to an RRR of -28.9%	0.01
Annualised rate of days hospitalised	Standard median (range): 4.00 (0.0, 130.7)	Standard median (range): 6.87 (0.0, 307.4)	Difference between medians: -41.8% HL median estimate difference (95% CI): 0.00 (-4.36, 0.00)	0.45
Time to first VOC	4.07 months	1.38 months	HR (95% CI): 0.50 (0.33, 0.74)	NR
Percentage VOC-free (*post hoc* outcome)	35.8%	16.9%	OR (95% CI): 2.85 (1.24, 6.56)	NR

Source: EPAR of crizanlizumab [1]; SUSTAIN CTD.
Abbreviations: CI=confidence interval; HL=Hodges-Lehmann estimator; HR=hazard ratio; N=number of analysed patients; NR=not reported; OR=odds ratio; RRR=relative risk reduction; VOC=vaso-occlusive crisis.

Subgroup analyses of the annualised rate of VOCs by concomitant HU use (yes vs no), genotype (HbSS vs other), and number of VOCs leading to healthcare visits in the previous 12 months (2-4 vs 5-10 crises) were performed. A statistically significant reduction in the annualised VOC rate was seen in patients not receiving HU/HC and patients with 5-10 VOCs prior to randomisation (Table 0.3). Results should, however, be interpreted with caution, since SUSTAIN was not powered to assess statistical significance in subgroups.

Table 0.3. Subgroup analyses for the primary outcome by concomitant HU/HC use, SCD genotype, and prior VOC frequency

SUSTAIN (A2201)		Crizanlizumab 5.0 mg/kg N=67	Placebo N=65	Treatment difference estimate (HL [95% CI])	*p*-value
HU/HC use, yes	N (%)	42 (62.7%)	40 (61.5%)	-1.01 (-2.44, 0.00)	0.084
	Standard median (range)	2.43 (0.0, 24.3)	3.58 (0.0, 13.5)		
HU/HC use, no	N (%)	25 (37.3%)	25 (38.5%)	-1.02 (-2.00, 0.00)	0.046
	Standard median (range)	1.00 (0.0, 11.8)	2.00 (0.0, 24.3)		
HbSS	N (%)	47 (70.1%)	47 (72.3%)	-1.01 (-2.18, 0.00)	0.060
	Standard median (range)	NR	NR		
Non-HbSS	N (%)	20 (29.9%)	18 (27.7%)	-1.01 (-2.01, 0.00)	0.223
	Standard median (range)	NR	NR		
2-4 VOCs prior to randomisation	N (%)	42 (62.7%)	41 (63.1%)	-0.05 (-1.56, 0.01)	0.279
	Standard median (range)	NR	NR		
5-10 VOCs prior to randomisation	N (%)	25 (37.3%)	24 (36.9%)	-2.74 (-5.00, -0.83)	0.005
	Standard median (range)	NR	NR		

Source: EPAR of crizanlizumab [1]; SUSTAIN CTD.
Abbreviations: CI=confidence interval; HbSS=homozygous sickle cell anaemia; HL=Hodges-Lehmann estimator; HU/HC=hydroxyurea/hydroxycarbamide; N=number of analysed patients; NR=not reported; VOC=vaso-occlusive crisis.

HRQoL did not differ between patients receiving crizanlizumab vs placebo in addition to standard care. There were no statistically significant changes in the 36-Item Short Form Health Survey (SF-36) or in

any domain of the Brief Pain Inventory (BPI) within treatment arms between baseline and later pre-specified study visits or between treatment arms (for results on HRQoL, see the company submission).

Supplementary analyses
Several aspects of the pre-specified analyses raised concerns at the regulatory level:

- *The statistical test used:* the pre-specified analyses showed a significant difference in the primary outcome using the stratified Wilcoxon's rank-sum test, but the CIs of the Hodges-Lehmann (HL) difference between medians of the annual rate of VOCs included 0. Negative binomial regression was deemed a more appropriate analysis, as it is used for count data and does not need a location shift assumption. Furthermore, it creates rate ratios (count divided by exposure) and provides effect estimates and CIs that can easily be interpreted;

- *The imputation method for handling missing data:* simple annualisation, as performed in the pre-specified analyses, assumed that the VOC remained constant despite the fact that patients stopped taking crizanlizumab. It was unclear if discontinuations occurred independently of disease status or the received treatment. The MAH provided several supportive analyses of the primary endpoint using different imputation methods. However, none of these imputation methods were considered conservative enough by the CHMP. The CHMP considered an analysis based on a "jump to reference" imputation for all subjects who discontinued in the intervention group and a "missing at random" assumption in the placebo group most appropriate because reliable reasons for discontinuation were difficult to ascertain. All outcomes were recalculated using this imputation method (M6);

- *The adjudication of VOC events:* VOCs were adjudicated both by the trial investigators and by an independent CRC consisting of three haematologists. Usually, a blinded adjudication by an independent review committee is preferred, since it minimises the risk of bias in the outcome assessment. However, in the SUSTAIN trial, Good Clinical Practice (GCP) inspectors did not recommend accepting CRC-adjudicated data due to many uncertainties. The most notable uncertainty related to the two-week rule, in which VOCs occurring within 14 days were not counted as separate events. This rule was not mentioned in the study protocol, and it was unclear if it was applied during the entire study. The CHMP requested supplementary analyses using the investigator-adjudicated data;

- *The exclusion of outlier patients:* one patient (subject ID 124-002) had 37 crises over six months. This would suggest more chronic pain with 'flares' and not separate acute VOCs. This patient drove the disconcordance between independently-adjudicated VOC and investigator-adjudicated VOC data. The CHMP agreed that patient 124-002 should be excluded when using the investigator-adjudicated data.

Results for all outcomes were recalculated using negative binomial regression, imputation method M6, and investigator-adjudicated VOC data without patient 124-002 (Table 0.4). Based on these supplementary analyses, there was no statistically significant difference between crizanlizumab and placebo in the annualised VOC rate (primary outcome) nor in the annualised rate of days hospitalised (key secondary outcome). The time to experience the first VOC after randomisation remained statistically significantly longer in the crizanlizumab group than the placebo group. The percentage of patients free from VOCs (*post hoc* endpoint) did not reach statistical significance.

Table 0.4. Supplementary analyses of all outcomes using negative binomial regression, imputation method M6, and investigator-adjudicated VOC data (with patient 124-002 excluded)

SUSTAIN (A2201)	Crizanlizumab 5.0 mg/kg N=66	Placebo N=65	Difference between means	Treatment difference estimate (active vs placebo)
Annualised rate of VOCs	Mean (±SD) 3.62 (4.12)	Mean (±SD) 4.95 (5.29)	-26.9%	Rate ratio 0.74 (95% CI 0.52, 1.06)
Annualised rate of days hospitalised	Mean (±SD) 18.24 (31.78)	Mean (±SD) 24.53 (46.80)	-34.0%	Rate ratio 0.77 (95% CI 0.40, 1.51)
Time to first VOC	3.78 months	1.15 months	+2.63	HR 0.54 (95% CI 0.36, 0.81)
Percentage VOC-free (*post hoc* outcome)	13 (20%)	5 (8%)	+12%	OR 3.05 (95% CI 1.00, 9.25)

Source: EPAR of crizanlizumab[1]; SUSTAIN CTD.
Abbreviations: CI=confidence interval; HL=Hodges-Lehmann estimator; HR=hazard ratio; N=number of analysed patients; OR=odds ratio; SD=standard deviation; VOC=vaso-occlusive crisis; vs=versus.

Since the supplementary analyses were based on the appropriate statistical test, calculated with the most appropriate imputation method, and used the more reliable investigator-adjudicated data, these results were used to rate the quality of evidence using GRADE. The summary of findings is presented in Table 0.4. The certainty of the efficacy outcomes varied between low and very low (annualised rate of days hospitalised) due to a serious risk of bias (large attrition, selection of reported results) and imprecision (crossing one default clinical relevance boundary or, in the case of very low evidence, crossing both default clinical relevance boundaries).

Safety

Treatment-emergent adverse events (AEs) were mostly balanced between treatment groups. Gastrointestinal disorders, musculoskeletal and connective tissue disorders, and general disorders such as pyrexia were more common in crizanlizumab-treated patients. However, the majority of AEs were mild and resolved by the end of the study. Similar safety profiles were observed for patients with concomitant HU/HC use and patients not taking HU/HC.

Post hoc calculations showed no statistically significant differences in overall AEs (risk ratio (RR) 0.97 [95% CI 0.85, 1.11]), treatment-related grade ≥3 AEs (RR 1.23 [95% CI 0.30, 4.40], discontinuation due to adverse events (RR 0.64 [95 CI 0.11, 3.69]), or fatal adverse events (RR 0.98 [95% CI 0.14, 6.68]) between the two treatment arms. The certainty of the safety outcomes varied between moderate (overall AEs) and very low (for other safety outcomes).

Discussion

Several limitations were identified regarding the evidence on the relative effectiveness and safety of crizanlizumab. The evidence consisted of one relatively small phase II study. Only 67 patients received crizanlizumab at the correct dose. Due to the high dropout rate of 35%, the question of whether the study was sufficiently powered to detect differences in efficacy and safety between the treatment arms arose.

The approved indication of crizanlizumab states that crizanlizumab can be added to standard care with or without HU/HC. Whilst chronic blood transfusions were an exclusion criterion in the SUSTAIN trial, they may be considered part of standard care for a small subpopulation of patients in whom HU/HC is inappropriate or inadequate. The comparator arm in the trial, which served as a proxy for standard care, did not capture the efficacy of chronic blood transfusions that may be received by this subpopulation.

Analysing data on VOC frequency using a different statistical method and imputation method for handling missing data produced different results and sometimes different conclusions (i.e., statistically significant results lost significance). This lack of consistency in the results between the pre-specified and the supplementary analyses lowers confidence that crizanlizumab has a robust treatment effect.

In the absence of a well-defined minimal clinically important difference in VOC rate, it is unclear when a reduction in VOCs is perceived as clinically relevant. This makes the estimated treatment effect of crizanlizumab difficult to interpret.

The primary outcome included only VOCs that led to a healthcare visit or hospitalisation. VOCs managed at home were not counted. VOCs managed at home are not necessarily less severe than those managed in hospital. Other reasons mentioned for not seeking medical support included a previous poor experience in hospital and the perception that medical professionals do not understand SCD. The lack of information on the total rate of VOCs is therefore an important limitation of the SUSTAIN trial.

The SUSTAIN trial only lasted for 58 weeks. Therefore, the trial design did not allow for the evaluation of differences in mortality or SCD-related complications between treatment arms. The upcoming STAND trial (to complete in 2027) has a follow-up duration of five years and might provide further insights into the long-term efficacy and safety outcomes associated with the continuous use of crizanlizumab.

Conclusions

Based on the randomised, double-blind, placebo-controlled phase II SUSTAIN trial, crizanlizumab showed to statistically significantly reduce the annualised rate of VOCs (primary outcome) compared to placebo in addition to best supportive care with or without HU/HC treatment. The annualised rate of days hospitalised did not differ between both treatment arms but the time to first VOC was statistically significantly longer with crizanlizumab compared to placebo. The percentage of patients VOC-event free (*post-hoc* endpoint) was higher in patients treated with crizanlizumab compared to those on placebo.

Supplementary analyses based on the appropriate statistical test, calculated with a more appropriate imputation method, and using the more reliable investigator-adjudicated data showed, however, no statistically significant difference in the annualised rate of VOCs (primary outcome) between crizanlizumab and placebo.

There were no differences in quality of life within the arms at different timepoints or between the treatment arms. The addition of crizanlizumab to standard care did not result in more overall AEs, treatment-related grade ≥3 AEs, discontinuations due to AEs, or fatal AEs (*post hoc* calculations). Due to the duration of the trial, differences in long-term outcomes, such as mortality or severe complications such as ACS, could not be detected.

A major limitation of the current assessment was the large dropout rate, which led to an increased risk of bias and a lack of statistical power. Further, different statistical analyses and imputation methods produced different results, thereby calling the robustness of the treatment effect of crizanlizumab into question. In the absence of a well-defined minimal clinically important difference in VOC rate, it is unclear when a reduction in VOCs is perceived as clinically relevant. This makes the estimated treatment effect of crizanlizumab difficult to interpret. It remains unclear if crizanlizumab lowers mortality and SCD-related complications in the longer term, since the study lasted only 58 weeks.

Table 0.5. Summary of findings of crizanlizumab (based on supplementary analyses requested by the CHMP)

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with crizanlizumab			
Annualised rate of VOC leading to healthcare visit	**Mean difference: -1.33**		**Rate ratio 0.74 (0.52 to 1.06)** [a]	132 (1 RCT)	⨁⨁◯◯ LOW [b,c]
	Mean (± SD) 4.95 (5.3)	**Mean (± SD) 3.62 (4.1)**			
Annualised rate of days hospitalised	**Mean difference: -6.29 days**		**Rate ratio 0.77 (0.40 to 1.51)** [a]	132 (1 RCT)	⨁◯◯◯ VERY LOW [d,e]
	Mean (± SD) 24.53 (46.80)	**Mean (± SD) 18.24 (31.78)**			
Time to first VOC leading to healthcare visits	**Difference in time: +2.63 months**		**HR 0.54 (0.36 to 0.81)** [a]	132 (1 RCT)	⨁⨁◯◯ LOW [b,c]
	3.78 months	1.15 months			
Quality of life	-	-	**Not estimable**	(1 RCT)	⨁⨁◯◯ LOW [d,f,g]
Patients free of VOC events (*post hoc outcome*)	77 per 1.000	**203 per 1.000 (77 to 435)**	**OR 3.05 (1.00 to 9.25)** [a]	132 (1 RCT)	⨁⨁◯◯ LOW [d,h]
Overall AEs [i]	887 per 1.000	**860 per 1.000 (754 to 985)**	**RR 0.97 (0.85 to 1.11)**	128 (1 RCT)	⨁⨁⨁◯ MODERATE [d]
Treatment-related grade ≥3 AEs [i]	48 per 1.000	**60 per 1.000 (15 to 213)**	**RR 1.23 (0.30 to 4.40)**	128 (1 RCT)	⨁◯◯◯ VERY LOW [d,e]
Discontinuations due to AEs [i]	48 per 1.000	**31 per 1.000 (5 to 179)**	**RR 0.64 (0.11 to 3.69)**	128 (1 RCT)	⨁◯◯◯ VERY LOW [d,e]
Fatal AEs [i]	31 per 1.000	**31 per 1.000 (4 to 209)**	**RR 0.98 (0.14 to 6.68)**	131 (1 RCT)	⨁◯◯◯ VERY LOW [d,e]

Notes:

[a] Based on the requested supplementary analyses by the CHMP (i.e., negative binomial regression, imputation method M6, investigator-adjudicated, exclusion of one patient who had >10 VOCs prior to randomisation), since these were deemed more appropriate analyses/ways to handle missing data. Further, the ratios are easier to interpret than the Hodges-Lehmann estimate calculated by the MAH.

[b] Serious risk of bias due to missing outcome data (35% dropout rate) and risk of bias in selection of the result (many different analyses – not all prespecified – with different results).

[c] Confidence interval crosses the default clinical relevance boundary of rate ratio/risk ratio 0.75 on one side.

[d] Serious risk of bias due to missing outcome data.

[e] Confidence interval crosses both default clinical relevance boundaries (rate ratio/risk ratio 0.75 and 1.25).

[f] Quality of life measures were completed at pre-set timepoints. Since VOCs can happen at any time, the questionnaire might not have captured potential changes in pain during a VOC in the crizanlizumab arm vs the placebo arm. Nevertheless, the overall quality of life of SCD patients is equally important, and this showed no changes based on the questionnaires. Therefore, we do not downgrade for indirectness.

[g] It is not possible to make any judgements on imprecision due to the lack of an aggregated end result. Since it would be undesirable to 'reward' this, we downgraded by one level.

[h] Confidence interval crosses the default clinical relevance boundary of rate ratio/risk ratio 1.25 on one side.

[i] Risk ratios and accompanying confidence intervals calculated *post hoc* by the Authoring Team.

Abbreviations: AE=adverse event; CI=confidence interval; HR=hazard ratio; HU/HC=hydroxyurea/hydroxycarbamide; OR=odds ratio; RCT=randomised controlled trial; RR=risk ratio; SD=standard deviation; VOC=vaso-occlusive crisis.

1 BACKGROUND

1.1 Overview of the disease or health condition

1.1.1 Pathophysiology

Sickle cell disease (SCD) is a collective term describing several hereditary genetic abnormalities affecting the structure of haemoglobin (Hb) and belonging to a group of red blood cell (RBC) disorders called haemoglobinopathies. The most common and severe genotype is homozygous sickle cell anaemia (HbSS). Other genotypes result from inheritance of the sickle cell gene in compound heterozygosity with other mutant beta globin genes, leading to disorders such as sickle cell/haemoglobin C (HbSC) disease and sickle cell beta thalassemia ($HbS\beta^0$ or $HbS\beta^+$) [2].

Clinically, SCD is characterised by the acute and unpredictable occurrence of vaso-occlusive pain crises (VOCs). VOCs are multifactorial. Abnormal haemoglobin S (HbS) is less soluble than normal Hb and prone to polymerisation upon deoxygenation, causing RBCs to become rigid, sticky, and change from being disc- to crescent-shaped (like a “sickle”) [3]. These sickled RBCs cause vaso-occlusion by interacting with other blood cells, plasma factors, and through abnormal endothelial interactions. As a result of vaso-occlusion and the presence of multi-cellular aggregates, insufficient oxygen is delivered to the surrounding tissues, resulting in ischaemic injuries, tissue damage, and inflammation [4]. This combination of hypoxia/reperfusion injury, ischaemic tissue damage, and inflammation makes SCD pain unique. Vaso-occlusion can occur throughout the entire vascular system and, as such, it has the potential to cause multi-organ damage and a range of acute and chronic complications [2]. The polymerization of deoxy-HbS is a primary determinant of SCD severity and is affected by factors such as the presence of other Hb mutations as well as the concentration of foetal Hb (HbF).

Other pathophysiological processes typical for SCD are haemolytic anaemia caused by rapid metabolism of deformed RBCs, endothelial dysfunction, activated inflammatory and coagulation systems, reperfusion-related damage, and low bioavailability of nitric oxide.

1.1.2 Clinical manifestations

The clinical presentation of SCD is highly heterogeneous. In more severe cases, symptoms can start in the first months of life when foetal haemoglobin (HbF) is replaced by defective HbS instead of transitioning to normal Hb.

In general, individuals with sickle cell anaemia (homozygous HbSS) and $HbS\beta^0$ have more severe manifestations and shorter lifespans than those with HbSC disease or $HbS\beta^+$. This clinical heterogeneity is influenced by other genes (i.e., HbF gene modulation), the environment, and psychosocial factors, which shape its phenotypes [5].

SCD is characterised by intermittent, acute, and unpredictable VOCs and chronic haemolytic anaemia [4, 6]. VOCs can be triggered by inflammation, cold, stress, increased blood viscosity, decreased blood flow, haemolysis, or adhesion of sickled RBCs to endothelial cells, platelets, and other factors. VOCs cause ischaemic injury to the supplied organ(s) and resultant excruciating pain. Any organ can be affected including the bones, lungs (acute chest syndrome; ACS), brain (stroke), finger/toes (dactylitis), spleen, liver, kidneys, penis (priapism), and joints. Dactylitis is often the earliest manifestation of SCD. Splenic infarction leads to functional hyposplenism early in life, which in turn increases the risk of bacterial infections. ACS and stroke are major causes of mortality in SCD patients. Chronic haemolysis can result in varying degrees of anaemia, jaundice, cholelithiasis, and delayed growth and sexual maturation.

VOCs are related to health-related quality of life (QoL), morbidity, and mortality. The higher the number of VOCs, the worse the patient’s QoL [7, 8]. Over time, VOCs cause increased organ and tissue damage and increase the likelihood of severe complications such as stroke, organ failure, and ACS, potentially leading to early death [9-12].

The survival rate of patients with SCD has improved over the last few decades, mainly due to preventative measures such as newborn screening, immunisations, antibiotics, patient and parent education, hydroxyurea (also called hydroxycarbamide, abbreviated to HU/HC) use, and more rapid prevention and

treatment of severe complications. Nevertheless, SCD patients still have a substantially higher morbidity and mortality rate than those without SCD (average life expectancy 42-53 years for men and 48-58 years for women [10, 13-15].

1.1.3 Prevalence and incidence

SCD is the most common haemoglobinopathy, with an approximate incidence of 300,000 new cases each year and millions of patients affected globally [4, 16]. SCD predominantly occurs in individuals of African descent but is also prevalent in individuals originating from the Eastern Mediterranean, Middle East, India, the Caribbean, and South and Central America. SCD is considered a rare disease, affecting ~2.6 in 10,000 people in the European Union (EU) [17]. This is equivalent to approximately 94,000 people based on 447.7 million EU inhabitants in 2020 [18], and similar to the estimated 100,000 individuals with SCD in the United States [19]. The prevalence of SCD is steadily rising in many European countries, mainly due to migration [20].

However, no data were found on the incidence of SCD in Europe. A lack of accurate global data regarding the epidemiology of SCD in Europe hampers the calculation of the real burden of the disease within the EU.

1.2 Current clinical practice

The only pharmacological treatment in Europe for the prevention of VOCs is HU/HC. Since the 1980s, HU/HC has been used off-label but, more recently, different oral dosage preparations have been registered in Europe (Siklos® tablets in 2007 [21]; Xromi® oral solution in 2018 [22]). HU/HC has been shown to reduce the frequency of VOCs by almost 50% [23]. Based on multiple European guidelines, HU/HC is the first choice treatment for most SCD patients experiencing multiple VOCs in a year (Appendix 1: Guidelines for diagnosis and management). Figure 1.1 shows the current treatment pathway for SCD patients based on European guidelines.

Whilst HU/HC has clinically significantly benefitted patients with SCD, its use can be limited for different reasons including contraindications (hypersensitivity to the active substance, severe hepatic or renal impairment, concomitantly administered antiretroviral medicines, and pregnancy and breastfeeding); side-effects (e.g., leg ulcers, cutaneous vasculitis); important toxicities (toxic ranges of myelosuppression); a requirement for blood monitoring; limited efficacy; and poor patient adherence [24, 25].

Therefore, not all eligible SCD patients receive HU/HC, are willing to take it, or are able to tolerate it. In some European countries, registered HU/HC products are not reimbursed. Also, some patients continue to experience acute VOCs despite HU/HC treatment. For these patients, best supportive care is the most common alternative treatment option. Best supportive care includes the treatment of VOC-related symptoms with pain management (non-steroidal anti-inflammatory drugs, opioids, and other analgesics) and other supportive care such as hydration with intravenous fluids, oxygen therapy, and/or acute blood transfusions) [26-30]. Other preventative measures include keeping warm; maintaining hydration; avoiding climate extremes, physical exhaustion, and high altitude; and also immunisations, penicillin prophylaxis, folic acid supplementation, and iron chelation therapy for those with iron overload [26-30].

Several guidelines recommend chronic blood transfusions as a preventative measure in patients experiencing frequent VOCs despite HU/HC treatment or who are at high risk of stroke or recurrent ACS [27, 28, 31]. Chronic blood transfusions are received by only a small proportion of SCD patients, mostly young children.

1.2.1 Other treatment options

The only potential cure for SCD is haematopoietic stem cell transplantation (HSCT) after a myeloablative conditioning regimen. HSCT is primarily limited to children and adolescents with a matched sibling donor. This means that only a minority of SCD patients are eligible due to a lack of suitable donors and concerns about the risks of this procedure [27, 28, 32].

Acute blood transfusions are not used to prevent VOCs but to treat severe anaemia (top-up transfusion) or for the treatment of complicated VOCs such as ACS, stroke, multi-organ failure, and liver crises (exchange transfusion) [26-30].

Investigative agents assessed in clinical trials include L-glutamine (Xyndari®) and voxelotor (Oxbryta®) as well as gene therapies such as lentiglobin [33]. A marketing authorisation application for L-glutamine (Xyndari®) to the European Medicines Agency (EMA) was withdrawn in September 2019 following a negative opinion from the CHMP. Voxelotor and lentiglobin have not yet received marketing authorisation from the EMA for patients with SCD.

The chronic nature of SCD means that families must invest time for regular medical appointments, imposing a large burden on both patients and their families. Patients describe stigma attached to seeking pain relief in hospital (particularly with opioids) and poor experiences in hospitals, providing additional and unwanted barriers to patients receiving the medical support they need [34].

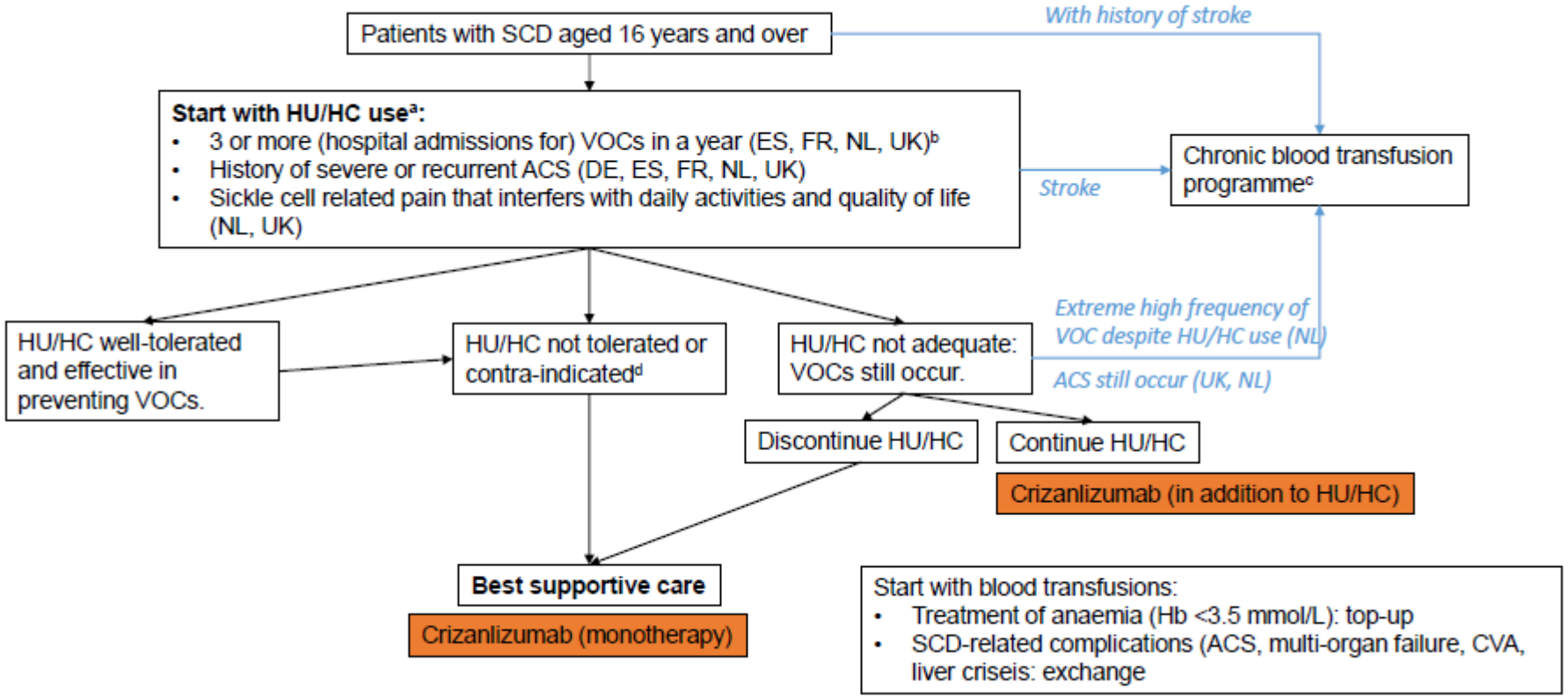

Figure 1.1 Care pathway for SCD patients with recurrent VOCs: positioning of crizanlizumab according to its registered indication

Source: Designed by the Authoring Team.
[a] Registered HU/HC products are not reimbursed in all European countries. European SCD patients may not all have access to HU/HC treatment.
[b] The German guideline states that every SCD patient should be treated with HU/HC after experiencing one (mild) VOC.
[c] For patients who have experienced a stroke: if transfusions are not possible or not acceptable (e.g., due to allo-immunisation) to patients, HU/HC and hematopoietic stem cell transplantation (for children only) can be considered for the secondary prevention of strokes.
[d] This includes side-effects, toxicities, and contra-indications such as pregnancy and breastfeeding; non-adherence to contraception; and difficulties with frequent monitoring.
Abbreviations: ACS=acute chest syndrome; CVA=cerebrovascular accident; DE=Germany; ES=Spain; FR=France; Hb=haemoglobin; HU/HC=hydroxyurea/hydroxycarbamide; NL=Netherlands; SCD=sickle cell disease; UK=United Kingdom; VOC=vaso-occlusive crisis.

1.3 Features of the intervention

Crizanlizumab is a selective IgG2 kappa humanised monoclonal antibody that binds with high affinity to P-selectin, an adhesion molecule expressed on activated endothelial cells and platelets. Crizanlizumab blocks interactions between P-selectin and its ligands including P-selectin glycoprotein ligand 1. P-selectin-mediated multi-cellular adhesion is a key factor in the pathogenesis of vaso-occlusion. By blocking P-selectin-mediated interactions between endothelial cells, platelets, RBCs, and leukocytes, crizanlizumab prevents vaso-occlusion and the occurrence of VOCs [35].

Crizanlizumab is indicated for the prevention of recurrent VOCs in SCD patients aged 16 years and older. Crizanlizumab can be given as an add-on therapy to HU/HC or as monotherapy in patients for whom HU/HC is inappropriate or inadequate. Figure 1.1 depicts the positioning of crizanlizumab according to the registered indication. Best supportive care with or without HU/HC represents the comparator of interest for this assessment. Thus, HU/HC is described as a potential component of the current standard of care as well as a potential component of the new therapeutic strategy [35, 36].

As HU/HC is a major component of the current treatment strategy for VOC prevention, we choose to include it as a comparator in Table 1.1 and Table 1.2.

Table 1.1. Features of crizanlizumab and HU/HC

Non-proprietary name	**Crizanlizumab**	**HU/HC**	
Proprietary name	Adakveo®	Siklos®	Xromi®
Registered EMA indication	Prevention of recurrent vaso-occlusive crises in patients with SCD aged 16 years and older. It can be given as an add on therapy to HU/HC or as monotherapy in patients for whom HU/HC is inappropriate or inadequate	Prevention of recurrent painful vaso-occlusive crises including ACS in adults, adolescents, and children older than two years of age suffering from symptomatic sickle cell syndrome	Prevention of vaso-occlusive complications of SCD in patients over two years of age
Prospective Marketing Authorisation Holder	Novartis Europharm Ltd	Addmedica	Nova Laboratories Ireland Limited
Contra-indications	Hypersensitivity to the active substance or to any of the excipients (Sucrose, Sodium citrate (E331), Citric acid (E330), Polysorbate 80 (E433), water for injections) Hypersensitivity to Chinese hamster ovary (CHO) cell products	Hypersensitivity to the active substance or to any of the excipients Severe hepatic impairment (Child-Pugh classification C) Severe renal impairment (creatinine clearance <30 ml/min) Toxic ranges of myelosuppression as described in SmPC Section 4.2 [25] Breastfeeding	Hypersensitivity to the active substance or to any of the excipients Severe hepatic impairment (Child-Pugh classification C) Severe renal impairment (creatinine clearance <30 ml/min) Toxic ranges of myelosuppression as described in SmPC Section 4.2 [24] Breastfeeding Pregnancy Concomitant anti-retroviral medicinal products for HIV disease
Drug class	Selective IgG2 kappa humanised monoclonal antibody	Antimetabolite	Antimetabolite
Active substance(s)	Crizanlizumab	Hydroxycarbamide	Hydroxycarbamide

Non-proprietary name	Crizanlizumab	HU/HC	
Proprietary name	Adakveo®	Siklos®	Xromi®
Pharmaceutical formulation(s)	Concentrate for solution for infusion (sterile concentrate), to be administered by intravenous infusion	Film-coated tablet	Oral solution
ATC code	B06AX01	L01XX05	L01XX05
In vitro diagnostics required	Not applicable	Not applicable	Not applicable
Monitoring required	Patients should be monitored for signs and symptoms of infusion-related reactions, which may include fever, chills, nausea, vomiting, fatigue, dizziness, pruritus, urticaria, sweating, shortness of breath, or wheezing. In the event of a severe reaction, crizanlizumab should be discontinued and appropriate therapy should be instituted Healthcare professionals are encouraged to report all pregnancy cases and complications during pregnancy (from 105 days prior to the last menstrual period onward) to the local representative of the MAH, in order to allow monitoring of these patients through the PRegnancy outcomes Intensive Monitoring programme (PRIM).	Treatment with Siklos® requires close clinical monitoring. The haematological status of the patient, as well as renal and hepatic functions, should be determined prior to and repeatedly during treatment. During treatment with Siklos®, blood counts must be monitored every two weeks at treatment initiation (i.e., for the first two months) and if the daily dose of hydroxycarbamide is up to 35 mg/kg body weight. Patients who are stable on lower doses should be monitored every two months	The complete status of the blood including bone marrow examination, if indicated, as well as kidney function and liver function should be determined prior to and repeatedly during treatment. Continuous follow-up of the growth of treated children and adolescents is recommended The full blood cell count with white cell differential, reticulate count, and platelet count should be monitored regularly (i.e., every two weeks for the first two months following treatment initiation and every 2-3 months once a maximum tolerated dose is established)
Orphan designation	Yes, orphan designation was granted by the EMA for humanised monoclonal antibodies against P-selectin for the treatment of SCD in August 2012 (EU/3/12/1034)	This product was originally designated an orphan medicine, but 10-year market exclusivity ended in July 2017. Therefore, it is no longer eligible for benefits arising from the orphan designation	No
ATMP	No	No	No

Source: Submission Dossier, SmPC of Adakveo®, SmPC of Siklos®, and SmPC of Xromi®.
Abbreviations: ATC=Anatomical; Therapeutic Chemical Classification System; ATMP=Advanced therapy medicinal products; EMA=European Medicines Agency; HU/HC=hydroxyurea/hydroxycarbamide; mg/kg =milligrams per kilogram; SCD-sickle cell disease; SmPC=summary of product characteristics; ml/min=millilitres per minute.

Table 1.2. Administration and dosing of the technology (crizanlizumab) and HU/HC

Non-proprietary name	Crizanlizumab	HU/HC	
Proprietary name	Adakveo®	Siklos®	Xromi®
Method of administration	Intravenous Crizanlizumab should be diluted with sodium chloride 9 mg/ml (0.9%) or dextrose 5% before administration and administered through a sterile non-pyrogenic 0.2 micron in-line filter by IV infusion over a period of 30 minutes. It must not be administered by IV push or bolus	Oral Conforming to the individual dose, half or quarter of the tablet should be taken once daily, preferably in the morning before breakfast and, where necessary, with a glass of water or a very small amount of food	Oral Two dosing syringes are provided for accurate measurement of the prescribed dose. It may be taken with or after meals at any time of the day, but patients should standardise the method of administration and time of day. Water should be taken after each dose
Doses	The posology should be based on the patient's body weight. The recommended dose of crizanlizumab is 5 mg/kg administered by IV infusion over a period of 30 minutes	The posology should be based on the patient's body weight. The starting dose of hydroxycarbamide is 15 mg/kg/day and the usual dose is between 10 and 30 mg/kg/day	The posology should be based on the patient's body weight. The starting dose of hydroxycarbamide is 15 mg/kg/day and the usual maintenance dose is between 20 and 25 mg/kg/day
Dosing frequency	The recommended dosing frequency is administration at week 0, week 2, and every 4 weeks thereafter	Once daily	Once daily
Standard length of a course of treatment	Crizanlizumab is a continuous therapy. Treatment is to be continued until the patient is no longer deemed to derive benefit or is no longer able to tolerate treatment	It is currently unknown how long patients should be treated with Siklos®. The duration of treatment is the responsibility of the treating physician and should be based on the clinical and haematological status of the individual patient	A clinical response to treatment with hydroxycarbamide may take 3-6 months and, therefore, a six-month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure (whether due to lack of adherence or failure to respond to therapy)
Standard interval between courses of treatments	Not applicable. Crizanlizumab is to be taken continuously at the recommended dosing frequency	Not applicable	Not applicable
Standard number of repeat courses of treatments	Not applicable. Crizanlizumab is to be taken continuously at the recommended dosing frequency	Not applicable	Not applicable

Non-proprietary name	Crizanlizumab	HU/HC	
Proprietary name	Adakveo®	Siklos®	Xromi®
Dose adjustments	Crizanlizumab must be dosed on the basis of body weight (5 mg/kg per administration). No dose adjustment is recommended	In case of non-response, the daily dose may be increased by steps of 2.5 to 5 mg/kg/day. Under exceptional circumstances, a maximum dose of 35 mg/kg/day might be justified. In the event a patient does still not respond when treated with the maximum dose (35 mg/kg/day) over three to six months, permanent discontinuation of Siklos® should be considered If blood counts are within the toxic range, Siklos® should be temporarily discontinued until blood counts recover. Treatment may then be reinstituted at a reduced dose	If dose escalation is warranted based on clinical and laboratory findings, the following steps should be taken: 1) dose to be increased by 5 mg/kg/day every 8 weeks; 2) increases in dose to be continued until mild myelosuppression is achieved, up to a maximum of 35 mg/kg/day. Full blood cell count with white cell differential and reticulocyte count to be monitored at least every four weeks when adjusting dosage A clinical response to treatment with hydroxycarbamide may take 3-6 months, therefore, a 6-month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure If neutropenia or thrombocytopenia occurs, hydroxycarbamide dosing should be temporarily discontinued. When blood counts have recovered, hydroxycarbamide should be reinstated at a dose 5 mg/kg/day lower than the dose given before onset of cytopenia

Source: Submission Dossier, SmPC of Adakveo®, SmPC of Siklos®, and SmPC of Xromi®.
Abbreviations: HU/HC=hydroxyurea/hydroxycarbamide; IV=intravenous; mg/kg/day=milligrams per kilogram per day.

2 OBJECTIVE AND SCOPE

The aim of this EUnetHTA Joint Relative Effectiveness Assessment is to compare the clinical effectiveness and safety of crizanlizumab in the target patient population(s) with relevant comparator(s). The target patient population and relevant comparators (based on the requirements of EUnetHTA Partners) are defined in the project scope below.

The assessment was based on the Submission Dossier submitted by the MAH (Novartis). The scope of the assessment is overall in line with the scope described in the project plan (Table 2.1).

Table 2.1. Scope of the assessment

Description	Assessment scope
PICO	Research question: What is the relative effectiveness and safety of crizanlizumab, added to standard of care with or without HU/HC, in SCD patients aged 16 years and older?
Population	Patients aged 16 years and over with SCD and recurrent VOCs
Intervention	Crizanlizumab (added to standard care, including HU/HC and/or best supportive care)
Comparison	1. HU/HC plus best supportive care 2. Best supportive care
Outcomes	**Clinical effectiveness** • Mortality • Annualised rate of VOCs leading to a healthcare visit or hospitalisation* • Time to first VOC* • Percentage of patients without VOC events* • Health-related quality of life* • Annualised rate of days hospitalised* **Safety** • Overall adverse events • Treatment-related severe adverse events* • Discontinuations due to treatment-related adverse events* • Fatal adverse events*

* Outcomes with an asterisk (*) were directly or indirectly mentioned by patient organisations to be of particular importance for SCD patients.
Abbreviations: HU/HC=hydroxyurea/hydroxycarbamide; VOC=vaso-occlusive crisis.

3 METHODS

The assessment was based on the data and analyses included in the Submission Dossier prepared by the MAH. During the assessment, the completeness of data and analyses in the Submission Dossier was verified. Furthermore, the data analysis and synthesis methods applied by the MAH were checked against the requirements of the Submission Dossier and applicable EUnetHTA Guidelines and assessed with regard to scientific validity.

3.1 Information retrieval

The evidence base with regard to the drug under assessment provided by the MAH was reviewed by the information specialist. The information specialist checked:

- for the presence of deviations between the MAH's methods and requirements for information retrieval in the Submission Dossier and the project plan;
- whether the MAH's search strategies contained errors or were incomplete.

The information specialist conducted supplementary searches in case of incompleteness of the study pool.

Table 3.1 provides a summary of the systematic literature review (SLR) and study selection by the MAH.

Table 3.1. Summary of information retrieval and study selection by the MAH

Elements	Details
List of studies submitted by MAH	In total, across the original SLR and the SLR update, 57 publications reporting 25 unique studies were included in the SLR. These included: • 13 publications (two studies) investigating crizanlizumab • 20 publications (nine studies) on HU/HC • 7 publications (seven studies) on HSCT • 2 publications (two studies) on blood transfusion • 5 publications (two studies) on L-glutamine • 5 publications (two studies) on voxelotor • 5 publications of a retrospective cohort study of patients from the SUSTAIN trial, in which no patients actually received crizanlizumab The Submission Dossier of the MAH only focused on the SUSTAIN trial (efficacy and safety) and the SOLACE-adults trial (safety)
Databases and trial registries searched	The following databases were searched: • MEDLINE • Embase • Cochrane Database of Systematic Reviews (CDSR) • Cochrane Controlled Register of Trials (CENTRAL) • Database of Abstracts of Reviews of Effects (DARE) The following major haematology conferences from 2017 to 2019 were hand-searched: • American Society of Hematology (ASH) Annual Meeting • Annual Congress of the European Haematology Association • Annual Symposium of the Foundation for Sickle Cell Disease Research • BSH Annual Scientific Meeting The SLR update also involved searching meetings of conferences that had taken place since completion of the original SLR, namely the 2019 ASH Annual Meeting (December 2019), which was searched in January 2020 The exclusion of abstracts from conferences prior to 2017 was justified under the assumption that high-quality research would since have been published in a peer-reviewed journal Additional supplementary searches included: • ClinicalTrials.gov website

Elements	Details
	• Bibliographies of any relevant SLRs and (network) meta-analyses identified during the course of both the original SLR and the SLR update
Search date	13th August 2019 (original SLR) and 27th January 2020 (SLR update)
Keywords	See Submission Dossier for exact search terms per interface
Inclusion criteria	**Population:** Patients ≥16 years with SCD **Intervention:** • Crizanlizumab with or without HU/HC • The following interventions reflecting supportive care or established clinical management without crizanlizumab: HU/HC, blood transfusions, HSCT, L-glutamine and voxelotor (also known as GBT440 and GBT-440) **Comparison:** Any or none (i.e., no restrictions regarding comparators for the eligible interventions were applied) **Outcomes:** Including but not limited to: • Sickle cell crises (number of events/rate of events/time to event) • Hospitalisations (number of events/rate of events/days spent) • Annual rate of acute chest syndrome • Non-fatal stroke • Mortality • Safety/AEs of treatment • Any HRQoL scales including but not limited to SF-36, HaemoQoL-A, EQ-5D, or the Brief Pain Inventory **Study designs:** 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 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
Exclusion criteria	**Population:** Population did not include patients ≥16 years with SCD **Intervention:** Studies not investigating a relevant intervention specifically for the prevention of VOCs **Comparison:** Not applicable **Outcomes:** • Studies not reporting any listed outcomes of relevance • Studies reporting relevant outcomes but in groups of a mixed population without reporting data specifically for the patient group of interest **Study designs:** 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
Date restrictions	For conference meetings: from 2017 to 2019
Other search limits or restrictions	• Studies on human subjects only • No language limits

Source: Submission Dossier.
Abbreviations: AE=adverse event; HRQoL=health-related quality of life; HSCT=haematopoietic stem cell transplantation; HU/HC=hydroxyurea/hydroxycarbamide; RCT=randomised controlled trial; SCD=sickle cell disease; SF-36=36-Item Short Form Health Survey; SLR=systematic literature review; VOC=vaso-occlusive crisis.

The study pool of the assessment was compiled on the basis of the following information:

Company sources in the Submission Dossier:

- Study list of MAH on crizanlizumab (status: 27th January 2020);
- Bibliographical databases (last search on 14th February 2020);
- Trials registries (last search on 14th February 2020).

Further supplementary searches were conducted by the information specialist to check for possible incompleteness of the study pool:

- Search in Medline, EMBASE, and Cochrane for studies on crizanlizumab between February and August (for complete search strategy, see Section 4.1).

3.2 Data extraction

Information used to assess clinical effectiveness and safety were extracted from the Submission Dossier and verified against the Clinical Technical Document (CTD) or other original documentation provided in the Submission Dossier (NB: the MAH did not submit the full Clinical Study Report, only the CTD).

3.3 Risk of bias assessment

The revised Cochrane risk-of-bias tool for randomised trials (RoB 2) quality rating tool (August 2019 version) was used to assess the risk of bias in randomised trials. Risk of bias at outcome level was assessed for the following five different domains to produce an overall risk of bias:

- Risk of bias arising from the randomisation process;
- Risk of bias due to deviations from the intended interventions;
- Missing outcome data;
- Risk of bias in measurement of the outcome;
- Risk of bias in selection of the reported result.

For each domain, two independent assessors judged the risk of bias ('low risk', 'some concerns', 'high risk', or 'unclear') on the basis of the information retrieved from the full-text publications, the protocols, and the Submission Dossier.

3.4 External validity

The external validity of the trial included was assessed using EUnetHTA guidelines on the applicability of evidence in the context of a REA of pharmaceuticals considering the following elements: population, intervention, comparator, outcomes, and setting [38].

3.5 Results and analyses of included studies

The information in the Submission Dossier on the study design, study methods, populations, endpoints (patient relevance, validity, and operationalisation) and study results were evaluated. The results of this evaluation are presented and were used to identify relevant analyses and considered for the conclusions of the assessment report.

3.5.1 Statistical methods

Pre-specified statistical analyses used for assessing the treatment effect of crizanlizumab are described in Section 4.6.

3.5.2 Subgroup analysis and other effect modifiers

During the assessment, subgroup analyses examining potential effect modifiers were presented in the Submission Dossier. The evaluation also includes the justification for the choice of cut-offs if quantitative characteristics were categorised.

The following pre-specified subgroups were considered relevant for the analysis: concomitant HU use (yes vs no), genotype (HbSS vs other), and number of VOCs in the last 12 months (2-4 vs 5-10 crises) [37].

3.5.3 Supplementary analyses

To evaluate the robustness of the results, supplementary analyses with regard to methodological factors requested by the CHMP and presented in the European Public Assessment Report (EPAR) were performed [1].

Of note, since the supplementary analyses requested by the CHMP were based on the appropriate statistical test, calculated with the most appropriate imputation method, and using the more reliable investigator-adjudicated data, these results were used to rate the quality of evidence using GRADE. See section 4.9.1 for more information.

3.5.4 Certainty of the evidence

The quality of evidence for each outcome across all studies (i.e., the body of evidence for an outcome) was rated according to the factors outlined in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, including the following five criteria that may lead to rating down the quality of evidence of RCTs [37]:

- Study limitations (risk of bias);
- Inconsistency of results;
- Indirectness of evidence;
- Imprecision;
- Publication bias.

Two assessors rated the GRADE criteria independently. Any disagreements were resolved by involving a third assessor.

3.6 Patient involvement

At the start of this Joint Assessment, EUnetHTA conducted an open call for involvement from patient organisations. General questions were asked to elicit patients' views on living with the disease, important outcomes to be considered in this assessment, and expectations about the drug under assessment. European and national patient organisations were asked to provide an organisational perspective on the questions in English. In all parts of the open call, the term patient referred to anyone living with, or who has lived with, the condition for which the new medicine is indicated. The key questions and a summary of the answers are presented in Section 5.

The information gathered from the open call was used to inform the scope of this assessment and in particular the considered outcomes. In the PICO in Table 2.1, the outcomes related to issues particularly emphasised by patient organisation are indicated with an asterisk (*). The vast majority of the outcomes were mentioned directly or indirectly by the patient organisations, ensuring clinical relevancy of the outcomes used in this assessment.

4 RESULTS

4.1 Information retrieval

The MAH provided an SLR conducted on 13th August 2019. The original SLR was updated on 27th January 2020. In total, from the original SLR and its update, 57 publications reporting 25 unique studies were included in the SLR. Of those 25 unique studies, three studies included crizanlizumab as the intervention (SUSTAIN, SOLACE-adults, and SUCCESSOR). The search strategy, PRISMA diagram, and a full list of retrieved publications with reason for exclusion were included in the Submission Dossier.

The PICO selected by the MAH for the SLR (Table 3.1) differed from the PICO proposed in the Project Plan (Table 2.1). Most importantly, the MAH PICO was much more broadly defined and included many interventions such as blood transfusions, HSCT, L-glutamine, and voxelotor. These were not selected in the Project Plan as relevant comparators in the current REA. Whether the comparators were relevant or not, search terms for these comparators were missing in the SLR but the results identified multiple studies for the comparators listed above. Furthermore, the preferred study designs were RCTs and observational studies, but the SLR also focused on, for example, abstracts and clinical trials. Lastly, the population did not focus on patients with *recurrent* VOCs, which was not in line with the registered indication of crizanlizumab.

There were some minor errors identified in the SLR by the information specialist:

- The free text (random$ adj2 (trial or stud$)) was missing with regards to the study design;
- No specific search was conducted in Cochrane and DARE focusing on crizanlizumab;
- In ClinicalTrials.gov, the search was limited to records with study results, which might be arguable since results are not always updated on ClinicalTrials.gov.

Regarding the completeness of the evidence base, any records published from February 2020 could be missing, since the SLR update was conducted in January 2020. An additional search was conducted by the information specialist on the 24th July 2020 using the following search strategy: Crizanlizumab OR SEG101 OR SelG1 OR Adakveo. Results were limited by publication date (in 2020) and by study design (RCT). The MEDLINE, Embase, and Cochrane databases were searched. There were no relevant records.

Finally, there were no additional studies submitted to the regulatory agency and not included in the Submission Dossier.

Overall, the SLR contained only minor flaws and did not miss any relevant studies. The completeness of the study pool is therefore not questioned.

4.2 Studies included in the assessment

Only the SUSTAIN study met the criteria in the PICO (Table 4.1).

Table 4.1. Study pool – list of relevant studies used for the assessment

Study reference/ID	Study category		
	Study for marketing authorisation of the technology under assessment (yes/no)	**Sponsored or third-party study**	**Available documentation**
SUSTAIN (A2201)	Yes[a]	Sponsored by Novartis	European Public Assessment Report [1] Submission Dossier SUSTAIN CTD SUSTAIN study [39, 40]

[a] The SUSTAIN study evaluated the efficacy and safety of SelG1. This will not be the commercialised formulation of crizanlizumab. Nevertheless, the CHMP concluded that SelG1 (SUSTAIN) and the to be commercialised version SEG101 (as assessed in the SOLACE-adults study) are considered comparable with regards to PK/PD characteristics.
Abbreviations: CHMP=Committee for Medicinal Products for Human use; CTD=clinical technical documentation.
Source: EPAR of crizanlizumab [1]; Submission Dossier; SUSTAIN CTD; SUSTAIN study [39, 40].

4.3 Excluded studies

The SOLACE-adults trial was deemed relevant by the MAH for the current assessment and was included in the Submission Dossier. The SOLACE-adults study is an ongoing single-arm, open-label pharmacokinetic/pharmacodynamic (PK/PD) study in SCD patients with a new formulation of crizanlizumab (SEG101) 5.0 mg/kg. The purpose of SOLACE-adults is to characterise the PK and PD of SEG101 at 5 mg/kg and to evaluate the safety and efficacy of SEG101 in SCD patients. To the time of acquisition, all pre-clinical and clinical studies, including SUSTAIN, used the crizanlizumab formulation manufactured by Reprixys (SelG1). Novartis has since continued technical development and production of crizanlizumab under the code SEG101 using an optimised process that leverages Novartis' proprietary Chinese hamster ovary (CHO) cell line in combination with an optimised manufacturing process.

The SOLACE-adults study could not inform the relative effectiveness assessment of crizanlizumab, since there is no comparison made with best supportive care with or without HU/HC. Therefore, we excluded the SOLACE-adults study from the analyses. Nevertheless, the study provides safety information on the to-be commercialised version of crizanlizumab and provides insights into the possible extrapolation of the results from SelG1 to SEG101. Therefore, the results of the safety outcomes from the SOLACE-adults study are presented in Appendix 5: Safety pool analysis including SOLACE-adults (supportive evidence) as supportive evidence.

SUCCESSOR was a retrospective cohort study aiming to evaluate the 52-week post-SUSTAIN occurrence of VOCs after withdrawal of treatment with crizanlizumab. No patient received treatment with crizanlizumab during the SUCCESSOR study period and therefore SUCCESSOR was excluded from the analyses.

An overview of the excluded studies on crizanlizumab is presented in Table 4.2.

Table 4.2. Excluded studies

Study reference/ID	Reason for non-consideration of the study
SOLACE-adults (A2202)	Uses the to-be commercialised version of crizanlizumab (SEG101) but: • Open-label PK/PD study; • No comparator included; • Study is still ongoing. Results on safety outcomes of the SOLACE-adults study are depicted as supportive evidence in Appendix 5: Safety pool analysis including SOLACE-adults (supportive evidence).
SUCCESSOR	None of the patients received treatment with crizanlizumab during the SUCCESSOR study period.

Source: Submission Dossier.
Abbreviations: PK/PD=pharmacokinetic/pharmacodynamics.

4.4 Characteristics of the included studies

SUSTAIN (A2201) was a randomised, double-blind, placebo-controlled, multi-centre phase II trial to determine the efficacy and safety of crizanlizumab in patients with SCD aged 16 to 65 years experiencing recurrent VOCs. The SUSTAIN trial was the primary source of evidence. Table 4.3 and Table 4.4 describe the characteristics of the SUSTAIN trial.

In SUSTAIN (A2201), SCD patients were randomised in a 1:1:1 ratio to 5 mg/kg crizanlizumab (high dose), 2.5 mg/kg crizanlizumab (low dose), or placebo. The study included a screening phase (30 days prior to randomisation), a 52-week treatment phase, and a follow-up evaluation phase of six weeks (a maximum total of 58 weeks). Patients were stratified by concomitant HU use (yes/no) and by the number of VOCs in the year prior to randomisation (2-4 vs 5-10).

Crizanlizumab (5 mg/kg or 2.5 mg/kg) or placebo was administered over a period of 30 minutes by intravenous infusion at day 1, day 15, and every 4 weeks ±3 days through to week 50 (final dose). Patients who participated in all scheduled dosing visits received a total of 14 doses.

Table 4.3. Characteristics of the SUSTAIN study

Study reference/ID	Study design	Patient population	Crizanlizumab (number of randomised patients)	Placebo (number of randomised patients)	Study duration and data cut-off(s)	Primary outcome; patient-relevant secondary outcomes
Direct comparison: crizanlizumab vs placebo (both in addition to standard care including the use of hydroxyurea)						
SUSTAIN (A2201)	Double-blind, randomised (1:1:1), placebo-controlled, multi-centre phase II trial (60 centres; 51 centres in US, eight centres in Brazil, and one centre in Jamaica) Stratification occurred according to the number of crises in the preceding year (2-4 or 5-10) and concomitant HU/HC use (yes or no)	Patients aged 16-65 years with confirmed diagnosis of SCD (including HbSS, HbSC, HbSβ^0-thalassemia or HbSβ^+-thalassemia patients) Patients experienced 2–10 VOCs within the 12 months before enrolment either by patient history or determined by patients' recall Patients receiving HU/HC must have been prescribed HU/HC for the preceding six months and be dose-stabilised for at least three months Key exclusion criteria: - on a chronic blood transfusion programme - planning or undergoing exchange transfusion during study - Hb <4.0 g/L - Planned initiation, termination, or dose alteration of HU/HC during study - Receiving chronic anticoagulation (e.g., warfarin, heparin) other than aspirin	Group 1: Crizanlizumab 5.0 mg/kg (N=67) Group 2: Crizanlizumab 2.5 mg/kg (N=66) As the recommended dose for crizanlizumab is 5 mg/kg, only data from the crizanlizumab 5 mg/kg arm of the SUSTAIN trial is of relevance for this assessment Information from the crizanlizumab 2.5 mg/kg arm is only included where necessary in the context of the overall SUSTAIN trial population	Group 3: Placebo (N = 65)	The trial consisted of a 30-day screening phase, a 52-week treatment phase, and a 6-week follow-up evaluation phase (trial duration: 58 weeks in total) Final analysis (study completed in March 2016)	Primary: Annualised rate of sickle cell-related pain crises Secondary: - annualised rate of days hospitalised - time to first crisis - time to second crises - annualised rate of uncomplicated crises - annualised rate of acute chest syndrome - patient-reported outcomes (SF-36 and BPI) - adverse events (frequency and severity)

Study reference/ID	Study design	Patient population	Crizanlizumab (number of randomised patients)	Placebo (number of randomised patients)	Study duration and data cut-off(s)	Primary outcome; patient-relevant secondary outcomes
		- History of stroke within past two years Full list of inclusion and exclusion criteria is presented in the European Public Assessment Report of crizanlizumab [1]				

Source: EPAR of crizanlizumab [1]; Submission Dossier; SUSTAIN CTD.
Abbreviations: BPI=Brief Pain Inventory; Hb=haemoglobin; HU/HC=hydroxyurea/hydroxycarbamide; N=number of participants; SF36=36-Item Short Form Health Survey; US: United States; VOC: vaso-occlusive crises.

Table 4.4. Characterisation of the interventions and comparators

Study reference / ID	Crizanlizumab	Placebo	Additional information
SUSTAIN (A2201)	Group 1: 5.0 mg/kg IV Group 2: 2.5 mg/kg IV	Group 3: placebo (IV; 0.9% sodium chloride solution in 100 ml infusion bottle or bag)	Concomitant medications that are consistent with standard of care for patients with SCD were allowed, including acute blood transfusions. Most frequently reported concomitant medications included HU/HC, folic acid, and medications for pain relief such NSAIDs and opioids. In patients not on HU/HC, HU/HC treatment was not to be initiated throughout the 52-week study treatment period. If a physician deemed it medically necessary to initiate, terminate, or alter HU/HC treatment in a patient during the course of the study, the medical monitor was to be notified

Source: SUSTAIN CTD.
Abbreviations: HU/HC=hydroxyurea/hydroxycarbamide; IV=intravenously; NSAID=non-steroidal anti-inflammatory drugs; SCD=sickle cell disease.

The planned treatment duration of SUSTAIN was 52 weeks. Together with a six-week evaluation phase, the total study duration was 58 weeks (406 days). The mean treatment duration of exposure was approximately 42 weeks in both treatment arms (293.8 days for crizanlizumab 5 mg/kg and 293.3 days for placebo). Table 4.5 shows the treatment duration of the patients in the SUSTAIN study.

Table 4.5. Information on the course of the SUSTAIN study (A2201)

Study population	Crizanlizumab 5 mg/kg	Placebo
ITT population	N=67	N=65
N (%) completed treatment phase	43 (64%)	41 (63%)
Median (min; max)	NR	NR
Mean treatment duration	293.8 days	293.3 days
Safety population[a]	N=66	N=62
Median (min; max)	53.9 weeks (4; 57)	54.0 weeks (4; 58)

Source: Submission Dossier; EPAR of crizanlizumab [1].
[a]Safety population includes all randomised patients who received at least one dose of the study drug.
Abbreviations: ITT=intention-to-treat; max=maximum; min=minimum; N=number of analysed patients; NR=not reported; RCT=randomised controlled trial; SD=standard deviation.

A total of 329 patients were screened for eligibility, of whom 198 were included in the study. Reasons for not being included were 'not meeting eligibility criteria' (n=118; not specified which exclusion criteria) and 'declined to participate' (n=13).

Approximately one third (69 out of 198; 34.8%) of patients discontinued the study prematurely. The main reasons for discontinuation were withdrawal by subject (n=19), lost to follow-up (n=14), and 'other' (n=14) (Table 4.6). The 'other' category included a broad range of reasons, the most frequent being pregnancy (two patients in the 5 mg/kg arm and one each in the 2.5 mg/kg and placebo arms).

Table 4.6. Discontinuations in the SUSTAIN study

	Treatment arm			
	Crizanlizumab 5 mg/kg n (%)	Crizanlizumab 2.5 mg/kg n (%)	Placebo n (%)	Total n (%)
Patients in the ITT population	**67 (100%)**	**66 (100%)**	**65 (100%)**	**198 (100%)**
Patients in the safety population[a]	66 (98.5%)	64 (97.0%)	62 (95.4%)	192 (97.0%)
Patients who completed study	43 (64.2%)	45 (68.2%)	41 (63.1%)	129 (65.2%)
Patients who discontinued from the study	24 (35.8%)	21 (31.8%)	24 (36.9%)	69 (34.8%)
Primary reason for early discontinuation				
Adverse event	1 (1.5%)	1 (1.5%)	3 (4.6%)	5 (2.5%)
Death	2 (3.0%)	1 (1.5%)	2 (3.1%)	5 (2.5%)
Lost to follow-up	4 (6.0%)	4 (6.1%)	6 (9.2%)	14 (7.1%)
Non-compliance with study	1 (1.5%)	3 (4.5%)	1 (1.5%)	5 (2.5%)
Physician decision	2 (3.0%)	2 (3.0%)	2 (3.1%)	6 (3.0%)
Withdrawal by patient/caregiver/ legal guardian	7 (10.4%)	6 (9.1%)	6 (9.2%)	19 (9.6%)
Lack of efficacy	0	1 (1.5%)	0	1 (0.5%)
Other	7 (10.4%)	3 (4.5%)	4 (6.2%)	14 (7.1%)

[a] The safety population consists of all randomised patients that received at least one dose of study drug.
Abbreviations: ITT=intention-to-treat.

The median age in the total study population was 28.0 years (range 16-63), and 55.1% were female. The vast majority of patients were black (91.9%) followed by white (4.5%) and other (3.5%). HbSS was the most prevalent genotype (71.2%). Furthermore, most patients were on HU/HC treatment (62.1%) and had 2-4 VOCs in the previous 12 months (62.6%). Table 4.7 shows the characteristics of the patients in the included study. Overall, baseline characteristics were well balanced between the treatment arms.

Table 4.7. Baseline characteristics of the SUSTAIN study population (ITT population)

Study reference/ID Characteristics Category	Crizanlizumab 5.0 mg/kg	Crizanlizumab 2.5 mg/kg	Placebo
SUSTAIN (A2201)	N=67	N=66	N=65
Age [years], median (range)	29 (16-63)	29 (17-57)	26 (16-56)
Sex [m], n (%)	32 (48)	30 (45)	27 (42)
Race, n (%)*			
Black	60 (90)	62 (94)	60 (92)
White	4 (6)	2 (3)	3 (5)
Other	3 (4)	2 (3)	2 (3)
Sickle cell disease genotype, n (%)			
HbSS	47 (70)	47 (71)	47 (72)
HbSC	9 (13)	15 (23)	8 (12)
HbSβ^0	3 (5)	2 (3)	7 (11)
HbSβ$^+$	7 (10)	2 (3)	1 (2)
Other	1 (2)	0 (0)	2 (3)
HU/HC use (yes), n (%)	42 (63)	41 (62)	40 (62)
No. of crises in previous 12 months			
2-4	42 (63)	41 (62)	41 (63)
5-10	25 (37)	25 (38)	24 (37)

Source: Submission Dossier.
*A patient could select more than one race.
Abbreviations: HU/HC=hydroxyurea/hydroxycarbamide; ITT=intention-to-treat; m=male; N=number of analysed patients; NR=not reported

Almost all patients used at least one concomitant medication (>95%). An overview of the concomitant medications used in >20% of patients is shown in Appendix 2: Concomitant medications. The most frequently used concomitant medications were folic acid (74.6% in crizanlizumab 5.0 mg/kg; 69.2% in placebo); HU/HC (49.3% in crizanlizumab 5.0 mg/kg; 55.4% in placebo); and morphine (44.8% in crizanlizumab 5.0 mg/kg; 47.7% in placebo). Differences (≥10%, with the placebo arm having higher numbers than the crizanlizumab arm) between the two treatment arms existed for the following medications: heparin (antithrombotic agent), hydromorphone (analgesic), miralax (laxative), ondansetron (antiemetic), and potassium chloride and sodium chloride (mineral supplements). No information was available on the reasons, dosing, or treatment duration of these medications. The number and percentage of patients receiving *ad hoc* transfusions were balanced across crizanlizumab 5 mg/kg (56 transfusions in 25 (37.3%)) patients and placebo (62 transfusions in 26 (40.0%)) patients.

4.5 Outcomes included

Table 4.8 shows the definition and the statistical methodology used for each outcome. Mortality was not formally included as an outcome in the SUSTAIN study.

Table 4.8. Definition and analysis of outcomes included in the assessment

Outcomes	Definition
Efficacy	
Annualised rate of VOCs	The primary outcome in the SUSTAIN trial was the annual rate of VOCs leading to a healthcare visit and was analysed following an intention-to-treat (ITT) principle including all patients who were randomised to treatment. Results are presented as the difference in medians between arms (pre-specified). To account for patients that discontinued the study, simple annualisation of the VOC frequency was performed, calculated as the total number of crises x 365 ÷ (end date − date of randomisation + 1), where the end date was the last dose date + 14 days. A VOC was defined as: • acute episode of pain; • with no medically defined cause other than a vaso-occlusive event; • resulting in a medical facility visit; • treated with oral or parenteral narcotic agents or with a parenteral NSAID. All crisis events identified by investigators were independently adjudicated in parallel by an independent review committee to determine whether reported sickle cell crises met the criteria for the primary efficacy outcome. ACS, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) were considered complicated VOCs. Stroke was not included in this definition. Uncomplicated VOCs leading to healthcare visits were defined as crises other than ACS, hepatic sequestration, splenic sequestration, or priapism.
Annualised rate of days hospitalised	Key secondary outcome of the SUSTAIN study. Defined as days hospitalised. Simple annualisation was used to account for those who discontinued the study, calculated as the total number of days hospitalised × 365 / (end date – date of randomisation + 1), where the end date was the last dose date + 14 days.
Time to first VOC	Defined as months from date of randomisation to first VOC leading to healthcare visit. A patient without VOC leading to healthcare visits before withdrawal or completion of the study was considered censored at the time of the end date.
Percentage of patients without VOCs	To be considered free from VOCs leading to healthcare visits, patients needed to have an annualised rate of VOCs leading to healthcare visits equal to zero, whether or not they completed the entire study.
Health-related quality of life	HRQoL was evaluated in SUSTAIN using the Brief Pain Inventory (BPI) and SF-36 v2.0 questionnaires. Both questionnaires were administered to patients at each treatment visit, i.e., at days 1 and 15, and then every four weeks from week 6 and at week 52 and the week 58 follow-up visit.
Safety	
Overall adverse events	Percentage of patients with adverse events.
Treatment-related severe adverse events	Percentage of patients with treatment-related severe adverse events.
Discontinuations due to treatment-related adverse events	Percentage of patients discontinuing the study due to adverse events related to the treatment.
Fatal adverse events	Number of fatal cases during the study and whether these were treatment-related.

Source: Submission Dossier.
Abbreviations: ACS=acute chest syndrome; BPI=brief pain inventory; NSAID=non-steroidal anti-inflammatory drug; QoL=quality of life; SF-36=36-Item Short Form Health Survey; VOC=vaso-occlusive crisis.

4.6 Statistical methods

In the SUSTAIN study, sample size calculations were performed based on the following assumptions:

- A 40% relative reduction (vs placebo) in the number of VOCs with a mean placebo event rate of 3.0 and standard deviation of 1.7;
- Patients were randomised in a 1:1:1 ratio into high dose, low dose, and placebo, stratified by concomitant usage of HU/HC (yes; no) and by number of prior VOCs (2-4; 5-10) per year.

Based on these assumptions, 50 patients per arm were required for the study to have an approximately 90% power to detect a 40% reduction in VOCs using Wilcoxon's rank-sum test (α=0.05). Assuming a 15% dropout rate, approximately 174 patients needed to be randomised into the SUSTAIN study.

The primary outcome (annualised rate of VOCs leading to a healthcare visit or hospitalisation) served as a gatekeeper for the key secondary endpoint (annualised rate of days hospitalised). The key secondary endpoint was only to be tested if at least one dose was statistically significant in the test of the primary endpoint, and the key secondary endpoint was to be restricted to the doses where the primary endpoint was statistically significant. There were no adjustments for multiplicity for other secondary efficacy analyses.

The pre-specified analyses of the primary outcome were conducted per independent review using Hodges-Lehmann estimates and simple annualisation for imputation of missing data. Annualisation of the observed rate of VOCs to one year was performed to account for early dropouts or lost to follow-up.

4.7 Risk of bias

The risk of bias was assessed in multiple domains for relevant outcomes in the SUSTAIN study. The answers to the questionnaire are presented in Appendix 3: Risk of bias 2.0. Risk of bias was deemed high for all outcomes due to the large attrition ("Missing outcome data"). More than one-third (35%) of participants discontinued prematurely. There was no information on the characteristics, VOC frequency, or prognostic factors of patients that discontinued, so it was not possible to compare discontinuers to patients completing the study. Nevertheless, reasons for discontinuation were mentioned that could relate to a participants' health status or the received treatment such as withdrawal by the patient, the physician's decision, and AEs. Furthermore, the rate of censoring in the time to first VOC event differed between the experimental and the control group. This could be related to the measured outcome: for example, more VOCs led to earlier discontinuation.

Another domain that could have led to biased estimates with regards to VOC-related outcomes was "Risk in the measurement of the outcome". VOCs were adjudicated both by the trial investigators and an independent crisis-review committee consisting of three haematologists. Usually, a blinded adjudication by an independent review committee is preferred, since it minimises the risk of bias in the outcome assessment. However, in the SUSTAIN trial, Good Clinical Practice (GCP) inspectors did not recommend accepting these data due to remaining uncertainties. In particular, a major uncertainty pertains to the 2-week rule (VOCs that occurred within 14 days were not counted as a separate event) as this timeframe was not (pre)defined in the study protocol and it cannot be followed whether it was consistently applied during the entire study. The GCP inspectors consequently recommended use of the investigator-adjudicated data. Analyses using these data were requested as supplementary analyses and are presented below ('Supplementary analyses of efficacy outcomes'). Of note, trial investigators were blinded to the intervention received by the participant.

Finally, the domain 'Risk of bias in selection of the reported result' was indicated as high. Multiple analyses were performed which produced substantially different results. It was unclear which imputation methods were pre-planned and which were *post hoc*. The variety of statistical analyses and imputation methods used producing substantially different results lowered confidence in a robust treatment effect.

4.8 External validity

4.8.1 Population

Almost one third of the screened patients were ineligible for inclusion in the study (118 out of 329). The exact reasons (and their respective proportions) for not being eligible are unclear. The generalisability of the study findings to the general SCD patient population is therefore questionable.

The majority of SUSTAIN patients were of African descent, similar to the European SCD population. [41] Furthermore, most included patients had the HbSS genotype (80%), which is also consistent with the distribution of the different genotypes [20, 28]. HU/HC was used in approximately 60% of the SUSTAIN population. There is not much information on the prevalence of HU/HC use in European SCD patients, although studies report varying percentages ranging from 18% to 39% [42-44]. Only patients with 2-10 VOCs in the previous 12 months were included in SUSTAIN. The CHMP did not recommend extrapolation to the entire SCD patient population, since having >10 VOCs per year is associated with higher P-selectin levels [1].

Patients who were on a chronic transfusion programme were not eligible to participate in the SUSTAIN study. According to the company submission, the rationale behind excluding those patients is the fact that there are only limited relevant data for the efficacy of chronic blood transfusions for the prevention of VOC specifically, a direct comparison of crizanlizumab to a standard of care comprising of regular blood transfusions is therefore not possible. Nonetheless, the comparator arm from the SUSTAIN study does not capture the efficacy of chronic blood transfusion that may be received by a small proportion of SCD patients.

4.8.2 Intervention

In the SUSTAIN study, a different version of crizanlizumab (SelG1) was used than the version that will be commercialised (SEG101). Differences were observed in the PK/PD properties between the two versions (i.e., SEG101 had a greater exposure and inhibition of P-selectin than SelG1). Nevertheless, the differences in P-selectin inhibition were attributed to the different PD assays used. Consequently, results on efficacy and safety with SelG1 can be extrapolated to SEG101 [1]. Additional information on SEG101 will be collected in the ongoing phase III STAND trial, which will be completed in 2027.

In the SUSTAIN study, participants were randomised to two different doses of crizanlizumab (5.0 mg/kg and 2.5 mg/kg). The recommended dose of crizanlizumab is 5.0 mg/kg. Therefore, this assessment focused on the difference in effect size between the crizanlizumab 5.0 mg/kg arm and the placebo arm.

4.8.3 Comparison

Concomitant therapy as part of standard of care was allowed during the SUSTAIN trial. This made the patients more representative of the real-world SCD patient population.

4.8.4 Outcomes

The outcomes were of clinical relevance. However, since the study duration was only one year, which was not completed by over one-third of patients, no robust conclusions on long-term morbidity and mortality can be drawn from the SUSTAIN study.

Stroke was not included as part of the definition of VOC in the SUSTAIN trial. Ischaemic stroke only occurred in one patient in the placebo arm and did not occur at all in the crizanlizumab 5 mg/kg arm (intracranial haemorrhage occurred in one patient in the crizanlizumab 2.5 mg/kg arm). Given the rarity of these events, the inclusion of stroke in the definition of complicated VOCs would be expected to have a minimal impact on the annualised rate of VOCs.

4.8.5 Setting

SUSTAIN was conducted in the US, Brazil, and Jamaica. Although no European citizens were included, the baseline characteristics of the included patients overall seem comparable to European SCD patients.

4.9 Results on clinical effectiveness and safety

Table 4.9 to Table 4.15 summarize the results of the comparison of crizanlizumab (5.0 mg/kg) with best supportive care with or without HU/HC in SCD patients aged 16-65.

4.9.1 Clinical effectiveness

Pre-specified analyses

Annualised rate of VOC leading to a healthcare visit or hospitalisation (primary outcome)
Table 4.9 shows the results of the annualised rate of VOCs leading to a healthcare visit or hospitalisation (primary outcome) for all VOCs and for uncomplicated VOCs. At the end of the treatment phase, the median annualised rate of VOCs leading to healthcare visits in the crizanlizumab 5 mg/kg arm was 1.63 (interquartile range, 0.00–3.97) compared to 2.98 (interquartile range, 1.25–5.87) in the placebo arm (HL median absolute difference of -1.01 [95% CI, -2.00, 0.00]; *p*=0.010).

The median rate of uncomplicated crises per year was 62.9% lower in the crizanlizumab 5 mg/kg arm than in the placebo arm (1.08 vs 2.91; HL median absolute difference of -1.00 [95% CI, -1.98, 0.00]).

Table 4.9. Annualised VOC rate leading to healthcare visit (primary outcome; based on pre-specified analyses)

SUSTAIN (A2201)	Crizanlizumab 5.0 mg/kg N=67	Placebo N=65	Crizanlizumab vs placebo
Overall VOCs			
Standard median (range)	1.63 (0, 24.3)	2.98 (0, 24.3)	Relative risk reduction: -45.3%
Mean (SD)	2.89 (4.20)	4.43 (4.86)	Relative risk reduction: -34.8%
Hodges-Lehmann median annual rate of VOCs	2.00	3.49	HL median estimate difference (95%CI): -1.01 (-2.00, 0.00; *p*=0.01) Relative risk reduction: -28.9% (calculated as median rate difference/rate placebo)
Uncomplicated VOCs[a]			
Standard median (range)	1.08 (0, 3.96)	2.91 (1.0, 5.0)	Relative risk reduction: -62.9%
Mean (SD)	NR	NR	NR
Hodges-Lehmann median annual rate of VOCs	1.97	3.00	HL median estimate difference (95%CI): -1.00 (-1.98, 0.00; p=0.02) Relative risk reduction: -33.3%

Source: EPAR of crizanlizumab [1]; SUSTAIN CTD.
[a] Uncomplicated VOC leading to healthcare visits were defined as crises other than ACS, hepatic sequestration, splenic sequestration or priapism.
Abbreviations: CI=confidence interval; HL= Hodges-Lehmann; n=number of patients with (at least one) event; N=number of analysed patients; NR=not reported; SD=standard deviation; VOC=vaso-occlusive crises; vs=versus.

In Table 4.10, the absolute numbers of VOC events are depicted and are divided into all VOC events, uncomplicated VOCs, and complicated VOCs. The majority of pain crises (~90%) were uncomplicated VOCs.

Table 4.10. Treatment-emergent VOCs[a] (based on the safety population of SUSTAIN)

VOC leading to healthcare visits event	Crizanlizumab, 5 mg/kg N=66		Placebo N=62	
	Patients, N (%)[b]	Events, N[b]	Patients, N (%)[b]	Events, N[b]
Any VOC leading to healthcare visits	48 (72.7)	148	54 (87.1)	202
Uncomplicated VOC leading to healthcare visits	45 (68.2)	129	50 (80.6)	184
ACS	14 (21.2)	18	13 (21.0)	15
Hepatic sequestration	0	0	0	0
Splenic sequestration	0	0	0	0
Priapism	0	0	1 (1.6)	1
Death[c]	1 (1.5)	1	2 (3.2)	2

Source: Submission Dossier.
[a] Treatment-emergent VOCs were defined as all VOCs starting (or increasing in severity) after the date of first dose of study medication. All treatment-emergent VOCs were adjudicated by the independent review committee.
[b] 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.
[c] While death was removed as an VOC event category by Amendment 2 to the Protocol, the independent review committee subsequently indicated that the four events (one in the crizanlizumab 2.5 mg/kg arm; not shown in table) meeting the criteria for VOC should be given the event classification of "death".
Abbreviations: ACS=acute chest syndrome; N=number of patients; VOC=vaso-occlusive crises.

Annualised rate of days hospitalised (key secondary outcome)

Table 4.11 presents the annualised rate of days hospitalised. There was no statistically significant difference in the annualised rate of days hospitalised between crizanlizumab and placebo (4.00 days vs 6.87 days; HL-estimate difference 0.00 [95% CI -4.36, 0.00]; *p*=0.45). Also, the rate of days hospitalised due to VOC (calculated *post hoc*) did not substantially differ between crizanlizumab and placebo.

Table 4.11. Annualised rate of days hospitalised (key secondary outcome; based on pre-specified analyses)

SUSTAIN (A2201)	Crizanlizumab 5.0 mg/kg N=67	Placebo N=65	Crizanlizumab vs placebo
Overall			
Standard median (range)	4.00 (0, 130.7)	6.87 (0, 307.4)	Relative risk reduction of -41.8%
Mean (SD)	16.03 (24.02)	24.97 (50.16)	Relative risk reduction of -35.9%
HL median annualised days hospitalised	12.48	13.00	HL median estimate difference (95%CI): 0.00 (-4.36,0.00; *p*=0.45)
Due to VOC (*post hoc*) [a]			
Standard median (range)	2.01 (0.0, 81.7)	5.03 (0.0, 307.4)	Relative risk reduction of -60.1%
Mean (SD)	12.39 (18.71)	18.64 (44.05)	Relative risk reduction of -33.6%
HL median annualised days hospitalised due to VOC	8.18	7.55	HL median estimate difference (95%CI): 0.00 (-3.00,0.00; *p*=0.72)

Source: EPAR of crizanlizumab [1]; SUSTAIN CTD.
[a] Exploratory outcome, defined as the total number of days with VOC leading to healthcare visits by the patient from randomisation, analysed using the same method for the primary efficacy analysis to determine an annualised rate
Abbreviations: CI=confidence interval; HL=Hodges-Lehmann; N=number of analysed patients; SD=standard deviation; VOC=vaso-occlusive crises; vs=versus.

Time to first VOC (secondary outcome)

The Kaplan-Meier (KM) estimate of the median time from randomisation to first VOC was statistically significantly longer for the 5 mg/kg arm (median time: 4.07 months) compared to the placebo arm (1.38 months), with a hazard ratio of 0.495 (95% CI: 0.331, 0.741; *p*=0.001).

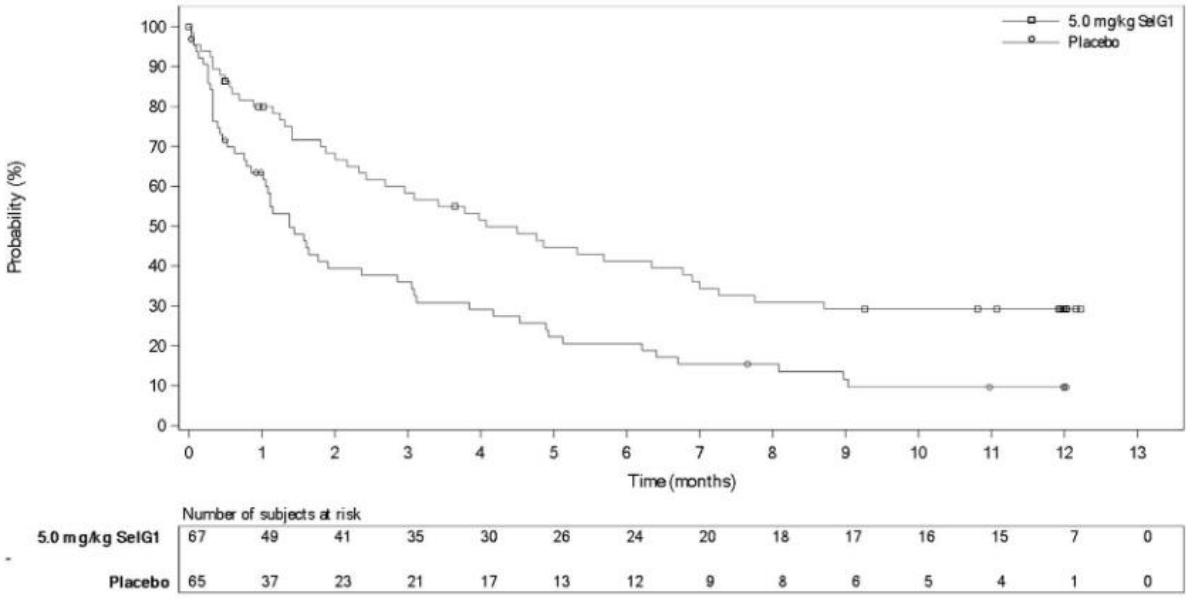

Figure 4.1. Kaplan-Meier curve for time to first VOC (based on pre-specified analyses)

Percentage of patients free of VOCs (*post hoc outcome*)

There was a statistically significant increase in the proportion of patients free from VOC leading to healthcare visits in the crizanlizumab 5 mg/kg arm compared with placebo (Table 4.12).

Table 4.12. Percentage of patients VOC-free (based on pre-specified analyses)

SUSTAIN (A2201)	Crizanlizumab 5.0 mg/kg N=67	Placebo N=65	Crizanlizumab vs placebo
Post-hoc analysis			
n (%)	24 (35.8)	11 (16.9)	OR (95% CI): 2.85 (1.24, 6.56)

Source: EPAR of crizanlizumab [1]; SUSTAIN CTD.
Abbreviations: CI=confidence interval; n=number of patients with (at least one) event; N=number of analysed patients; OR=odds ratio; vs=versus.

Quality of life (secondary outcome)

There were no statistically significant differences in the SF-36 questionnaire or any domain of the BPI *within* treatment arms between baseline and later pre-specified study visits or *between* treatment arms. The results of both QoL measures are shown in the Submission Dossier of crizanlizumab.

Subgroup analyses of efficacy outcomes

Subgroup analyses for the primary outcome based on HU/HC use, genotype, and prior VOC frequency are shown in

Table 4.13. A statistically significantly lower annualised VOC rate was seen in patients not using HU/HC, with 5-10 VOCs prior to the study, treated with crizanlizumab versus placebo. Results should, however, be interpreted with caution, since SUSTAIN was not powered to assess statistical significance in subgroups.

Table 4.13. Subgroup analyses for annualised VOC rate (based on pre-specified analyses)

SUSTAIN (A2201)		Crizanlizumab 5.0 mg/kg N=67	Placebo N=65	Treatment difference estimate (HL [95% CI])	*p*-value
HU/HC use, yes	n (%)	42 (62.7%)	40 (61.5%)	-1.01 (-2.44, 0.00)	0.084
	Standard median (range)	2.43 (0.0, 24.3)	3.58(0.0, 13.5)		
	HL median	2.55	4.00		
HU/HC use, no	n (%)	25 (37.3%)	25 (38.5%)	-1.02 (-2.00, 0.00)	0.046
	Standard median (range)	1.00 (0.0, 11.8)	2.00 (0.0, 24.3)		
	HL median	1.47	2.51		
HbSS	n (%)	47 (70.1%)	47 (72.3%)	-1.01 (-2.18, 0.00)	0.060
	Standard median (range)	NR	NR		
	HL median	2.01	3.73		
Non-HbSS	n (%)	20 (29.9%)	18 (27.7%)	-1.01 (-2.01, 0.00)	0.223
	Standard median (range)	NR	NR		
	HL median	1.99	2.99		
2-4 VOC prior to randomisation	n (%)	42 (62.7%)	41 (63.1%)	-0.05 (-1.56, 0.01)	0.279
	Standard median (range)	NR	NR		
	HL median	1.98	2.12		
5-10 VOC prior to randomisation	n (%)	25 (37.3%)	24 (36.9%)	-2.74 (-5.00, -0.83)	0.005
	Standard median (range)	NR	NR		
	HL median	2.51	6.08		

Source: Submission Dossier.
Abbreviations: CI=confidence interval; HL=Hodges-Lehmann estimator; HU/HC=hydroxyurea/hydroxycarbamide; n=number of patients with (at least one) event; N=number of analysed patients; NR=not reported; VOC=vaso-occlusive crises.

Supplementary analyses of efficacy outcomes

The pre-specified efficacy analyses mentioned above were performed on independent review-adjudicated data using the HL estimator based on Wilcoxon's rank-sum test and simple annualisation for imputation of missing data. The CHMP questioned several aspects of the pre-specified analyses:

- *The choice of statistical test:* the pre-specified analyses showed a significant difference in the primary outcome using a stratified Wilcoxon's rank-sum test (p=0.010), but the CIs of the HL difference between medians of the annualised rate of VOC included 0. This is contradictory. A negative binomial regression was deemed more appropriate, as it is used for count data and does not need a location shift assumption. Furthermore, it creates rate ratios (counts divided by exposure) and provides effect estimates and CIs that can be easily interpreted;
- *The imputation method:* the imputation method for handling missing data: simple annualisation, as performed by the MAH, assumed that the VOC remained constant despite the fact that patients stopped taking crizanlizumab. It is not fully certain that discontinuation occurred independently of the disease status or the treatment. The MAH provided several supportive analyses of the primary endpoint using different imputation methods (M1-4):
    - M1: Imputing the annual rate of VOCs leading to healthcare visits in patients who discontinued early by assessing the mean annual rate of the completers from the same treatment/strata if the patient's own annual rate was less than this mean annual rate of completers and then analyse as for the primary endpoint;

- M2: Same analysis as M1, but in the subset of patients completing the study, discontinuing, or having at least one VOC. Patients early discontinuing before having any VOC were excluded from the analysis;
- M3: For patients who discontinued early without reporting any VOC, multiple imputation of the counts of VOC post-discontinuation was performed based on data from completers/patients with at least one crisis by matching treatment/strata. The annual rate of VOC was then computed based on imputed data and analysed using a negative binomial regression model;
- M4: For patients who discontinued early, imputation was performed according to the "jump to reference" strategy for patients who withdrew for a reason potentially related to treatment in the 5 mg/kg treatment arm or "missing at random" for patients in the placebo arm and patients who withdrew for a reason not potentially related to treatment in the 5 mg/kg arm. Data were analysed using a negative binomial regression model.

None of the imputation methods were considered conservative enough by the CHMP. In M1-3, data were imputed from completers in patients that discontinued the study. However, it could not be assumed that completers were comparable to discontinuers, since completers did not stop taking crizanlizumab. M4 used a conservative method by imputing missing data in those that discontinued using data from the reference (placebo) group. This was only performed in a subset of patients in whom study withdrawal could potentially be linked to the treatment. However, few or no treatment discontinuations might be truly independent from a perceived lack of efficacy or for safety reasons, even if not formally announced by the patient. Therefore, the CHMP requested two additional supplementary analyses (M5 and M6):

- M5: For each patient who did not complete six months of study, whatever treatment arm, the patient's annual rate of VOC was imputed using the patient's annual rate of VOC prior to randomisation. Study duration was imputed to one year. Data were analysed using a negative binomial regression model;
- M6: For patients who discontinued early, the missing period was imputed using a "jump to reference" method for patients in the 5 mg/kg treatment arm and a "missing at random" approach for patients in the placebo arm.

The CHMP considered an analysis based on the "jump to reference" imputation (as is done in M6) for all subjects who discontinued in the treatment group most appropriate, because reliable reasons for discontinuation were difficult to ascertain. Therefore, all outcomes were recalculated using imputation method M6;

- *The adjudication of VOC events*: as previously described, GCP inspectors did not recommend accepting the CRC-adjudicated data due to many uncertainties. The CHMP requested supplementary analyses using the investigator-adjudicated data. Trial investigators were blinded to the treatment received by the patient;
- *The exclusion of outlier patients*: one patient (subject ID 124-002) had 37 crises over six months. This would suggest chronic pain with 'flares' rather than acute VOCs. It also drove the disconcordance between independently adjudicated VOC and investigator-adjudicated VOC data. It was agreed by the CHMP that patient 124-002 should be excluded when using investigator-adjudicated data.

Results of the primary outcome using different imputation methods are shown in Table 4.14.

Table 4.14. Imputation methods of the primary outcome measure (number of VOCs leading to a healthcare visit) based on CRC-adjudicated data

SUSTAIN (A2201)	Crizanlizumab 5.0 mg/kg N=67	Placebo N=65	Difference between medians	Treatment difference estimate	*p*-value
Simple annualisation (pre-specified)[a]	1.63	2.98	-45.3%	HL (95% CI): -1.01 (-2.00, 0.00)	0.010
Simple annualisation[b]	NR	NR	NR	Rate ratio (95% CI): 0.65 (0.47, 0.90)	NR
M1[a]	2.00	3.03	-34.0%	HL (95% CI): -1.28 (-2.08, -0.75)	<0.001
M2[a]	1.99 (n=58)	3.32 (n=59)	-40.1%	HL (95% CI): -1.70 (-2.50, -0.28)	0.004
M3[b]	NR	NR	NR	Rate ratio (95% CI): 0.66 (0.46, 0.96)	NR
M4[b]	NR	NR	NR	Rate ratio (95% CI): 0.67 (0.48, 0.92)	NR
M5[b]	NR	NR	NR	Rate ratio (95% CI): 0.72 (0.54, 0.95)	NR
M6 [b]	NR	NR	NR	Rate ratio (95% CI): 0.74 (0.54, 1.03)	NR

Source: EPAR of crizanlizumab [1]; SUSTAIN CTD.
[a] Using a stratified Wilcoxon's rank-sum test.
[b] Based on a negative binomial regression model.
Abbreviations: CI=confidence interval; CRC=central review committee; HL=Hodges-Lehmann estimator; HR=hazard ratio; N=number of analysed patients; NR=not reported.

Results for all outcomes were recalculated using negative binomial regression, imputation method M6, and investigator-adjudicated VOC data without patient 124-002 (Table 4.15). Since the supplementary analyses were based on the appropriate statistical test, calculated with a more appropriate imputation method, used the more reliable investigator-adjudicated data, and resulted in easily interpretable ratios, these results were used to rate the quality of evidence using GRADE. In the absence of a well-defined minimal clinically important difference in VOC rate, the default clinical relevance boundaries of 0.75 and 1.25 were used [45]. The GRADE evidence profile is presented in Appendix 4: GRADE evidence profile.

Table 4.15. Supplementary analyses of all outcomes using negative binomial regression, imputation method M6, investigator-adjudicated VOC data (with patient 124-002 excluded)

SUSTAIN (A2201)	Crizanlizumab 5.0 mg/kg N=66	Placebo N=65	Difference between means	Treatment difference estimate (active vs placebo)
Annualised rate of VOCs	Mean (SD) 3.62 (4.12)	Mean (SD) 4.95 (5.29)	-26.9%	Rate ratio 0.74 (95% CI 0.52, 1.06)
Annualised rate of uncomplicated VOCs	Mean (SD) 3.39 (3.99)	Mean (SD) 4.79 (5.49)	-28%	Rate ratio 0.72 (95% CI) 0.49, 1.05)
Annualised rate of days hospitalised	Mean (SD) 18.24 (31.78)	Mean (SD) 24.53 (46.80)	-34.0%	Rate ratio 0.77 (95% CI 0.40, 1.51)
Time to first VOC	3.78 months	1.15 months	+2.63	HR 0.54 (95% CI 0.36, 0.81)
Percentage VOC-free (*post hoc* outcome)	13 (20%)	5 (8%)	+12%	OR 3.05 (95% CI 1.00, 9.25)

Source: EPAR of crizanlizumab [1]; SUSTAIN CTD.
Abbreviations: CI=confidence interval; HR=hazard ratio; N=number of analysed patients; OR=odds ratio; SD=standard deviation; VOC=vaso-occlusive crisis; vs=versus.

The supplementary analyses showed no statistically significant difference between crizanlizumab and placebo in the annualised VOC rate (primary outcome). The certainty of the evidence was graded as

low due to a serious risk of bias and serious imprecision of the treatment effect. The annualised rate of days hospitalised (key secondary outcome) was also not statistically significantly different between crizanlizumab and placebo. The certainty of the evidence was graded as very low due to the serious risk of bias and very serious imprecision (crossing both clinical relevance boundaries). The time to experience the first VOC starting from randomisation was statistically significantly longer in the crizanlizumab vs placebo arm. The certainty of the evidence was graded as low due to a serious risk of bias and serious imprecision. The percentage of patients free of VOCs (*post hoc* endpoint) did not reach statistical significance. The certainty of the evidence was graded as low due to a serious risk of bias and serious imprecision in the treatment effect.

Subgroup analyses were not recalculated based on negative binomial regression, imputation method M6, and investigator-adjudicated data (with patient 124-002 excluded). The European Public Assessment Report (EPAR) of crizanlizumab presents subgroup analyses using negative binomial regression, imputation method M6, and CRC-adjudicated data [1]. In these subgroup analyses, patients that did not use HU/HC, had 5-10 crises prior to randomisation, and with the HbSS genotype showed a statistically significant reduction in VOCs in the crizanlizumab arm vs placebo. Again, results should be interpreted with caution, since SUSTAIN was not powered to assess statistical significance in subgroups.

4.9.2 Clinical safety

Table 4.16 summarises the safety results of the comparison between crizanlizumab and best supportive care with or without HU/HC in SCD patients aged 16-65 years (SUSTAIN).

SUSTAIN study

Treatment-emergent AEs were mostly balanced between treatment groups. Gastrointestinal disorders, musculoskeletal and connective tissue disorders, and general disorders like pyrexia were more common in crizanlizumab-treated patients. However, the majority of AEs were mild and resolved by the end of the study. Similar safety profiles were observed with the concomitant use of HU/HC and patients without HU/HC.

Overall AEs
The vast majority of patients experienced at least one AE: 86.4% in the crizanlizumab arm vs 88.7% in the placebo arm. There was no statistically significant difference between the two treatment arms (RR 0.97 [95% CI 0.85,1.11], calculated *post hoc* by the Authoring Team). Certainty of the evidence was downgraded by one level due to a serious risk of bias (moderate). There was no imprecision, since the entire confidence interval was between the default clinical relevance boundaries of RR 0.75 and 1.25.

Treatment-related grade ≥3 AEs
Treatment-related grade ≥3 AEs occurred more often in the crizanlizumab arm than in the placebo arm, albeit not significantly (6.1% vs 4.8%; RR 1.23 [95% CI 0.30, 4.40], calculated *post hoc* by the Authoring Team). The certainty of the evidence was downgraded three times due to the serious risk of bias and very serious imprecision (both RR 0.75 and RR 1.25 crossed). The evidence for the outcome was graded as very low.

Discontinuation due to AEs
Discontinuation due to AEs did not differ between crizanlizumab and placebo (3.0% vs 4.8%, respectively; RR 0.64 [95% CI 0.11, 3.63], calculated *post hoc* by the Authoring Team). The certainty of the evidence was downgraded three times due to the serious risk of bias and very serious imprecision (both RR 0.75 and RR 1.25 crossed). The evidence for the outcome was graded as very low.

Fatal AEs
In total, there were five deaths: two in the crizanlizumab 5.0 mg/kg arm, one in the crizanlizumab 2.5 mg/kg arm, and two in the placebo arm. None of these five deaths had a suspected relationship with the study drug. Fatal AEs did not significantly differ between crizanlizumab and placebo: RR 0.98 (95% CI 0.14, 6.68; calculated *post hoc* by the Authoring Team). The certainty of the evidence for this outcome was graded as very low due to the serious risk of bias and very serious imprecision (wide confidence interval due to rarity of the event).

Comparability with SOLACE-adults

Appendix 5: Safety pool analysis including SOLACE-adults (supportive evidence) shows the safety analysis of the ongoing, observational SOLACE-adults study, which evaluated the to-be commercialised formulation of crizanlizumab (SEG101). Forty-five patients were included, who received SEG101 5.0 mg/kg. Some differences were observed, but this did not raise any concerns at the regulatory level. Overall, the results were comparable between SelG1 and SEG101.

Table 4.16. Adverse events of crizanlizumab vs placebo in SUSTAIN

Study: SUSTAIN (A2201)									
System organ/ class/adverse events	**Frequency (very common, common, uncommon, rare, very rare, not known)**	**All grades**				**Grades ≥3**			
		Crizanlizumab 5 mg/kg (n=66) n (%)	**Placebo (n=62) n (%)**	**Relative** risk **(95% CI)**	**Risk difference (95% CI)**	**Crizanlizumab 5 mg/kg (n=66) n (%)**	**Placebo (n=62) n (%)**	**RR (95% CI)**	**RD (95% CI)**
AEs in the Safety Population									
Patients with ≥ 1 AE	NR	57 (86.4)	55 (88.7)	0.97 (0.85-1.11)	-0.02 (-0.14-0.10)	NR	NR	NA	NA
Total SAEs n (%)	NR	17 (25.8)	17 (27.4)	0.94 (0.53-1.67)	-0.02 (-0.17-0.14)	7 (10.6)	8 (12.9)	0.82 (0.33-2.06)	-0.02 (-0.14-0.09)
SAEs repeated in ≥1 patient									
Pyrexia	NR	2 (3.0)	1 (1.5)	1.88 (0.25-14.16)	0.01 (-0.06-0.09)	NR	NR	NA	NA
Pneumonia		3 (4.5)	3 (4.8)	0.94 (0.22-3.95)	-0.003 (-0.09-0.08)				
ADRs by System Organ Class, n (%)									
Gastrointestinal disorders, n (%)									
Nausea	Very common	12 (18.2)	7 (11.3)	1.61 (0.68-3.83)	0.07 (-0.06-0.20)	NR	NR	NA	NA
Abdominal pain	Common	8 (12.1)	3 (4.8)	2.51 (0.70-9.02)	0.07 (-0.03-0.18)				
Diarrhoea	Common	7 (10.6)	2 (3.2)	3.29 (0.71-15.22)	0.07 (-0.02-0.18)				
Vomiting	Common	5 (7.6)	3 (4.8)	1.57 (0.39-6.28)	0.03 (-0.07-0.12)				
General disorders and administration site conditions, n (%)									
Pyrexia	Very common	7 (10.6)	4 (6.5)	1.64 (0.51-5.34)	0.04 (-0.06-0.15)	NR	NR	NA	NA
Infusion site reaction*	Common	1 (1.5)	1 (1.6)	0.94 (0.06-14.70)	-0.001 (-0.07-0.07)				
Injury, poisoning, and procedural complications, n (%)									

Study: SUSTAIN (A2201)									
System organ/ class/adverse events	**Frequency (very common, common, uncommon, rare, very rare, not known)**	**All grades**				**Grades ≥3**			
		Crizanlizumab 5 mg/kg (n=66) n (%)	**Placebo (n=62) n (%)**	**Relative** risk **(95% CI)**	**Risk difference (95% CI)**	**Crizanlizumab 5 mg/kg (n=66) n (%)**	**Placebo (n=62) n (%)**	**RR (95% CI)**	**RD (95% CI)**
Infusion-related reaction	Common	2 (3.0)	0	NA	NA	NR	NR	NA	NA
Musculoskeletal and connective tissue disorders, n (%)									
Back pain	Very common	10 (15.2)	7 (11.3)	1.34 (0.54-3.31)	0.04 (-0.08-0.16)	NR	NR	NA	NA
Arthralgia	Very common	12 (18.2)	5 (8.1)	2.25 (0.84-6.03)	0.10 (-0.02-0.22)				
Musculoskeletal chest pain	Common	5 (7.6)	0	NA	NA				
Myalgia	Common	5 (7.6)	0	NA	NA				
Respiratory, thoracic and mediastinal disorders, n (%)									
Oropharyngeal pain	Common	4 (6.1)	1 (1.6)	3.76 (0.43-32.70)	0.04 (-0.03-0.13)	NR	NR	NA	NA
Skin and subcutaneous tissue disorders, n (%)									
Pruritus**	Common	5 (7.6)	3 (4.8)	1.57 (0.43-32.70)	0.03 (-0.07-0.12)	NR	NR	NA	NA
Adverse events of special interest (AESI), n (%)									
Infections	NR	35 (53.0)	33 (53.2)	1.0 (0.72-1.38)	0.05 (-0.11-0.20)	5 (7.6)	3 (4.8)	1.57 (0.43-32.70)	0.03 (-0.07-0.12)
Infusion-related reactions – standard search	NR	23 (34.8)	13 (21.0)	1.66 (0.93-2.98)	0.14 (-0.02-0.29)	0	0	NA	NA
Infusion-related reactions – severe reactions search	NR	2 (3.0)	0	NA	NA	0	0	NA	NA
Effect on haemostasis - haemorrhage	NR	11 (16.7)	8 (12.9)	1.29 (0.56-3.00)	0.04 (-0.09-0.16)	1 (1.5)	0	NA	NA

Study: SUSTAIN (A2201)									
System organ/ class/adverse events	**Frequency (very common, common, uncommon, rare, very rare, not known)**	**All grades**				**Grades ≥3**			
		Crizanlizumab 5 mg/kg (n=66) n (%)	**Placebo (n=62) n (%)**	**Relative** risk **(95% CI)**	**Risk difference (95% CI)**	**Crizanlizumab 5 mg/kg (n=66) n (%)**	**Placebo (n=62) n (%)**	**RR (95% CI)**	**RD (95% CI)**
Total deaths n (%)	NR	2 (3.0)	2 (3.2)	0.94 (0.14-6.47)	-0.002 (-0.08-0.08)	2 (3.0)	2 (3.2)	0.94 (0.14-6.47)	-0.002 (-0.08-0.08)
Discontinuation due to AE (%)	NR	2 (3.0)	3 (4.8)	0.63 (0.11-3.62)	-0.02 (-0.11-0.06)	1 (1.5)	2 (3.2)	0.47 (0.06-3.51)	-0.02 (-0.10-0.05)

Source: Submission Dossier; SUSTAIN CTD.
*Infusion site reaction: infusion site extravasation, infusion site pain, and infusion site swelling.
**Pruritus and vulvovaginal pruritus.
Relative risk and risk difference are calculated *post hoc* by the Authoring Team.
Abbreviations: ADR=adverse drug reactions; AEs=adverse events; AESI=adverse events of special interest; CI=confidence interval; MAH=marketing authorisation holder; NA=not applicable; NR=not reported; RD=risk difference; RR=relative risk; SAEs=serious adverse events; SOC=System Organ Class.

5 PATIENT INVOLVEMENT

Two patient organisations provided input in response to the open call for patient input published on 27th September 2019: the French Federation for Sickle Cell Disease and Thalassemia (France) and Sickle Cell and Thalassaemia Ireland (Republic of Ireland). Both patient organisations stressed the fact that the biggest challenge for SCD patients is the unpredictability of VOCs, which can brutally interrupt participation in daily life. Patients often avoid any activities that can lead to a VOC and can find themselves unable to get a proper education or a job. Patients often spend many days in the hospital and depend on caregivers, relatives, and family members. Pain and fatigue also limit social interactions. Although the clinical manifestations of SCD can vary in individuals (mild, moderate, or severe SCD), all patients experience various difficulties at particular stages in their lives.

Both organisations pointed out that the current treatment options (HU/HC, chronic blood transfusions, HSCT) do not completely avoid VOCs. Adherence to therapies and attending regular monitoring visits can often be challenging. Also, among African communities, scientific developments in medications can be seen as causing more damage (i.e., through side-effects), when taking the frequency and long-term use of medications into account.

Regarding expectations for the new drug, the ultimate hope is for a cure or to eliminate the pain entirely. However, the new drug should at least be able to reduce VOCs in a way that can be felt immediately or in the very short term by the patient (e.g., through less pain and fatigue). This could also lead to fewer hospitalisations and admissions to emergency rooms. The side effects of the new drug should be less than experienced with existing drugs.

6 DISCUSSION

Several limitations were identified with regard to the evidence on crizanlizumab:

- Evidence was only available from one relatively small study. Only 67 patients received crizanlizumab at the correct dose. Although the dropout rate of 35% is consistent with another recent placebo-controlled trial in SCD patients [46], the question of whether the study was sufficiently powered to detect differences in efficacy and safety between treatment arms arose. Furthermore, the efficacy and safety of crizanlizumab were tested in a phase II study, which remains an exploratory trial; a phase III study with increased statistical power would be needed to confirm (or dispute) previously drawn conclusions;

- The approved indication of crizanlizumab states that it can be added to standard care with or without HU/HC. Chronic blood transfusions were an exclusion criterion for the SUSTAIN trial, but nevertheless may be considered a part of standard care for a small subpopulation of patients where HU/HC use is inappropriate or inadequate. The comparator arm in the trial, which served as a proxy for standard care, did not capture the efficacy of chronic blood transfusions that may be received by this subpopulation;

- More than a third (131/329) of screened patients did not meet the eligibility criteria of SUSTAIN. The large proportion of patients ineligible for inclusion in the study (and a lack of information about the reasons why) calls into question whether the included study population was representative of the real SCD population;

- Analysing the data in a different way with regard to the statistical and imputation methods produced different results and led to different conclusions (e.g., significant results lost significance). The lack of consistent results reduced confidence that the treatment effect of crizanlizumab was robust;

- The primary outcome included only VOCs that led to a healthcare visit or hospitalisation. VOCs managed at home were not counted. According to the MAH, this was done to increase the objectivity of the primary endpoint, as collection of VOCs leading to a healthcare visit was considered more reliable because of the healthcare visit documentation than the collection of patient reported accounts of VOC they managed at home. Of note, VOCs managed at home are not necessarily less severe than those managed in hospital. Based on the experiences and perceptions of SCD patients, there is also stigma attached to seeking medical support. Reasons for not seeking medical support can include previous poor experiences in hospital, the opinion that medical assistance was not required, and the perception that medical professionals do not understand SCD. It is therefore an important limitation of the SUSTAIN trial that there was no information on the total rate of VOCs. In the ongoing phase III STAND trial, the primary outcome is the annualised rate of VOCs, including VOCs managed at home *or* leading to a healthcare visit or hospitalisation [47];

- It is unclear when a reduction in VOCs is perceived as clinically relevant. This makes the estimated treatment effect of crizanlizumab difficult to interpret. The MAH, in consultation with medical experts, proposed a reduction of 40% in annualised VOC rate compared to placebo. In both the pre-specified analysis (HL treatment estimate difference: -28.9%) and the supplementary analysis (-26.9%), this average reduction of 40% in VOC rate was not reached. The patient organisations mentioned a clinically-relevant effect as one that is felt by the patient immediately or in the very short term, meaning less pain, less fatigue, and more able to participate in daily activities. Quality of life questionnaires, however, did not show overall improvements in pain. Since VOCs are extremely painful and can trigger severe complications such as ACS and stroke, every prevented VOC might be seen as a clinically-relevant effect. Based on the pre-specified analyses, SUSTAIN patients had *on average* an absolute reduction of more than 1 VOC. Using the supplementary analyses requested by the CHMP, no statistically significant reduction in annualised VOC rate was identified when using crizanlizumab compared to placebo;

- The outcomes studied were of clinical relevance and supported by patient organisations. Deaths and the occurrence of other serious complications during the study period were rare, balanced between treatment arms and the assessment that none were considered treatment-related can be followed. However, since the study duration was only one year, the SUSTAIN trial did not capture long-term outcomes to determine the impact of crizanlizumab on mortality and SCD complications such as ACS. There may be a relationship between the frequency of VOCs and the occurrence of these longer-term outcomes, as indicated by additional database analyses presented as part of the

company submission, but this is unknown based on the short duration of SUSTAIN. The STAND trial has a follow-up duration of five years and will provide further insights into the long-term use of crizanlizumab;

- Quality of life measures showed no statistically significant differences in patients on crizanlizumab vs placebo. The MAH argued that this was due to the pre-set time points in which the HRQoL questionnaires were completed, meaning that, instead of measuring the impact of decreased VOC rates on HRQoL, the methodology employed might have captured the HRQoL of patients between VOC (both questionnaires had a one-week recall). It remains unclear if HRQoL did not show an improvement because it was measured at an incorrect time or it did not improve because VOC frequency was not (clinically relevantly) reduced in patients in the intervention arm compared to the placebo arm;

- In subgroup analyses, there was no significant difference in annualised VOC rates between crizanlizumab and placebo in patients that had already used HU/HC. It remains unclear if there is really no difference in this subgroup or whether this was due to a lack of statistical power, as SUSTAIN was not powered to assess statistical significance in subgroups.

7 CONCLUSION

Based on the randomised, double-blind, placebo-controlled phase II SUSTAIN trial, crizanlizumab showed to statistically significantly reduce the annualised rate of VOCs (primary outcome) compared to placebo in addition to best supportive care with or without HU/HC treatment. Furthermore, the time to first VOC was statistically significantly longer with crizanlizumab compared to placebo. Percentage of patients VOC-event free (*post hoc* endpoint) was higher in patients treated with crizanlizumab compared to those on placebo.

Supplementary analyses based on the appropriate statistical test, calculated with a more appropriate imputation method, and using the more reliable investigator-adjudicated data showed, however, no statistically significant difference in the annualised rate of VOCs (primary outcome) between crizanlizumab and placebo.

There were no differences in quality of life within the arms at different timepoints or between the treatment arms. Despite the addition of an active treatment (crizanlizumab) to standard care, overall AEs, treatment-related grade ≥3 AEs, discontinuation due to AEs, and fatal AEs were not statistically significantly higher in the intervention arm compared to the placebo arm (*post hoc* calculations). Due to the duration of the trial, differences in long-term outcomes, such as mortality or severe complications such as ACS, could not be detected.

A major limitation of the current assessment was the large dropout rate, which led to an increased risk of bias and a lack of statistical power. Further, different statistical analyses and imputation methods produced different results, thereby calling the robustness of the treatment effect of crizanlizumab into question. In the absence of a well-defined minimal clinically important difference in VOC rate, it is unclear when a reduction in VOCs is perceived as clinically relevant. This makes the estimated treatment effect of crizanlizumab difficult to interpret. It remains unclear if crizanlizumab lowers mortality and SCD-related complications in the longer term, since the study lasted only 58 weeks.

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APPENDIX 1: GUIDELINES FOR DIAGNOSIS AND MANAGEMENT

Table A1. Overview of guidelines used for this assessment

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Enfermedad de Células Falciformes. Guía de Práctica Clínica Sociedad Española de Hematología y Oncología Pediátricas SEHOP-2019 Sickle Cell Disease. Clinical Practice Guide Spanish Society of Pediatric Hematology and Oncology SEHOP-2019	2019	Spain	HU indication: -3 or more admissions for vaso-occlusive pain / year. - 2 or more admissions for acute chest syndrome in the last 2 years. - Any combination of 3 or more episodes of pain crisis or acute chest syndrome (ACS) / year. –1 episode of severe ACS, priapism, avascular necrosis of the femoral or humeral head, cerebrovascular accident (if chronic transfusion cannot be performed), or other serious vaso-occlusive complications.	Indication with moderate or high evidence.
Sickle Cell Society 2018. Standards for Clinical Care of Adults with Sickle Cell Disease in the UK, 2nd Edition	2018	UK	The goals of management are to improve survival, reduce acute and chronic complications, and improve quality of life. Patients require ongoing continuity of care, starting in early infancy and continuing throughout the life course. - In adults with SCA and sickle cell/β0 thalassaemia with three or more moderate to severe pain crises in a 12-month period, recommend treatment with hydroxicarbamide (HC). - In adults with SCA and sickle cell/β0 thalassaemia who have a history of severe and/or recurrent ACS, recommend treatment with HC. - HC should be offered to adults with SCA and sickle cell/β0 thalassaemia and sickle associated pain or severe symptomatic anaemia that interferes with quality of life (QOL) or activities of daily living (ADL). - HC should be discussed with adults with sickle cell/β+ thalassemia or sickle cell/haemoglobin C disease who have three or more moderate to severe VOC in a 12-month period, a history of severe/recurrent ACS or recurrent pain that interferes with QoL or ADL.	NR
Linee-guida per la gestione della malattia drepanocitica in eta'pediatrica in Italia. Versione 3. Associazione Italiana	2018	Italy	In patients in whom regular blood transfusions cannot be performed due to immunization, autoantibody formation, lack of vascular access, non-compliance with transfusion or chelation, treatment with hydroxyurea should be considered.	C

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Ematologia Oncologia Pediatrica Guidelines for the management of sickle cell disease in the pediatric age group in Italy. Version 3. Italian Association of Pediatric Hematology Oncology			Treatment with HU is indicated in children, already from the first months of life, and in young people adults, who have one or more of the following conditions:	
			Severe recurring painful crises.	A
			Recurrent acute pulmonary syndrome and / or a single severe episode.	A
			Dactylitis.	A
			Pulmonary hypertension.	C
			Chronic moderate / severe or symptomatic anaemia.	B
			Primary prevention of stroke in patients on chronic transfusion regimen for at least one year for abnormal TCD, in the absence of severe MR angiography vasculopathy, after normalization of TCD and under close clinical and instrumental control.	A
			Secondary prevention of stroke in patients in whom the transfusion regimen is not feasible (to immunization, non-compliance with the transfusion regimen or iron chelation therapy).	B
Richtlijn Sikkelcelziekte Sickle Cell Disease Guideline	2017	The Netherlands	Hydroxycarbamide is indicated when:	
			HbSS / HbSβ^0 patients with ≥3 severe vaso-occlusive pain crises per year.	A1
			HbSS / HbSβ^0 patients with sickle cell related pain that interferes with daily activities and quality of life.	A2
			Children (from 9 months) with HbSS / HbSβ^0 independent of clinical presentation after informed decision-making.	A1 (for children aged 9-42 months). A2 (for children aged 42 months and older).
			HbSS / HbSβ^0 patients with status after severe (requiring ventilation) or recurrent acute chest syndrome.	A2
			HbSS / HbSβ^0 patients with severe symptomatic anaemia that interferes with daily activities and quality of life.	A2
			HbSS / HbSβ^0 patients with chronic renal failure and erythropoietin use.	C3
			In patients with other forms of sickle cell disease, hydrea can be considered in the above indications in consultation with a centre of expertise	B3

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
French guidelines for the management of adult sickle cell disease: 2015 update	2015	France	Blood transfusion is rarely offered for the purpose of raising haemoglobin, the anaemia of patients with repanocytosis being chronic and most often well tolerated. Likewise, uncomplicated vaso-occlusive bone crisis is not an indication for transfusion. The benefit of transfusion in sickle cell anaemia is to rapidly decrease the proportion of red blood cells containing haemoglobin S, and therefore to stop the deleterious pathophysiological cascade. Different methods of implementation exist: simple transfusion or transfusion exchange (the transfusion is preceded by bleeding, either manually or by erythrapheresis on a machine), one-off indication or regular program, curative or preventive treatment, primary or secondary prevention.	NR
			The indications for treatment with hydroxyurea concern patients with homozygous SS sickle cell disease or composite $S\beta^0$-thalassemia heterozygosity, with one of the following two criteria: • three hospitalisations in one year for vaso-occlusive crisis; • severe acute thoracic syndrome (see recommendation "Acute thoracic syndrome" or recurrence of acute chest syndrome. The repeated occurrence of ambulatory crises, with personal or social repercussions, even in the absence of hospitalization, is an indication for hydroxyurea.	NR
AWMF-Leitlinie 025/016: Sichelzellkrankheit AWMF guideline 025/016: Sickle cell disease	2014	Germany	Acute pain. Long-term therapy concept. Recurrent pain crises are an indication for treatment with hydroxycarbamide. If this does not lead to success, in individual cases with a very high level of suffering, the patient can be included in a regular transfusion program. The stem cell transplant option should go with the Patient or his parents are discussed. It has also been shown in several studies that regular transfusions reduce the frequency of acute chest syndromes and pain crises	NR

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Prise en charge de la drépanocytose chez l'enfant et l'adolescent. HAS / Service des recommandations professionnelles / Septembre 2005 Management of sickle cell anaemia in children and adolescents. HAS / Professional recommendations service / September 2005	2005	France	Hydroxyurea, at the starting dose of 10 to 15 mg / kg / 24 h, is only recommended in severe forms of sickle cell disease in children over 2 years of age (grade B). Its indications are: - the occurrence of more than 3 vaso-occlusive crises requiring hospitalization or hyperalgesia per year and or - the existence of more than 2 acute thoracic syndromes. It is recommended to discuss the initiation of treatment with hydroxyurea with a centre specialising in the management of sickle cell anaemia. Serious adverse events have not been reported in treated children. However, it is recommended that families and children be informed of the risks of azoospermia, the need for contraception for adolescents and the long-term uncertainties of this treatment, especially on oncogenesis.	B

Abbreviations: NR=not reported; SCD=sickle cell disease; SCA=sickle cell anaemia; HU=hydroxyurea; HC=hydroxycarbamide; TCD=transcranial doppler; ACS=acute chest syndrome; MR=magnetic resonance.

APPENDIX 2: CONCOMITANT MEDICATIONS

Table A2. Concomitant medications taken during the SUSTAIN trial.

Concomitant medication	Crizanlizumab, 5 mg/kg, N=67	Placebo, N=65
Number of patients with ≥1 concomitant medication[a,b] – n (%)	66 (98.5)	62 (95.4)
Acetaminophen	17 (25.4)	16 (24.6)
Benadryl	18 (26.9)	20 (30.8)
Dilaudid	27 (40.3)	29 (44.6)
Diphenhydramine	11 (16.4)	17 (26.2)
Folic acid	50 (74.6)	45 (69.2)
Heparin	8 (11.9)	16 (24.6)
Hydromorphone	13 (19.4)	20 (30.8)
HU/HC[c]	33 (49.3)	36 (55.4)
Ibuprofen	25 (37.3)	24 (36.9)
Ketorolac	12 (17.9)	14 (21.5)
Miralax	6 (9.0)	15 (23.1)
Morphine	30 (44.8)	31 (47.7)
Ondansetron	10 (14.9)	17 (26.2)
Oxycodone	14 (20.9)	16 (24.6)
Percocet	12 (17.9)	17 (26.2)
Phenergan	10 (14.9)	15 (23.1)
Potassium chloride	5 (7.5)	13 (20.0)
Sodium chloride	12 (17.9)	19 (29.2)
Toradol	15 (22.4)	21 (32.3)

Source: Submission Dossier.
[a] Medications were coded using WHO 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 8 (11.9%) and 0 patients, respectively, in the crizanlizumab 5 mg/kg arm and 4 (6.2%) and 1 (1.5%), respectively, in the placebo arm.
Abbreviations: HU/HC=hydroxyurea/hydroxycarbamide
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APPENDIX 3: RISK OF BIAS 2.0

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	No information on allocation concealment, but CHMP deemed the randomisation process adequate.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No large differences in baseline characteristics were detected.	N
Risk-of-bias judgement	The allocation was adequately concealed: – allocation sequence was random; – baseline differences observed between intervention groups are compatible with chance.	**Low**
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Double-blind study (patients and study personnel blinded)	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	ITT analysis for efficacy outcomes; 'per protocol' analysis (restricted to participants who received the intended intervention) for safety outcomes	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement	Participants and study personnel were unaware of intervention groups and an appropriate analysis was used to estimate the effect of assignment to intervention	**Low**
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	There was only data available in 65% of the randomised participants (dropout rate 35%).	N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Various imputation methods showed different results under a range of plausible assumptions about the relationship between missingness in the outcome and its true value.	N

3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Although there is no information on characteristics of patients that discontinued, there are reasons mentioned that can relate to a participants' health status (such as withdrawal by patient, physicians' decision, or adverse events).	PY
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	---- Reported reasons for missing outcome data provide evidence that missingness in the outcome depends on its true value. Rate of censoring for the time to first VOC outcome differed between experimental and control group.	PY
Risk-of-bias judgement		**High**
Optional: What is the predicted direction of bias due to missing outcome data?		Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Both the independent review committee as well as the trial investigators were not aware of the intervention received by participants. QoL: patient (=outcome assessor) was blinded.	N

4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	VOC-related outcomes: PY Annualised rate of hospitalisations: NI	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Mortality: PN Quality of life: PN AE: NI; depends on how objective the adverse event can be measured. --- There was a large discrepancy between investigator and independent adjudicated VOC data, so it did matter who the outcome assessor was.	NA
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	For some methods that were "pre-specified" in the protocol, a different method for missing data handling was applied. But most of the primary efficacy analyses were done as stated in the study protocol (leaving out the ancillary analyses requested by CHMP which occurred after finalisation of the study report).	PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Data on QoL was reported for both measures, all subscales and all time visits.	PN

5.3 ... multiple eligible analyses of the data?	Data on VOC were calculated in different statistical ways. The rationale for some (supplementary) analyses is not clear and it cannot be excluded that the choice of specific analysis options has been done in a data-driven way.	PY
Risk-of-bias judgement		**High**
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental

Overall risk of bias

Risk-of-bias judgement	The study is judged to be at high risk of bias in at least one domain.	**High**
Optional: What is the overall predicted direction of bias for this outcome?		Unpredictable

APPENDIX 4: GRADE EVIDENCE PROFILE

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	crizanlizumab	placebo	Relative (95% CI)	Absolute		
Annualised rate of VOC leading to healthcare visit (assessed by trial investigators)												
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	66	64	**(Predicted) rate ratio** **0.74** (0.52, 1.06)	**Mean difference:** **-1.33** Absolute mean (±SD): 3.62 (4.1) vs 4.95 (5.3)	⨁⨁◯◯ LOW	CRITICAL
Annualised rate of days hospitalised												
1	randomised trials	serious [d]	not serious	not serious	very serious [e]	none	67	65	**(Predicted) rate ratio** **0.77** (0.40, 1.51)	**Mean difference:** **-6.29 days** Absolute mean (±SD): 18.24 (31.78) vs 24.53 (46.80)	⨁◯◯◯ VERY LOW	CRITICAL
Time to first VOC leading to healthcare visits												
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	67 participants	65 participants	**HR 0.54** (0.36 to 0.81) [c]	**Difference in time: -2.63 months**	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	crizanlizumab	placebo	Relative (95% CI)	Absolute		
Quality of life												
1	randomised trials	serious [d]	not serious	not serious [g]	serious [h]	none	NR	NR	not estimable since there was not one aggregated end result on quality of life (different measures used with different subscales at different visits)		⊕⊕◯◯ LOW	CRITICAL
Patients free of VOC-events (post-hoc)												
1	randomised trials	serious [b]	not serious	not serious	serious [f]	none	67	65	**OR 3.05** (1.00 to 9.25)	**126 more per 1.000** (from 0 more to 358 more) 20% vs 8%	⊕⊕◯◯ LOW	IMPORTANT
Overall adverse events												
1	randomised trials	serious [d]	not serious	not serious	not serious	none	57/66 (86.4%)	55/62 (88.7%)	**RR 0.97** (0.85 to 1.11) [i]	**27 fewer per 1.000** (from 133 fewer to 98 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Treatment-related grade 3-4 adverse events												
1	randomised trials	serious [d]	not serious	not serious	very serious [e]	none	4/66 (6.1%)	3/62 (4.8%)	**RR 1.23** (0.30 to 4.40) [i]	**11 more per 1.000** (from 34 fewer to 165 more)	⊕⊕◯◯ LOW	CRITICAL
Discontinuation due to adverse events												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	crizanlizumab	placebo	Relative (95% CI)	Absolute		
1	randomised trials	serious [d]	not serious	not serious	very serious [e]	none	2/66 (3.0%)	3/62 (4.8%)	**RR 0.64** (0.11 to 3.69) [i]	**17 fewer per 1.000** (from 43 fewer to 130 more)	⊕⊕◯◯ LOW	CRITICAL
Fatal adverse events												
1	randomised trials	serious [d]	not serious	not serious	very serious [e]	none	2/67 (3.0%)	2/64 (3.1%)	**RR 0.98** (0.14 to 6.68) [i]	**1 fewer per 1.000** (from 27 fewer to 178 more)	⊕⊕◯◯ LOW	CRITICAL

Explanations

a. Based on the requested analyses by the CHMP (i.e., negative binomial regression, imputation method M6, investigator-adjudicated VOC data with one outlier patient excluded), since these are deemed more appropriate analyses/ways to handle missing data. Further, the ratios are easier to interpret than the Hodges-Lehmann estimates calculated by the MAH.
b. Serious risk of bias due to missing outcome data (35% dropout rate) and risk of bias in selection of the result (many different analyses – not all pre-specified – with substantially different results).
c. Confidence interval crosses the default clinical relevance boundary of RR 0.75 on one side.
d. Serious risk of bias due to missing outcome data.
e. Confidence interval crosses both default clinical relevance boundaries (RR 0.75 and 1.25).
f. Confidence interval crosses the default clinical relevance boundary of RR 1.25 on one side.
g. Quality of life measures were filled out at pre-set time points. Since VOC can happen at all times, the questionnaire might not have captured potential changes in pain during a VOC in the crizanlizumab arm vs the placebo arm. Nevertheless, the overall quality of life of SCD patients did not show an improvement based on the questionnaires. Therefore, we do not downgrade for indirectness.
h. It is not possible to make any judgements on imprecision due to the lack of an aggregated end result. Since it would be undesirable to 'reward' this, we downgraded with one level.
i. Risk ratios and accompanying confidence intervals are calculated *post hoc* by authoring team.

APPENDIX 5: SAFETY POOL ANALYSIS INCLUDING SOLACE-ADULTS (SUPPORTIVE EVIDENCE)

Table A3. Safety pool analysis including SOLACE-adults

	SUSTAIN (A2201) (exposure: 43.8 weeks)				SOLACE (A2202) (exposure: 35.4 weeks)		Safety pool*	
System Organ Class/AEs	**Crizanlizumab 5 mg/kg**		**Placebo**		**Crizanlizumab 5 mg/kg**		**Crizanlizumab 5 mg/kg**	
	N=66		**N=62**		**N=45**		**N=111**	
	All grades	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
AEs	57 (86.4)	12 (18.2)	55 (88.7)	12 (19.4)	37 (82.2)	14 (31.1)	94 (84.7)	26 (23.4)
Treatment-related AEs	27 (40.9)	4 (6.1)	15 (24.2)	3 (4.8)	9 (20.0)	1 (2.2)****	36 (32.4)	5 (4.5)****
SAEs	17 (25.8)	7 (10.6)	17 (27.4)	8 (12.9)	7 (15.6)	5 (11.1)	24 (21.6)	12 (10.8)
Treatment-related SAEs	6 (9.1)	3 (4.5)	2 (3.2)	1 (1.6)	0	0	6 (5.4)	3 (2.7)
Fatal SAEs**	2 (3.0)	2 (3.0)	2 (3.2)	2 (3.2)	0	0	2 (1.8)	2 (1.8)
AEs leading to discontinuation	2 (3.0)	1 (1.5)	3 (4.8)	2 (3.2)	1 (2.2)	1 (2.2)	3 (2.7)	2 (1.8)
Treatment-related	1 (1.5)	0	2 (3.2)	1 (1.6)	0	0	1 (0.9)	0
AEs leading to dose interruption***	5 (7.6)	2 (3.0)	4 (6.5)	1 (1.6)	2 (4.4)	0	7 (6.3)	2 (1.8)
AEs requiring additional therapy	47 (71.2)	6 (9.1)	40 (64.5)	8 (12.9)	29 (64.4)	11 (24.4)	76 (68.5)	17 (15.3)

	SUSTAIN (A2201) (exposure: 43.8 weeks)				SOLACE (A2202) (exposure: 35.4 weeks)		Safety pool*	
System Organ Class/AEs	**Crizanlizumab 5 mg/kg**		**Placebo**		**Crizanlizumab 5 mg/kg**		**Crizanlizumab 5 mg/kg**	
	N=66		**N=62**		**N=45**		**N=111**	
	All grades	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
AEs by System Organ Class, n (%)								
General disorders and administration site conditions	24 (36.4)	1 (1.5)	18 (29.0)	1 (1.6)	18 (40.0)	0	42 (37.8)	1 (0.9)
Injury, poisoning and procedural complications	10 (15.2)	0	3 (4.8)	0	3 (6.7)	1 (2.2)	13 (11.7)	1 (0.9)
Musculoskeletal and connective tissue disorders	27 (40.9)	1 (1.5)	18 (29.0)	1 (1.6)	14 (31.1)	1 (2.2)	41 (36.9)	2 (1.8)
Respiratory, thoracic and mediastinal disorders	13 (19.7)	1 (1.5)	16 (25.8)	0	8 (17.8)	3 (6.7)	21 (18.9)	4 (3.6)
Skin and subcutaneous tissue disorders	12 (18.2)	0	9 (14.5)	2 (3.2)	8 (17.8)	0	20 (18.0)	0

Source: Study A2201 (crizanlizumab 5 mg vs placebo) data extracted from Submission Dossier and SUSTAIN CTD.
* Pooled arm of 5 mg/kg crizanlizumab from Study A2201 + Study A2202.
** None of the fatal SAE was treatment related.
*** Only dose interruptions were authorized (adjustment/reduction of the dose were not authorized).
**** One case of grade 3 hypoxia with no suspected relationship to the study treatment in Study A2202 was incorrectly entered into the database as possibly drug related.
Abbreviations: AEs=Adverse events; SAEs=Serious adverse events; SOC=System Organ Class; MAH=marketing authorization holder; SD=Submission Dossier; SCS=Summary of Clinical Safety.

APPENDIX 6: EVIDENCE GAPS

Table A4. Recommendations for research

Additional evidence generation needs	
Research question 1: What is the comparative efficacy and safety of crizanlizumab, when taking into account all VOCs instead of only those that lead to healthcare visits or hospitalisation?	
Evidence	Only evidence on VOCs that lead to healthcare visits or hospitalisation were available. VOCs managed at home were not counted. This does not necessarily imply that VOCs managed at home are less severe than those managed in the hospital. Based on the experiences and perceptions of patients with SCD, there is also a stigma attached to seeking medical support. Reasons for not seeking medical support can include a previous poor experience at hospital, the opinion that medical assistance was not required, and the perception that medical professionals do not understand SCD.
Population	SCD patients aged 16 years and older
Intervention	Crizanlizumab
Comparator	Standard of care with or without HU/HC
Outcome(s)	Annualised VOC reduction, including VOCs managed at home and VOCs that lead to a healthcare visit or hospitalisation
Time stamp	1.10.2020
Study design	RCT
Ongoing studies	STAND trial (A2301; NCT03814746): started July 2019; planned results of primary analysis in December 2025.
Research question 2: What is the long-term comparative efficacy and safety of crizanlizumab?	
Evidence	The SUSTAIN trial had a duration of 58 weeks. The follow-up period was too short to collect data on mortality or draw conclusions on the treatment effect of crizanlizumab on long term SCD complications such as acute chest syndrome and stroke.
Population	SCD patients aged 16 years and older
Intervention	Crizanlizumab
Comparator	Standard of care with or without HU/HC
Outcome(s)	Mortality, complicated VOCs (such as ACS and stroke), safety outcomes
Time stamp	1.10.2020
Study design	RCT
Ongoing studies	STAND trial (A2301; NCT03814746): started July 2019; planned results of primary analysis in December 2025.
Research question 3: What is the efficacy and safety of crizanlizumab in addition to standard care with or without HU/HC compared to standard care with or without HU/HC including chronic blood transfusions?	
Evidence	The comparator arm of SUSTAIN did not include patients that were on a chronic blood transfusion programme, whereas in real life this is a treatment that a small proportion of patients will receive and also lowers the frequency of VOC.
Population	SCD patients aged 16 years and older
Intervention	Crizanlizumab
Comparator	Standard of care with or without HU/HC including chronic blood transfusions
Outcome(s)	Annualised VOC frequency
Time stamp	1.10.2020
Study design	RCT
Ongoing studies	STAND trial (A2301; NCT03814746): started July 2019; planned results of primary analysis in December 2025.

Research question 4: What is the relationship between VOC frequency and health-related quality of life?	
Evidence	In SUSTAIN, health-related quality of life (HRQoL) was measured using the Brief Pain Inventory and the SF-36 Health Survey. In the BPI, questions are asked about pain in the last 24 hours. In the SF-36, the time frame is the last 4 weeks. Questionnaires were filled out at pre-specified time points. However, this does not necessarily mean that in those time frames VOCs occurred.
Population	SCD patients aged 16 years and older
Intervention	Crizanlizumab
Comparator	Standard of care with or without HU/HC
Outcome(s)	HRQoL using BPI and SF-36, measured before, during, and after a VOC.
Time stamp	1.10.2020
Study design	RCT
Ongoing studies	It is not clear from clinicaltrials.gov if HRQoL is included in the ongoing STAND trial and how this will be measured.
Research question 5: What is the effect of crizanlizumab on haemorrhage, coagulation, and haemostasis?	
Evidence	The to be commercialised formulation of crizanlizumab has a 100% P-selectin inhibition. Some uncertainties remain with regard to haemostasis. In SUSTAIN, no patients with an increased risk of bleeding were included.
Population	SCD patients aged 16 years and older
Intervention	Crizanlizumab
Comparator	Standard of care with or without HU/HC
Outcome(s)	Haemorrhage, coagulation, infections
Time stamp	1.10.2020
Study design	RCT
Ongoing studies	STAND trial (A2301; NCT03814746): started July 2019; planned results of primary analysis in December 2025.