PTJA10 – Core Sumission Dossier

Crizanlizumab
for the Prevention of Recurrent Vaso-Occlusive Crises in Sickle Cell Disease

Submitted by: Novartis

Contact details for administrative purposes

Name of contact person:
Kalitsa Filioussi
European Market Access Director, Hematology
Address of contact:
Novartis Oncology Region Europe
Largo Umberto Boccioni, 1
Orrigio, Varese
Italy
Telephone number: +39 34 875 525 39
Email address: Kalitsa.filioussi@novartis.com

Name of contact person:
Daniel Ribes
HE&OR Manager
Address of contact:
Novartis Campus
WSJ-340.8
4056 Basel
Switzerland
Telephone number: +41 79 801 3923
Email address: daniel.ribes_arbones@novartis.com

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List of abbreviations

Abbreviation	Definition
ACS	Acute chest syndrome
ADR	Adverse drug reaction
AE	Adverse event
A&E	Accident and emergency
ASH	American Society of Haematology
ATC	Anatomical Therapeutic Chemical
BP	Body pain
BPI	Brief Pain Inventory
BSH	British Society for Haematology
CDSR	Cochrane Database of Systematic Reviews
CfB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Confidence limit
CNS	Central nervous system
CRC	Crisis Review Committee
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
EHA	European Haematology Association
EMA	European Medicines Agency
ENERCA	European Network for Rare and Congenital Anaemia
EQ-5D	EuroQol five dimensions
EU	European Union
FDA	Food and Drug Administration
GH	General health
Hb	Haemoglobin
HbS	Sickle haemoglobin
HbSS	Homozygous sickle haemoglobin
HC/HU	Hydroxycarbamide/hydroxyurea
HES	Hospital Episode Statistics
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
HSUV	Health state utility values
HTA	Health technology assessment

ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th edition
IQR	Inter-quartile range
IRR	Incident rate ratio
ITT	Intention-to-treat
IV	Intravenous
MCS	Mental Component Scores
MH	Mental health
NHLBI	National Heart, Lung and Blood institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NSAID	Non-steroidal anti-inflammatory drug
ONS	Office for National Statistics
OS	Overall survival
PCS	Physical Component Scores
PD	Pharmacodynamics
PF	Physical functioning
PK	Pharmacokinetics
PP	Per-protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcomes
PSGL-1	P-selectin glycoprotein ligand 1
RCT	Randomised control trial
RE	Role emotional
RP	Role physical
SAE	Serious adverse events
SCD	Sickle cell disease
SCPC	Sickle cell-related pain crises
SE	Standard error
SF	Social functioning
SF-36	Short Form 36-item questionnaire
SLR	Systematic literature review
SmPC	Summary of product characteristics
SWAY	Sickle Cell World Assessment Survey
TEAE	Treatment-emergent adverse event
VOC	Vaso-occlusive crises
WHO	World Health Organization

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Submission Summary

- Sickle cell disease (SCD) describes a group of genetic, haematological disorders characterised by severe and acute episodes of pain, known as vaso-occlusive crises (VOC), which are a consequence of vaso-occlusion.[1] Vaso-occlusion is caused by the adherence of leukocytes, platelets and sickled erythrocytes to the endothelium (mediated by various adhesion molecules, including P-selectin as one of the best characterised in this category), which leads to the entrapment of sickled erythrocytes in the multi-cellular aggregates that frequently form in the microvasculature.[2, 3] Each VOC induces severe pain, increases morbidity, decreases health-related quality of life (HRQoL), and can result in organ damage/failure and death.[4-7] VOC can be recurrent and unpredictable, and the pain experienced by patients with SCD as a result of vaso-occlusion can be severe and highly debilitating, often leading patients to seek medical support.[2, 8] As vaso-occlusion can occur throughout the body, multiple organ systems can be affected, resulting in a broad range of symptoms and complications[9]
- The main goals of SCD management involve treating and preventing VOC and other complications in order to reduce morbidity and mortality. Hydroxyurea/hydroxycarbamide (HU/HC) is currently the only licensed option for the prevention of VOC, however, some patients who receive treatment continue to experience recurrent VOC and many are either intolerant or have contraindications to HU/HC, or are not willing to receive HU/HC due to concerns related to toxicity and potentially serious side effects[1, 10, 11]
- Crizanlizumab is a selective IgG2 kappa humanised monoclonal antibody (mAb) that binds with high affinity to P-selectin, blocking P-selectin-mediated interactions between endothelial cells, platelets, red blood cells and leukocytes, thus preventing vaso-occlusion.[12] Crizanlizumab is expected to be indicated for the prevention of recurrent VOC 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. This is consistent with the pivotal trial evidence for crizanlizumab (i.e. the SUSTAIN trial) and the expected use of crizanlizumab in clinical practice
- In the randomised, double-blind, placebo-controlled, phase II SUSTAIN trial, crizanlizumab demonstrated efficacy in the reduction of VOC in patients with SCD with or without concomitant HU/HC.[3] Specifically, crizanlizumab demonstrated a statistically significant and clinically meaningful reduction in the annualised rate of VOC leading to healthcare visits, a more than two-fold increase in the proportion of patients who remained free of VOC leading to healthcare visits, and a delay in the time to first and second VOC leading to healthcare visits when compared with placebo.[3] In the SUSTAIN trial, patients were permitted to receive concomitant medication that was consistent with standard of care, and so the placebo arm of the trial is considered to be representative of supportive care with and without HU/HC[3]
- The importance of reducing VOC frequency for other relevant outcomes (e.g. complications, mortality and HRQoL) has been demonstrated in analyses of the Hospital Episode Statistics (HES) database and LEGACY registry, which showed that patients who had ≥3 VOC in the previous 12 months had worse outcomes compared to those who had zero VOC[13-15]
- Crizanlizumab therefore presents a valuable and effective treatment option for the clinical management of SCD either as an add-on therapy to HU/HC or as a monotherapy in patients for whom HU/HC is inappropriate or inadequate[3]

1 Description and technical characteristics of the technology

Summary of the characteristics of the technology

- Crizanlizumab is a selective IgG2 kappa humanised mAb that binds with high affinity to P-selectin – an adhesion molecule expressed on activated endothelial cells and platelets.[12] P-selectin mediated multi-cellular adhesion is a key factor in the pathogenesis of vaso-occlusion and thus by blocking P-selectin-mediated interactions between endothelial cells, platelets, red blood cells and leukocytes, crizanlizumab acts to prevent vaso-occlusion[12]
- Crizanlizumab is expected to be indicated for the prevention of recurrent VOC 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. This is consistent with the pivotal trial evidence for crizanlizumab and the expected use of crizanlizumab in clinical practice
- The recommended dose of crizanlizumab is 5.0 mg/kg administered over a period of 30 minutes by intravenous (IV) infusion at Week 0, Week 2, and every 4 weeks thereafter[12]
- The randomised, double-blind, placebo-controlled, phase II SUSTAIN trial investigated the efficacy of crizanlizumab compared with placebo, both administered in addition to standard of care (with or without concomitant HU/HC), as a treatment for the prevention of recurrent VOC in patients with SCD who had experienced between 2–10 VOC leading to healthcare visits in the previous 12 months[3]
- Crizanlizumab demonstrated a statistically significant and clinically meaningful reduction in the annualised rate of VOC leading to healthcare visits, a more than two-fold increase in the proportion of patients who remained free of VOC leading to healthcare visits, and a delay in the time to first and second VOC leading to healthcare visits when compared with placebo.[3] A reduction in annualised rate of VOC leading to healthcare visits was also observed across different patient subgroups, including concomitant HU/HC use (yes or no), history of VOC leading to healthcare visits (2–4 or 5–10 crises in the 12 months prior to the study) and SCD genotype (homozygous sickle haemoglobin [HbSS] or non-HbSS).[3] This outcome is highly relevant for patients with SCD and expected to confer additional benefits beyond the frequency of pain crises, for example with regards to other serious complications of SCD and patients' HRQoL. As such, crizanlizumab would provide a valuable treatment option as a monotherapy for patients for whom HU/HC is inappropriate or inadequate, and also as an add-on therapy for patients who continue to experience recurrent VOC with HU/HC alone
- Orphan designation was granted by the European Medicine Agency (EMA) for humanised monoclonal antibody against P-selectin for the treatment of SCD in August 2012 (EU/3/12/1034).[16] A conditional marketing authorisation application for crizanlizumab as a treatment for the prevention of recurrent VOC in SCD patients aged 16 years and older has since been submitted, which is currently undergoing review by the EMA, with Committee for Medicinal Products for Human Use (CHMP) opinion anticipated in July 2020 and marketing authorisation in October 2020. Data from the ongoing STAND trial are expected to support the conversion from a conditional to full marketing authorisation[17]

1.1 Characteristics of the technology

1. In Table 1 provide an overview of the technology.

Table 1: Features of the technology

Non-proprietary name	Crizanlizumab
Proprietary name	Adakveo®
Marketing authorisation holder	Novartis Europharm Ltd.
Class	Selective IgG2 kappa humanised mAb
Active substance(s)	Crizanlizumab
Pharmaceutical formulation(s)	Concentrate for solution for infusion (sterile concentrate), to be administered by intravenous infusion
ATC code	B06AX01
Mechanism of action	Crizanlizumab is a selective IgG2 kappa humanised mAb that binds to P-selectin with high affinity and blocks the interaction with its ligands, including P-selectin glycoprotein ligand 1 (PSGL-1), thereby preventing vaso-occlusion and the occurrence of VOC as a result of the decreased adhesion of erythrocytes, leukocytes and platelets to endothelial cells[12] Although polymerisation of sickle haemoglobin (HbS) is the primary event in the pathophysiology of SCD, the pathogenesis of vaso-occlusion is complex, with sickling alone not enough to cause vaso-occlusion.[18] P-selectin is an adhesion molecule expressed on activated endothelial cells and platelets.[12] It plays an essential role in the initial recruitment of leukocytes and the aggregation of platelets to the site of vascular injury during inflammation. In the chronic pro-inflammatory state associated with SCD, P-selectin is over-expressed and circulating blood cells and the endothelium are activated and become hyper-adhesive.[12] P-selectin-mediated multi-cellular adhesion is a key factor in the pathogenesis of vaso-occlusion and VOC. Binding P-selectin on the surface of the activated endothelium and platelets has been shown to effectively block interactions between endothelial cells, platelets, red blood cells and leukocytes, thereby preventing vaso-occlusion[12, 19, 20] Therefore, the use of crizanlizumab to block the activity of P-selectin in patients with SCD offers a therapeutic approach for the prevention of VOC and potentially subsequent complications associated with VOC[21]

Abbreviations: HbS: sickle haemoglobin; mAb: monoclonal antibody; PSGL-1: P-selectin glycoprotein ligand-1; SCD: sickle cell disease; VOC: vaso-occlusive crises.

2. In table 2, summarise the information about administration and dosing of the technology.

Table 2: Administration and dosing of the technology

Method of administration	Crizanlizumab should be diluted with sodium chloride 9 mg/ml (0.9%) or dextrose 5% before administration, and the diluted crizanlizumab solution must be 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
Doses	The recommended dose of crizanlizumab is 5 mg/kg administered by intravenous infusion over a period of 30 minutes
Dosing frequency	The recommended dosing frequency is administration at week 0, week 2, and every 4 weeks thereafter
Average 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
Anticipated average interval between courses of treatments	Not applicable Crizanlizumab is to be taken continuously at the recommended dosing frequency
Anticipated number of repeat courses of treatments	Not applicable Crizanlizumab is to be taken continuously at the recommended dosing frequency
Dose adjustments	Crizanlizumab must be dosed on the basis of body weight (5 mg/kg per administration). No dose adjustments are recommended in the D181 SmPC. If a dose is missed, crizanlizumab should be administered as soon as possible: • If crizanlizumab is administered within 2 weeks after the missed dose, dosing should be continued according to the patient's original schedule • If crizanlizumab is administered more than 2 weeks after the missed dose, dosing should be continued every 4 weeks thereafter

Abbreviations: SmPC: Summary of Product Characteristics.
Source: Crizanlizumab D181 SmPC.[12]

3. State the context and level of care for the technology (for example, primary healthcare, secondary healthcare, tertiary healthcare, outside health institutions or as part of public health or other).

Crizanlizumab is anticipated to be used in the secondary healthcare setting. The specific setting, however, may vary by country.

Treatment with crizanlizumab should be initiated by physicians experienced in the management of SCD.[12]

4. State the claimed benefits of the technology, including whether the technology should be considered innovative.

Crizanlizumab is a humanised mAb with a novel, selective and well described mechanism of action, which was designed to specifically target a key component of the pathogenesis of vaso-occlusion and VOC – P-selectin-mediated multi-cellular adhesion.[12] In recognition of this novel mechanism of action, the World Health Organization (WHO) created a new Anatomical Therapeutic Chemical (ATC) fourth-level code (B06AX – Other haematological agents) and assigned the B06AX01 ATC code to crizanlizumab.

VOC, as the major hallmark of SCD, are acute, debilitating and severe episodes of pain that have been associated with increased mortality, reduced HRQoL and the development of SCD-related complications. VOC are recurrent and unpredictable, and are the primary reason for patients with SCD to seek medical support, as well as the primary reason for admission to hospital.[22, 23] However, not all VOC will be managed at hospital with some patients choosing to manage crises at home despite the severe and debilitating pain associated with VOC.[24] Reducing all VOC, regardless of where they are managed, is a primary treatment goal for clinicians and an important outcome for patients; and may be expected to result in improved outcomes associated with survival, HRQoL, medical facility utilisation and the development of SCD-related complications.

The management of VOC in patients with SCD includes symptomatic treatment of pain (using non-steroidal anti-inflammatory drugs [NSAIDs], opioids and other analgesics) and supportive care (e.g. hydration with IV fluids and oxygen therapy), neither of which avoid the mortality risk or long-term impacts associated with VOC.[9, 25-27] For the prevention of VOC specifically, HU/HC is currently the only licensed treatment for patients with SCD in Europe.[28, 29] Whilst HU/HC has brought significant benefit to patients with SCD, its use is often limited by side-effects and significant toxicities, the requirement for blood monitoring and poor adherence.[10, 28, 30] Further to this, some patients continue to experience acute painful episodes despite treatment with HU/HC. For those patients for whom HU/HC is inappropriate or inadequate, the alternative options for the prevention of VOC are limited to supportive care measures only (i.e. hydration and keeping warm), chronic blood transfusion, or the participation in clinical trials investigating new treatments. There is therefore a considerable unmet need for novel, effective and well-tolerated treatments for the prevention of recurrent VOC in patients with SCD. Crizanlizumab will present a valuable treatment option for the clinical management of SCD, offering a much-needed, additional approach for the prevention of recurrent VOC, based on a mechanism of action that is distinct and complimentary to available therapies, targeting a key component involved in the pathogenesis of vaso-occlusion and VOC.

The SUSTAIN trial has demonstrated the efficacy of crizanlizumab, with or without concomitant HU/HC, as a treatment for the prevention of recurrent VOC (called sickle cell-related pain crises [SCPC] in the context of the trial) leading to healthcare visits in patients with SCD who have experienced between 2–10 VOC leading to healthcare visits in the previous 12 months.[3] When compared to the placebo arm, crizanlizumab 5 mg/kg was associated with a statistically significant and clinically meaningful reduction in the median annualised rate of VOC leading to healthcare visits (with an indicated 45.3% lower rate with crizanlizumab 5 mg/kg; Hodges-Lehmann median absolute difference of -1.01 [95% CI, -2.00, 0.00]; P = 0.010), a more than two-

fold increase in the proportion of patients who remained free of VOC leading to a healthcare visits at the end of the 52-week trial (35.8% versus 16.9%, OR, 2.85 [95% CI, 1.24, 6.56]), and a delay in the time to first VOC (HR, 0.50 [95% CI, 0.33, 0.74]) and time to second VOC (HR, 0.53 [95% CI, 0.33, 0.87]) (see Section 5.4.3 and Section 5.4.4).[3, 31, 32] A reduction in the median annualised rate of VOC leading to healthcare visits was also observed across different patient subgroups, including concomitant HU/HC use (yes or no), history of VOC leading to healthcare visits (2–4 or 5–10 crises in the 12 months prior to the study) and SCD genotype (HbSS or non-HbSS) (see Section 5.4.5).[3, 12, 31] The reduction of VOC rates is an important and highly relevant outcome for patients with SCD, with the potential of conferring additional benefits beyond the frequency of painful crises. This is based on the relationship between VOC and the risk of serious complications, including organ damage and death, as well as the burden placed on patients' HRQoL and also healthcare resource utilisation as a result of painful VOC and SCD-related complications.[6, 7, 33-36]

In conclusion, crizanlizumab would provide a valuable treatment option as a monotherapy in patients for whom HU/HC is inappropriate or inadequate, and also as an add-on therapy for patients who continue to experience recurrent VOC with HU/HC alone, thus representing a step-change in the prevention of recurrent VOC for patients affected by SCD. In recognition of the potential for crizanlizumab to provide significant improvements in the prevention of a serious condition, crizanlizumab received its first approval from the Food and Drugs Administration (FDA) in the US (15th November 2019) after receiving Breakthrough Therapy designation in December 2018 and following Priority Review.[37, 38] Since November 2019, crizanlizumab has also been approved in a number of other countries, as described in Section 1.2.

1.2 Regulatory status of the technology

1. Complete Table 3 with the marketing authorisation status of the technology.

Details of the marketing authorisation status of crizanlizumab globally are presented in Table 3.

2. State any other indications not included in the assessment for which the technology has marketing authorisation.

Crizanlizumab has not received marketing authorisation for any other indication. The assessment is for the first indication for crizanlizumab for which marketing authorisation has been sought, and no other indications have been submitted for regulatory approval.

3. State any contraindications or groups for whom the technology is not recommended.

Crizanlizumab is anticipated to be indicated for the prevention of recurrent VOC 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.

Crizanlizumab is contraindicated in patients with hypersensitivity to the active substance, Chinese Hamster Ovary (CHO) cell products, or to the following excipients: sucrose, sodium citrate, citric acid, polysorbate 80, or water for injections.[12]

In addition to the above contraindications, crizanlizumab is further associated with following special warnings and precautions for use.[12]

Infusion-related reactions: in clinical studies, infusion-related reactions (defined as occurring within 24 hours) were observed in two patients (1.8%) treated with crizanlizumab; as such, it is recommended that patients 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.[12]

Laboratory test interference (automated platelet counts): interference with automated platelet counts (i.e. platelet clumping) has been observed in patients treated with crizanlizumab in clinical studies, in particular when tubes containing ethylenediaminetetraacetic acid (EDTA) were used. This may lead to unevaluable or falsely decreased platelet counts. There is no evidence that crizanlizumab causes a reduction in circulating platelets or has a pro-aggregant effect *in vivo.* To mitigate the potential for laboratory test interference, it is recommended to run the test as soon as possible (within 4 hours of blood collection) or use citrate tubes. When needed, platelet counts can instead be estimated via a peripheral blood smear.[12]

Excipients with known effect: crizanlizumab contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially sodium-free.[12]

Traceability: in order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.[12]

4. List the other countries in which the technology has marketing authorisation.

Details of the marketing authorisation status of crizanlizumab globally are presented in Table 3.

Table 3: Regulatory status of the technology

Country	Organisation issuing approval	Verbatim wording of the (expected) indication(s)	(Expected) Date of approval	Launched (yes/no). If no include proposed date of launch
Country of application				
Member States of the European Union (EU) and the European Economic Area (EEA)	EMA	Crizanlizumab is expected to be indicated for the prevention of recurrent VOC 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	Marketing authorisation is expected in October 2020	Not available
Other countries				
USA	FDA	Crizanlizumab is a selectin blocker indicated to reduce the frequency of VOC in adults and paediatric patients aged 16 years and older with SCD	15th November 2019	18th November 2019
Brazil	The Brazilian Health Regulatory Agency	Crizanlizumab is indicated for the prevention of vaso-occlusive crises VOC in SCD patients aged 16 years and over	2nd March 2020	Expected Q3 2020
Bahrain	National Health Regulatory Authority	Crizanlizumab is used: in people 16 years of age and older who have SCD to help reduce how often certain episodes (crises) happen	7th January 2020	17th February 2020
Albania	National Agency on Drugs and Medical Devices	Crizanlizumab is indicated for the prevention of VOC in SCD patients aged 16 years and over	11th March 2020	Expected June 2021

India	Central Drugs Standard Control Organization	Crizanlizumab is indicated to reduce the frequency of VOC in adults and paediatric patients aged 16 years and older with SCD	30th March 2020	Expected Q4 2020
United Arab Emirates	Ministry of Health	Crizanlizumab is used: in people 16 years of age and older who have SCD to help reduce how often certain episodes (crises) happen	22nd April 2020	Expected Q2 2020
Oman	Ministry of Health Sultanate of Oman	Crizanlizumab is indicated to reduce the frequency of VOC in adults and paediatric patients aged 16 years and older with SCD	11th May 2020	Expected Q2 2020

Abbreviations: EEA: European Economic Area; EMA: European Medicines Agency; EU: European Union; FDA: Food and Drugs; HC: hydroxycarbamide; HU: hydroxyurea; Prescribing Information: PI; SCD: sickle cell disease; VOC: vaso-occlusive crises.

A conditional marketing authorisation application been submitted to the EMA, with CHMP opinion anticipated in July 2020 and conditional marketing authorisation in October 2020. Conditional marketing authorisation will be based on evidence from the SUSTAIN trial, however, it is expected that a subsequent conversion to full marketing authorisation will also be based on results from the phase III STAND trial. The STAND trial will assess the efficacy and safety of two doses of crizanlizumab (5 mg/kg and 7.5 mg/kg) compared with placebo in patients with SCD aged 12 years and older with history of VOC leading to healthcare visit (see Appendix B [Section 6.2] for more details).[17] The SUSTAIN and STAND trials form part of the SENTRY clinical development programme for crizanlizumab, which includes both currently active and planned clinical studies designed to generate an array of additional data on the role crizanlizumab plays in the management of SCD.[39]

2 Health problem and current clinical practice

Summary of issues relating to the health problem and current clinical practice

- SCD describes a group of genetic, haematological disorders caused by a single mutation in the β-globin chain, leading to the synthesis of HbS, and is characterised by severe, acute and unpredictable episodes of pain, known as VOC, which are a consequence of vaso-occlusion.[1] While advances in early detection and preventive/symptomatic treatments have improved outcomes and increased life expectancy of patients with SCD, life expectancy is still reduced by approximately 20–30 years in high-income settings[40, 41]
- In Europe, the prevalence of SCD is low (estimated as below 2.11 per 10,000), however, the prevalent population has increased over time predominantly due to migration from areas of higher prevalence. The number of individuals affected by SCD varies considerably amongst European countries[9, 16, 42-45]
- Vaso-occlusion is caused by the adherence of leukocytes, platelets and sickled erythrocytes to the endothelium (mediated by various adhesion molecules, including P-selectin as one of the best characterised in this category), which leads to the entrapment of sickled erythrocytes in the multi-cellular aggregates that frequently form in the microvasculature. Occlusion of the microvasculature results in reduced blood flow and, eventually, insufficient oxygen delivery to the surrounding tissues, which causes ischemia and tissue damage, and in some instances acute pain in the form of VOC.[2, 3] Each VOC induces severe pain, increases morbidity, decreases HRQoL, and can result in organ damage/failure and death.[4-7] VOC can be recurrent and unpredictable, and the pain experienced by patients with SCD as a result of vaso-occlusion can be severe and highly debilitating, often leading patients to seek medical support.[2, 8] As vaso-occlusion can occur throughout the body, multiple organ systems can be affected, resulting in a broad range of symptoms and complications, including acute chest syndrome (ACS) as the most serious, and often life-threatening, complication of SCD[9]
- The main goals of SCD management involve treating and preventing VOC and other complications in order to reduce morbidity and mortality. HU/HC is currently the only licensed option for the prevention of VOC, however, some patients who receive treatment continue to experience recurrent VOC and many are either intolerant or have contraindications to HU/HC, or are not willing to receive HU/HC due to concerns related to toxicity and potentially serious side effects[1, 10, 11]
- Crizanlizumab has demonstrated efficacy in the reduction of VOC in patients with SCD with or without concomitant HU/HC and therefore presents a valuable and effective treatment option for the clinical management of SCD either as an add-on therapy to HU/HC or as a monotherapy in patients for whom HU/HC is inappropriate or inadequate[3]
- Long-term, supportive evidence of the importance in reducing the frequency of VOC, in terms of SCD-related complications, mortality and HRQoL, is available from the analyses of the HES database and the LEGACY registry[13-15]

2.1 Overview of the disease or health condition

1. Define the disease or health condition in the scope of this assessment.

2.1.1 Disease overview

The relevant International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10) codes for SCD are: ICD-10-CM D57.0 (sickle-cell anaemia with crisis); ICD-10-CM D57.1 (sickle-cell anaemia without crisis); ICD-10-CM D57.2 (double heterozygous sickling disorders).[46]

SCD describes a group of genetic, haematological disorders caused by a single missense mutation in the β-globin gene (Glu6Val), leading to the synthesis of a structurally abnormal variant of haemoglobin (Hb) – HbS – the polymerisation of which causes erythrocytes to become rigid and adopt a sickle-like shape upon deoxygenation.[1, 47] Although polymerisation of HbS is the primary event in the pathophysiology of SCD, sickling alone is not enough to cause vaso-occlusion.[18] P-selectin-mediated multi-cellular adhesion is also a key factor in the pathogenesis of vaso-occlusion, which in turn leads to VOC, as described below.

SCD is a systemic disease, characterised by chronic haemolytic anaemia, VOC and organ damage. Prognostic factors for early mortality include high white blood cell count, low fetal Hb, renal failure, seizures, and ACS.[35] VOC are the primary cause of hospital admissions for patients with SCD, and are associated with progression to organ damage and early mortality.[22, 48] Even a single VOC can be fatal through complications such as ACS, and experiencing ≥3 VOC in a 12-month period is associated with an increased risk for 17 different forms of end-organ damage.[13] SCD genotypes include HbSS, HbS C disease (HbSC), HbS β^0-thalassemia, HbS β^+-thalassemia, and others.[9] The most common form of SCD occurs in patients with the HbSS genotype, and while patients with other genotypes (with the exception of HbS β^0-thalassemia) may present with a less severe form of the disease, individual patients may present with severe SCD regardless of their genotype.[27] Whether patients might be considered for treatment with crizanlizumab is independent of genotype, and determined by whether they are experiencing recurrent VOC, and are therefore at an increased risk of SCD-related complications and death.

Pathophysiology of SCD

SCD progresses early on into a systemic, life-shortening disease which is characterised by severe, acute and unpredictable episodes of pain, known as VOC, which are a consequence of vaso-occlusion. Vaso-occlusion is the hallmark of SCD and can lead to ischemia and tissue damage, potentially resulting in serious complications. As a result of vaso-occlusion and the presence of a multi-cellular aggregate, insufficient oxygen is delivered to the surrounding tissues which results in ischemic injuries and severe pain.[2] Vaso-occlusion can occur throughout the vascular system and as such, it has the potential to lead to multi-organ damage and a range of acute and chronic complications.[9]

Vaso-occlusion is caused by the adherence of leukocytes, platelets and sickled erythrocytes to the endothelium and the subsequent entrapment of additional circulating sickled erythrocytes in the multi-cellular aggregates that frequently form in the microvasculature, leading to occlusion of the vascular lumen.[2] The multi-cellular adhesion underlying vaso-occlusion is mediated by various adhesion molecules, including P-selectin as the most common and best characterised representative. P-selectin is expressed on activated endothelial cells and platelets, and plays an

essential role in the initial recruitment of leukocytes and the aggregation of platelets to the site of vascular injury during inflammation.[12] In the chronic pro-inflammatory state associated with SCD, P-selectin is over-expressed and circulating blood cells and the endothelium become activated and hyperadhesive.[12, 19, 49] In this environment, sickled erythrocytes, leukocytes, and platelets adhere to each other and to the vascular endothelium, resulting in obstruction of the vasculature, or vaso-occlusion, tissue ischemia and damage. Ischemia-reperfusion injury secondary to intermittent vascular occlusion can further promote chronic inflammation and tissue damage.[2] It is important to note that without abnormally increased intercellular adhesion between blood cells and the endothelium, erythrocyte sickling is not sufficient on its own to initiate a vaso-occlusive episode.[18]

P-selectin-mediated multi-cellular adhesion is thus a key factor in the pathogenesis of vaso-occlusion and consequently, binding P-selectin on the surface of the activated endothelium and platelets has been shown to effectively block interactions between endothelial cells, platelets, red blood cells and leukocytes, thereby preventing vaso-occlusion.[12]

2. Present an estimate of prevalence and/or incidence for the disease or health condition including recent trends.

Due to the protection that the sickle cell trait (i.e. heterozygosity for the sickle cell mutation in the β-globin gene) provides against severe malaria, SCD is most prevalent throughout large areas in sub-Saharan Africa, the Mediterranean basin, the Middle East, and India.[50] Increasing immigration has however led to a rise in the number of individuals affected by SCD outside these regions, and improved healthcare and management of the disease have contributed to a higher prevalence amongst adolescents and adults via improvements in life expectancy.[45, 50] While advances in early detection and preventive/symptomatic treatments have improved outcomes and increased life expectancy of patients with SCD, mainly in developed countries, progress has been limited and even with the best care, quality of life remains poor, and life expectancy is still reduced by approximately 20–30 years in high-income settings.[40, 41] SCD remains a largely neglected disease, particularly in low-income settings where a high proportion of individuals with SCD will die in childhood, and often without a diagnosis.[9, 51]

Globally, approximately 300,000 new cases of SCD occur each year.[50, 52] In Europe, the prevalence of SCD is low (estimated as below 2.11 per 10,000) and the number of individuals affected by SCD varies considerably amongst European countries, with prevalence ranging from 0.13 (Spain; paediatric population) to 2.11 (England).[9, 16, 42, 43, 45, 53] The UK, France, Belgium and Spain are some of the EU countries with greater SCD patient populations due to the high degree of immigration into these countries during the last decade.[54-57] Orphan designation for humanised monoclonal antibody against P-selectin was granted by the EMA in August 2012.[16] This designation was granted in recognition of the low prevalence of SCD in Europe, the chronically debilitating nature of the disease and the significant benefit that P-selectin inhibition may provide to those affected by the condition, as a novel mechanism of action that may result in the reduction of VOC and related complications.[16]

3. Describe the symptoms and burden of the disease or health condition for patients.

The signs and symptoms of SCD are related to increased haemolysis and recurrent VOC causing multi-organ, systemic and progressive disease.[9] Occlusion of the microvasculature results in reduced blood flow and, eventually, insufficient oxygen delivery to the surrounding

tissues, which causes ischemia and in some instances acute pain.[2, 3] VOC can be recurrent and are often unpredictable, and the pain experienced by patients with SCD as a result of vaso-occlusion can be severe and highly debilitating, often leading patients to seek medical support in the community (e.g. local physician visits and specialised SCD crisis centre visits) and at hospital (e.g. inpatient admissions and emergency care unit visits).[2, 8, 24] In addition, VOC are a major cause of disease morbidity, and while some VOC can be self-managed by patients at home, VOC constitute the primary cause of hospitalisation among patients with SCD.[8] An analysis of the international SWAY study, which surveyed patients with SCD (N=2,145) across 16 countries (including France, Germany, Italy, Netherlands, UK), reported that 33% of VOC led to overnight hospitalisation, 24% were managed at home and 18% were treated in the emergency room.[58]

Based on the experiences and perceptions of patients with SCD, there is also a stigma attached to seeking pain relief at hospital (particularly from opioids, when the individuals themselves otherwise look fit and healthy), which provides an additional and unwanted barrier for patients receiving the medical support they need. The SWAY analysis showed that of the aforementioned 24% of VOC that were managed at home by patients, the reasons for not seeking medical support included: a previous poor experience at hospital (39%); the opinion that medical assistance was not required (30%); and the perception that medical professionals do not understand SCD (26%) (multiple reasons could be given).[58] Therefore, it is important to note that the site of care (e.g. management at home) is not an appropriate proxy for the severity of any individual pain crisis.

As vaso-occlusion can occur throughout the body, multiple organ systems can be affected, resulting in a broad range of symptoms and complications.[9] Ongoing ischaemia and reperfusion is associated with chronic tissue damage resulting in both acute and chronic complications.[1] The most serious outcome of VOC is ACS – an acute and life-threatening complication of SCD – which has an incidence rate of 12.8 per 100 patient years (PY) and is responsible for up to 25% of SCD-related deaths.[59-61] The prevalence of ACS amongst cohorts of patients with SCD has been shown to be significantly associated with the frequency of VOC.[6, 62] Other acute and chronic complications of SCD include gallstones, avascular necrosis, ischaemic stroke and silent infarcts, splenic sequestration, leg ulcers, pulmonary hypertension, and infection.[22, 63] Haemolysis, as the other main feature of SCD, can lead to anaemia and subsequently other symptoms such as fatigue.[22, 63] The clinical signs and symptoms of SCD typically present in early childhood, and patients continue to experience complications related to SCD throughout their entire lifetime.[64] The avoidance of each and every single crisis is an important outcome to patients due to the severe pain often experienced during VOC. However, regardless of how painful an individual crisis is, every VOC is clinically important as it is difficult to determine how much organ damage will have occurred or predict which crises will result in catastrophic consequences, and each VOC induces severe pain, increases morbidity, decreases quality of life, and can result in organ damage/failure, stroke and/or death.[9, 48]

- Every VOC leads to ischemia/tissue damage
- Every VOC is a debilitating/traumatising experience for the patient
- Every VOC can potentially necessitate hospitalisation and use of strong analgesics (i.e. opioids), and typically requires complex work-up/health care utilisation
- Every VOC has an impact on daily activity of life (work, school, etc.)

VOC are associated with early mortality.[1] In 1991, prior to the introduction of HU/HC, a study examining the impact of recurrent annual VOC clearly demonstrated that patients with ≥1 VOC annually had worse survival outcomes compared to patients with <1 VOC annually; and that the

mortality risk increased for patients with ≥3 VOC annually (see Figure 2-1 of Platt et al 1991).[65] Furthermore, the number of VOC experienced in the past 12 months has also been shown to be associated with a significantly increased risk of death.[5] As such, life-expectancy for patients with SCD is much lower than the general population, and is reduced by approximately 20–30 years in high-income settings.[35, 40, 41] For example, a recently conducted meta-analysis of mortality risk factors in patients with SCD included two European studies reporting a median age at death for patients with SCD of 49 years (range, 25–82 years; England) and 53 years (interquartile range, 37–60 years; Netherlands) respectively.[5, 66, 67] Mortality rates have been shown to be lower amongst patients who receive therapies that reduce the frequency of VOC, thus supporting the clinical need for effective treatments for the prevention of recurrent VOC.[33-36] However, even after the introduction of VOC rate-reducing treatments such as HU/HC, patients who continue to experience ≥1 VOC annually still remain at a significantly increased risk of death compared to patients with <1 VOC, as demonstrated by a recent analysis of the HES database (see Section 2.1.2).

Patients with SCD experience substantial reductions in HRQoL as a result of the pain associated with VOC, and also due to the impact and symptoms of SCD-related complications.[4, 9, 68] The acute pain associated with VOC is known to have the most proximal impact on HRQoL. Correspondingly, an assessment of the patient-reported impact of VOC conducted in the UK showed a significant reduction in utility score at the time of hospitalisation and for a period of up to one week post-discharge, before returning to baseline.[4] The wider consequences and negative impact of recurrent VOC on patients' wellbeing is supported by results of the SWAY study (from an analysis of 299 included UK patients), where patients with SCD reported a higher emotional impact with increasing VOC burden (52%, 66%, 77% and 86% for 0–1, 2–4, 5–10 and 11+ VOC per year, respectively).[69]

In 2014, the FDA held a public meeting to hear the perspectives of patients with SCD.[70] Patients described VOC as excruciating and incapacitating. These debilitating symptoms have important consequences for patients as they limit their ability to perform in school, pursue careers, have a family and maintain relationships. From patient's words, patients with SCD "live with constant reminders that they are not able to live a normal life". They also "fear about dying early from their disease". These perspectives are reflective of what patients with SCD experience despite existing therapies and are also relevant for patients with SCD in Europe, given the similarities in disease management between Europe and the US (e.g. at the time of the public meeting in 2014, HU was the only treatment approved for SCD in the US).

It is further acknowledged that SCD and VOC-related pain have broader impacts on distal HRQoL including fatigue, cognitive functioning, emotional impact, sleep impact and impact on activities of daily living, including school and work attendance.[70] In a US-based observational study it was shown that 22% of adults with SCD had missed more than 20 days of work and that 15% of children with SCD had missed more than 20 days of school over the span of a year.[71] Results from the international SWAY study further state that 53% of employed patients with SCD taking part in the survey had reduced their working hours, 43% considered leaving their job and 46% reported often missing school in the past.[58] Additionally, patients with SCD may experience higher rates of unemployment, and a study comparing patients with SCD to their healthy siblings showed that significantly fewer patients with SCD were employed compared to their siblings (25% versus 65%).[72] Importantly, higher rates of VOC are associated with a negative impact on employment status. In a US-based study, 73% of patients who had experienced ≥4 VOC in the previous year reported that SCD negatively impacted their employment status, compared with 45% of patients who had experienced 0–3 VOC in the previous year.[73]

2.1.2 The relationship between VOC and other relevant outcomes (complications, mortality and HRQoL)

Long-term, supportive evidence of the relationship between the frequency of VOC and SCD-related complications, mortality and HRQoL, are available from the analyses of two sources of real-world evidence – the HES database and the LEGACY registry.

HES database analysis

The analysis undertaken was a retrospective observational cohort study using the HES database, which contains details of all admissions, outpatients and emergency room visits at UK National Health Service (NHS) hospitals and therefore provides real-world evidence of hospital resource utilisation for patients in the UK. The inclusion period for the study ranged from 1st January 2008 to 30th September 2018.[31]

The primary objective of the HES database analysis was to assess the long-term association between the annualised rate of VOC (leading to hospitalisation) and mortality among patients with SCD aged 16 years or older. Similarly, an analysis was conducted to assess the relationship between the annualised rate of VOC and SCD-related complications (including ACS and other acute complications).

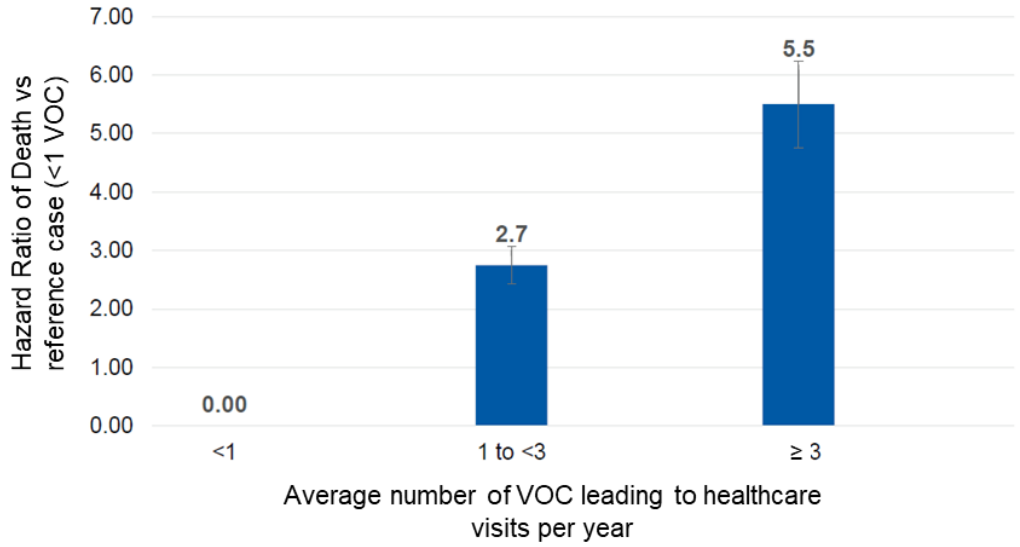
For inclusion in the analysis, patients identified in the HES database were required to meet the following criteria:

- Patients aged 16 years or older as of 1st January 2008
- Patients with a recorded hospital appointment (inpatient, outpatient, or accident and emergency [A&E]) due to any cause during the period 1st January 2008 to 30th September 2018
- Patients with a hospitalisation for SCD (principal, related or associated diagnosis) during the period 1st January 2008 to 30th September 2018, with a hospitalisation due to SCD defined as a visit that was reimbursed and relating to one of the following ICD-10 codes:
    - D57.0 – Sickle-cell anaemia with crisis
    - D57.1 – Sickle-cell anaemia without crisis
    - D57.2 – Double heterozygous sickling disorders

A total of 15,076 people with SCD aged 16 years or older (as of 1st January 2008) were identified from the HES database, of which 60% were of African or Caribbean ethnicity and 62% were female. The mean age of patients included in the study was 37.1 years.[13] Patients were followed from their individual index date (defined as 12 months after the first recorded hospitalisation due to VOC and/or a relevant complication during the inclusion period) until the end of the study (30th September 2018), or until the patient died or was flagged as lost to follow up (24 months without any hospital-related activity), whichever came first.[31] Deaths were identified by matching to the Office of National Statistics (ONS) data on deaths. Overall, deaths occurred in 8% of patients included in the analysis and the median age of death for those individuals who had died was 56 years.[15] A 12-month ‘follow-back period’ (prior to the index date) was required in order to establish the number of VOC experienced by patients in the 12 months prior to baseline.[31]

As shown in Figure 1, an increase in the likelihood of death was observed with increasing annualised VOC rates.[13, 15]

Figure 1: Mortality risk by average annualised rate of VOC leading to healthcare visits



Abbreviations: VOC: vaso-occlusive crises.
Source: Bailey et al. (2019).[13]

VOC were the most common reason for hospitalisation, with 39% of all identified patients having experienced inpatient hospital admissions related to VOC.[15] Further to this, of the 20 SCD-related complications identified, 17 were shown to have increased likelihood of occurrence in patients with ≥3 VOC in the previous 12 months as compared to zero VOC (with a hazard ratio [HR] ≥5 for ACS, osteomyelitis and priapism) (Taken together, the presented results of the HES database analysis support the short- and long-term impact of VOC in SCD, and suggest that reducing the annual incidence of VOC may positively impact disease morbidity and mortality in patients with SCD.

Table 4).[13] Similarly, 18 complications were shown to have increased likelihood of occurrence in patients with 1–2 VOC in the previous 12 months as compared to zero VOC.[13]

Taken together, the presented results of the HES database analysis support the short- and long-term impact of VOC in SCD, and suggest that reducing the annual incidence of VOC may positively impact disease morbidity and mortality in patients with SCD.

Table 4: Relationship of the number of VOC in the previous year and SCD-complications; and sensitivity analysis for unmeasured confounding of the relationship using E-values

Complication	0 VOC, HR (95% CI)	≥3 VOC, HR (95% CI)[a]	≥3 VOC, E-value for HR (CL)[b]
Acute complications			
ACS	Ref	5.33 (4.29, 6.62)	10.13 (8.05)
Gall stones		2.70 (1.83, 3.99)	4.84 (3.06)
Sepsis		2.76 (1.67, 4.57)	4.96 (2.73)
Pulmonary hypertension		2.60 (1.42, 4.75)	4.64 (2.19)

Cardiac complications (e.g. arrest and arrhythmia)		1.29 (0.58, 2.89)	1.90 (1.00)
CNS complications		2.63 (1.23, 5.64)	4.7 (1.76)
Leg ulcers		2.10 (0.94, 4.68)	3.62 (1.00)
Pulmonary embolism		1.11 (0.57, 2.16)	1.46 (1.00)
Cellulitis		2.35 (1.05, 5.23)	4.13 (1.28)
Hyposplenism		3.55 (1.86, 6.77)	6.56 (3.12)
Retinal vascular occlusion		0.87 (0.32, 2.34)	1.56 (1.00)
Osteomyelitis		6.59 (3.42, 12.71)	12.66 (6.3)
Priapism		7.58 (4.07, 14.1)	14.64 (7.6)
Acute kidney injury		3.81 (1.11, 13.0)	7.08 (1.46)
Chronic complications			
Avascular necrosis	Ref	2.48 (1.62, 3.80)	4.40 (2.62)
Cardiomegaly		3.07 (2.0, 4.72)	5.59 (3.41)
Chronic kidney disease		0.14 (0.05, 0.31)	13.77 (5.91)
Orthopaedic joint implant		1.16 (0.45, 3.01)	1.59 (1.00)
Cardiomyopathy		0.57 (0.21, 1.55)	2.9 (1.00)
Liver – chronic passive congestion and other specified diseases		3.11 (0.73, 13.25)	5.67 (1.00)

[a]As the HR were calculated across all patient years, variations in the proportion of patients reported for each VOC category are expected, due to movement of patients between VOC categories.
[b]E-values were used to assess the minimum strength of association that an unmeasured confounder would have to have with both exposure (VOC) and outcome in order to fully explain the observed relationship. Large E-values (≥3) suggest results are robust to considerable unmeasured confounding, while small values imply greater fragility.
Abbreviations: ACS: acute chest syndrome; CI: confidence interval; CL: confidence limit; CNS: central nervous system; HR: hazard ratio; Ref: reference; SCD: sickle cell disease; VOC: vaso-occlusive crises.
Source: Bailey et al. (2019).[13]

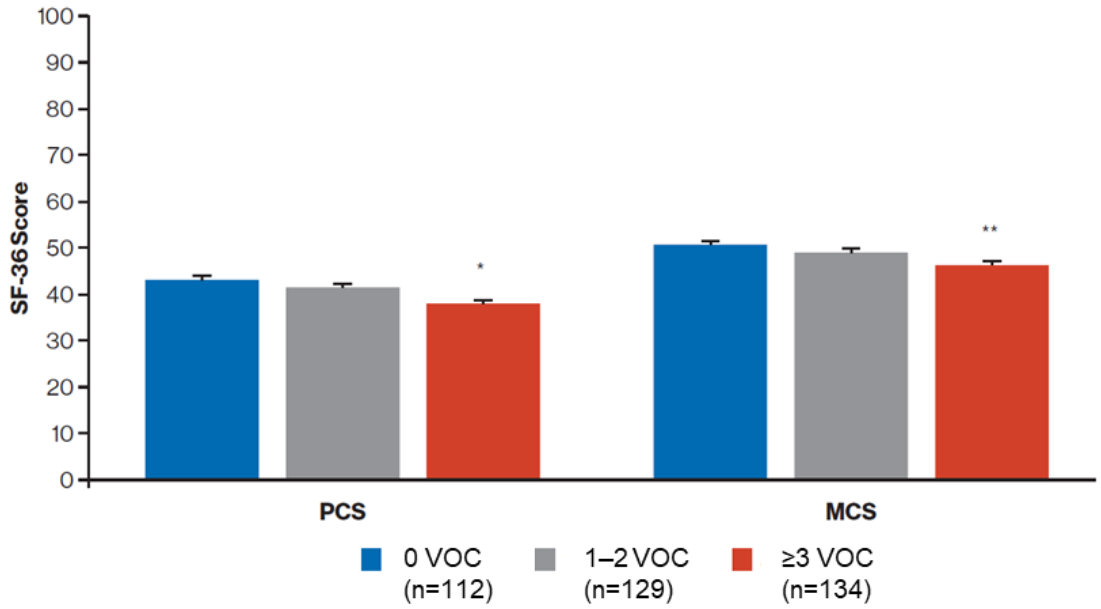
LEGACY registry study

The LEGACY registry study was a 3-year, prospective, non-interventional multicentre registry in 498 patients with SCD.[14] The study was conducted from 13th January 2010 to 30th September 2014, and enrolled patients from 54 centres in the USA. The primary objective was to document clinical outcomes in patients with SCD, under current treatment practices and one of the outcomes assessed in this study was HRQoL of patients with SCD (measured using the Short Form 36-item questionnaire [SF-36] collected every six months).

In the analyses published by Besser et al. (2019), SF-36 data collected from adult patients during the study were first stratified by the number of VOC experienced by patients in the previous 12 months (from the time of each SF-36 administration), and were then mapped to EuroQol five dimensions (EQ-5D) questionnaire.[14] The study showed that patients with ≥3 VOC in the previous 12 months had lower Physical Component Scores (PCS) and Mental Component Scores (MCS) compared to those with 0 VOC in the previous 12 months (Figure 2).[14] Additionally, patients with SCD with ≥3 VOC in the previous 12 months had lower HRQoL across all subscales of SF-36 compared to patients with fewer VOC (Figure 3).[14] The study also showed, via mapping to EQ-5D, that these responses translate to lower utility scores for patients with SCD who had experienced ≥3 VOC in the previous 12 months (Table 5).[14]

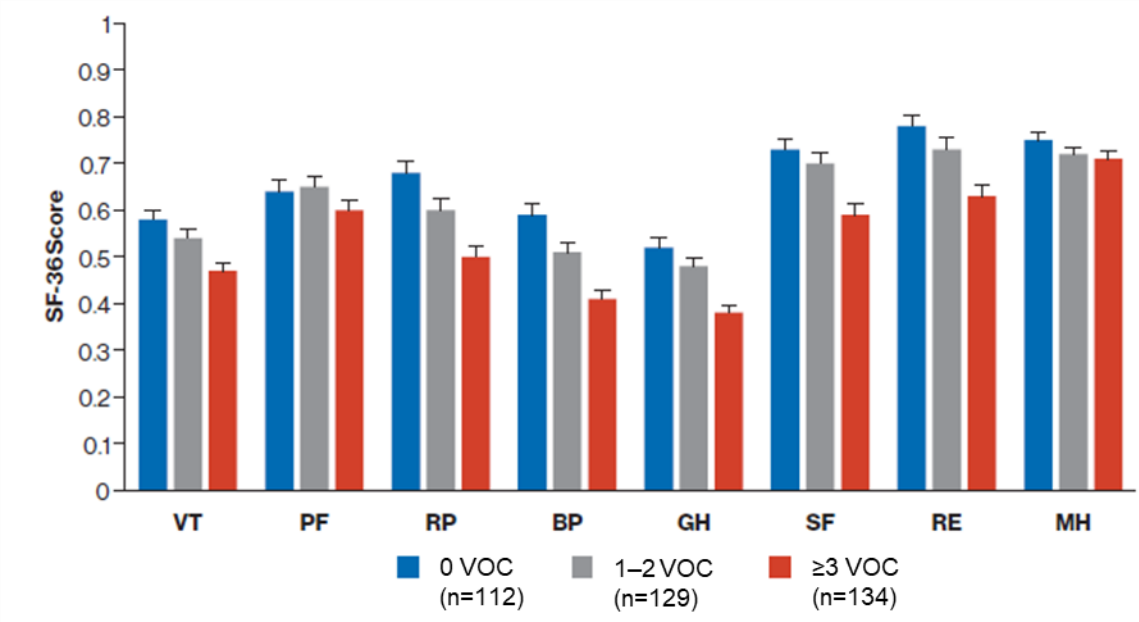
The results from the LEGACY registry analysis showed that patients with ≥3 VOC in the previous 12 months experienced poorer HRQoL compared to those with 0 VOC in the previous 12 months, and demonstrate the long-term impact of recurrent VOC on the patients' HRQoL.

Figure 2: SF-36 component scores (MCS and PCS) for patients with 0, 1 to 2, or ≥3 VOC in the previous 12 months



*P<0.0001 compared to 0 VOC. **P=0.0004 compared to 0 VOC. Error bars represent standard errors.
Abbreviations: MCS: Mental Component Scores; PCS: Physical Component Scores; SF-36: Short Form 36-item questionnaire; VOC: vaso-occlusive crises.
Source: Besser et al. (2019).[14]

Figure 3: SF-36 domain scores for patients with 0, 1 to 2, or ≥3 VOC in the previous 12 months



Abbreviations: BP: body pain; GH: general health; MH: mental health; PF: physical functioning; RE: role emotional; RP: role physical; SF: social functioning; SF-36: Short Form 36-item questionnaire; VOC: vaso-occlusive crises; VT: vitality.
Source: Besser et al. (2019).[14]

Table 5: Summary of mapped EQ-5D values for patients with SCD with 0, 1 to 2, or ≥3 VOC in the previous 12 months

	Utility value
Patients with SCD with 0 VOC in previous 12 months	0.73
Patients with SCD with 1–2 VOC in previous 12 months	0.70
Patients with SCD with ≥3 VOC in previous 12 months	0.62

Abbreviations: EQ-5D: EuroQol 5 dimensions; SCD: sickle cell disease; VOC: vaso-occlusive crises.
Source: Besser et al. (2019).[14]

2.2 Target population

1. Describe the target population and the proposed position of the target population in the patient pathway of care.

Crizanlizumab is anticipated to be indicated for the prevention of recurrent VOC 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. The proposed decision problem presented in this submission is based on the full, anticipated licensed indication of crizanlizumab. The expected target population is thus patients with SCD aged 16 years and older who are experiencing recurrent VOC. Recurrence would apply for any new VOC in patients with SCD who had experienced a previous VOC.

2. Provide a justification for the proposed positioning of the technology and the definition of the target population.

In clinical practice, crizanlizumab in addition to standard of care is expected to be used either as an add-on therapy to HU/HC for those patients who continue to experience recurrent VOC with HU/HC alone, or as a monotherapy for those patients for whom HU/HC is inappropriate or inadequate, as per the anticipated licensed indication. HU/HC is the only currently licensed treatment for patients with SCD in the EU, and thus forms a major component of standard of care, and is also commonly prescribed in childhood for the majority of patients with SCD. It is therefore expected that patients would have at least been offered (if not actually received) treatment with HU/HC by the time that they are considered for treatment with crizanlizumab.

The target population and proposed positioning of crizanlizumab that is presented in this submission is consistent with the anticipated EMA indication for crizanlizumab and the project plan for this assessment.

3. Estimate the size of the target population. Include a description of how the size of the target population was obtained and whether it is likely to increase or reduce over time.

Detailed information about the epidemiological burden of SCD across the whole EU population is not available. However, the prevalence of SCD in Europe is expected to be low and is estimated as below 2.11 per 10,000, although this might also increase over time due to migration.[9, 16, 45] Prevalence estimates for SCD in the general population were obtained using the number of prevalent cases identified in published studies/surveys in individual EU countries divided by the total population of the given country at the same time period (Table 6). Estimated prevalence in the general population in EU ranged from 0.13 per 10,000 (in Spain) to 2.11 per 10,000 (in England). The prevalence of SCD in the general population may be underestimated because of the paucity of published data from established national registers and possible incompleteness of case reporting in other types of studies. However, these calculations may in some instances be overestimated because the ascertainment of SCD cases in several of the studies were conducted in regions with a known high prevalence of SCD.

Table 6: Crude prevalence (per 10,000 population) of SCD in European countries with published information

Publication	Country	Study Period	Prevalence[a] (per 10,000 Population)
Gulbis et al. (2008)[56]	Belgium	2006	0.32
Kyrri et al. (2009)[74]	Cyprus	1982–1986	0.90
National Haemoglobinopathy Registry (NHR) (2019)[44]	UK/England	2018	2.11
Kohne and Kleihauer (2010)[75]	Germany	1971–2007	0.38
Voskaridou et al. (2012)[76]	Greece	2000–2010	0.97
Voskaridou et al. (2019)[77]	Greece	2010–2015	0.96
Peters et al. (2010)[78]	Netherlands	2003	1.94 (paediatric population)
Cela et al. (2017)[42]	Spain	2015	0.13 (paediatric population)
Hemminki et al. (2015)[79]	Sweden	1987–2010	0.58

[a] Number in the numerator obtained from data presented in the study. Population in the denominator obtained from Eurostat.[43]
Abbreviations: NHR: National Haemoglobinopathy Registry; SCD: sickle cell disease; UK: United Kingdom.

2.3 Clinical management of the disease or health condition

1. Describe the clinical pathway of care for different stages and /or subtypes of the disease being considered in the assessment.

There is a high unmet medical need for patients with SCD who experience recurrent VOC. Current interventions for the prevention of VOC are limited to a few available options, and it has been decades since a new and effective treatment has been made available for the SCD community.

Currently, there are no potentially curative treatments available for patients with SCD other than haematopoietic stem cell transplantation (HSCT). However, only a minority of patients are eligible for HSCT due to a lack of suitable donors and substantial concerns around transplant-related mortality and long-term toxicity (e.g. graft failure and chronic graft-versus-host disease, secondary malignancy and infertility) remain.[80] As such, only 216 patients with SCD across Europe received HSCT in 2017.[81] The main goals of disease management therefore involve treating and preventing complications in order to reduce morbidity and mortality. The management of VOC in patients with SCD includes symptomatic treatment of pain (NSAIDs, opioids and other analgesics) and best supportive care (e.g. hydration with IV fluids, oxygen therapy and keeping warm).[9, 25-27, 64] Other common concomitant medications include, folic acid and antibiotics.[24]

HU/HC is currently the only licensed treatment for the prevention of VOC for patients with SCD in Europe and is available through several branded medicines:

- Siklos® is approved in Europe for the prevention of recurrent painful VOC, including ACS, in adults, adolescents and children older than 2 years of age suffering from symptomatic sickle cell syndrome[28]
- Xromi® has also recently been approved in Europe for the prevention of vaso-occlusive complications of sickle cell disease in patients over 2 years of age[29]

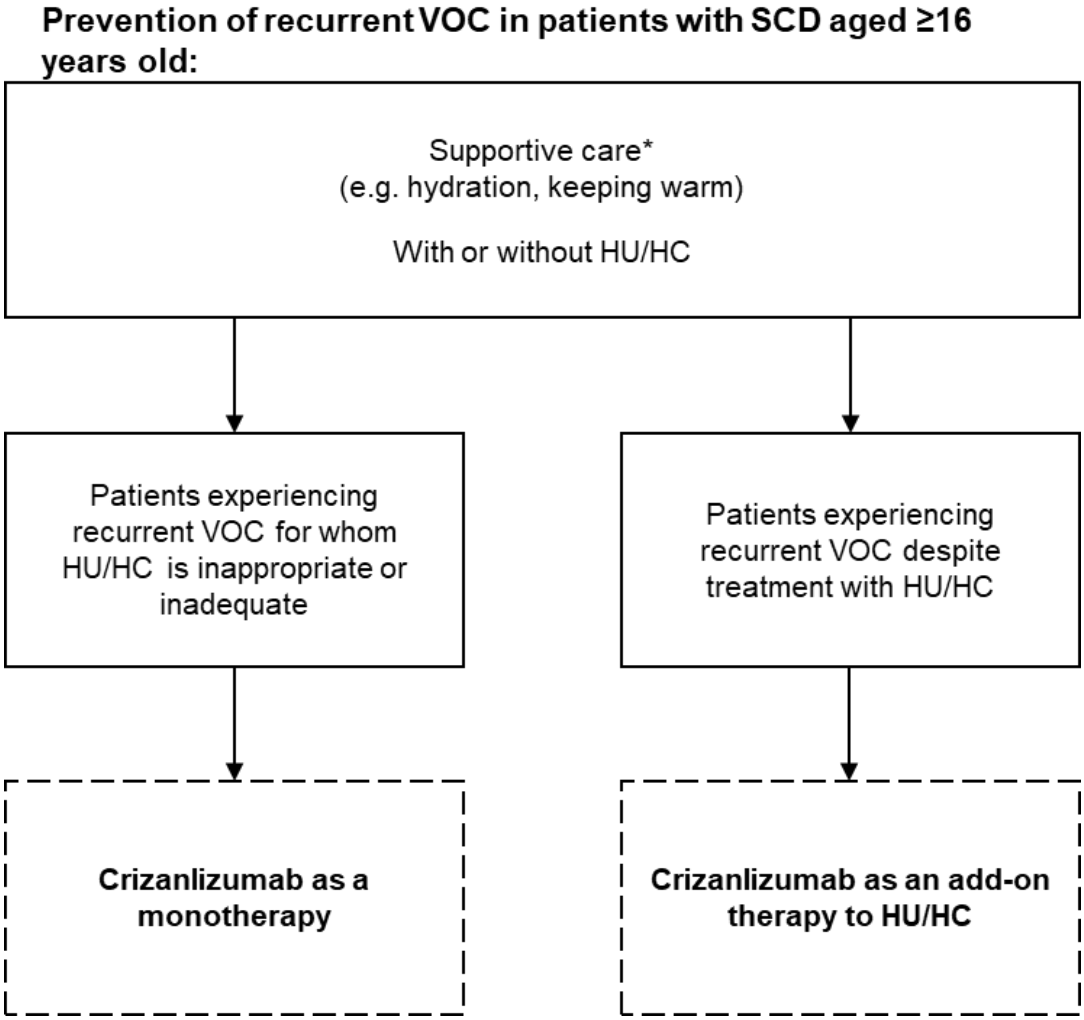
Whilst HU/HC has brought significant benefit to patients with SCD, its use is limited by side-effects and significant toxicities, the requirement for blood monitoring, limited efficacy, and poor patient adherence. HU/HC is cytotoxic, myelosuppressive and teratogenic, potentially carcinogenic, impacts fertility and has a number of contraindications, special warnings and precautions for its use. Further to this, some patients continue to experience acute painful episodes despite HU/HC treatment.[28, 30] For those patients who do continue to experience recurrent VOC, the risk of SCD-related complications and death is considerably higher than those who do not experience VOC.[13, 15] As such, not all patients with SCD will receive treatment with HU/HC and those that do must be monitored closely and undergo routine complete blood and reticulocyte counts every 8–12 weeks for the entire duration of treatment.[11, 82] In the SWAY study, ongoing use of HU/HC was overall reported by 23% of patients with SCD.[24] It should be noted however, that observing active HU/HC use may not provide an accurate representation of overall HU/HC exposure, as patients may have discontinued treatment with HU/HC before the survey.

For those patients for whom HU/HC is inappropriate or inadequate, the alternative options for the prevention of VOC are limited to supportive care measures only (e.g. hydration and keeping warm), chronic blood transfusions, or participation in clinical trials investigating new treatments. Patients who continue to experience VOC despite receiving HU/HC alone may also continue to receive HU/HC (if appropriate), due to the unmet medical need to further reduce the frequency of VOC and the lack of other available treatment options.

Use of chronic blood transfusions for the prevention of recurrent VOC is supported in clinical treatment guidelines despite a lack of evidence from randomised controlled trials demonstrating safety and efficacy.[83, 84] Whilst typically prescribed for stroke prevention, use of regular transfusions specifically for VOC prevention appears limited, likely driven by low blood supply levels and the risk of complications associated with long-term use.[83-85] The SWAY study showed that approximately 11% of patients with SCD reported receiving ongoing treatment with blood transfusions.[58] In addition, evidence from an audit of transfusions in the UK and Ireland suggests that less than one in five (17%) elective transfusions are for the prevention of recurrent VOC specifically.[86] The proportion of patients who receive regular blood transfusions specifically for the prevention of VOC is therefore expected to be low.

The expected use of crizanlizumab in relation to other available therapies for the prevention of recurrent VOC is presented in Figure 4.

Figure 4: Interventions for the prevention of recurrent VOC (including the expected use of crizanlizumab)



*Patients who fail treatment with HU/HC, or for whom HU/HC is contraindicated or not acceptable may receive blood transfusions for the prevention of VOC. Additionally, the proportion of patients expected to receive regular blood transfusions specifically for the prevention of VOC is expected to be low (~10%) and patients receiving chronic blood transfusions would not be expected to receive treatment with crizanlizumab alongside their chronic transfusion programme. HSCT has not been included due to the limited number of patients with SCD aged ≥16 years who undergo transplantation and because treatment with crizanlizumab is not expected to displace HSCT or alter the number of patients who receive HSCT.
Abbreviations: HSCT: haematopoietic stem cell transplantation; HC: hydroxycarbamide; HU: hydroxyurea; IV: intravenous; SCD: sickle cell disease; VOC: vaso-occlusive crises.

Investigative agents which have been under assessment in clinical trial programs include L-glutamine (Xyndari™) and voxelotor, as well as gene therapies, such as lentiglobin. A marketing authorisation application for L-glutamine (Xyndari™) to the EMA has however been withdrawn (September 2019) following a negative opinion from the CHMP.[87, 88] Voxelotor and lentiglobin have not yet received marketing authorisation from the EMA for patients with SCD.

A summary of the relevant guidelines for diagnosis and management of SCD is presented in Table 7.

Table 7: Relevant guidelines for diagnosis and management

Name of society/organisation issuing guidelines	Date of issue or last update	Country/ies to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)
[a]European Network for Rare and Congenital Anaemia (ENERCA), 2010[89]	August, 2010	European	• HU/HC can be used in children with recurrent episodes of acute pain (≥3 year) or ≥2 episodes of ACS • Chronic blood transfusions can be used in children for the prevention of cerebrovascular events or for recurrent splenic sequestrations • HSCT is the only curative therapy for SCD, however there is immediate risk of death and long-term uncertainties about fertility
French guidelines for the management of adult sickle cell disease: 2015 update[90]	May, 2015	France	• HU/HC is recommended for use in patients with HbSS/HbSβ^0 SCD with one of the two following criteria: o Three hospital admissions for vaso-occlusive attacks in one year o Severe ACS or recurrence of ACS • Occasional exchange transfusions are recommended for severe anaemia, strokes and other severe sickle cell related complications • A chronic transfusion programme is recommended for the primary or secondary prevention of severe complications, including repeated severe ACS, and for patients with frequent VOC while waiting for HU/HC to become effective, if HU/HC treatment fails, or if HU/HC is contraindicated
Workgroup for non-oncological haematology of the Netherlands Association for Haematology: SCD Treatment Guidelines[91]	October, 2017	Netherlands	• HU/HC is recommended for use in: o Patients with HbSS/HbSβ^0 with ≥3 severe vaso-occlusive pain crises per year (score: A1) o Patients with HbSS/HbSβ^0 with sickle cell related pain, which interferes with daily activities and quality of life (score: A2)

			○ In patients with other forms of SCD, HU/HC may be considered for the above indications in consultation with a centre of expertise (score: B3) • Acute blood transfusions are recommended for symptomatic anaemia and for severe sickle cell related complications (score: A3) • Chronic blood transfusions are recommended in exceptional cases in patients with very frequent VOC or other serious complications who do not respond to HU/HC (score: C3)
Spanish Society of Paediatric Haematology and Oncology: SCD Clinical Practice Guidelines[92]	April, 2019	Spain	• HU/HC is recommended for use in patients aged 9 months and older with: ○ ≥3 admissions for vaso-occlusive pain per year (moderate or high evidence) ○ ≥2 admissions for ACS in the last two years (moderate or high evidence) ○ Any combination of ≥3 episodes of pain crises or ACS per year (moderate or high evidence) ○ ≥1 episode of severe ACS, priapism, avascular necrosis of femoral or humeral head, cerebrovascular accident (where chronic transfusion cannot be performed) or other severe vaso-occlusive complications (moderate or high evidence) • Blood transfusions are recommended for acute complications, including acute anaemia, aplastic crisis, acute pain crisis (if haemolysis is exacerbated or if other complications are added) and moderate or severe ACS • Chronic blood transfusions are recommended for the prevention of recurrent ACS (that has not been enhanced with HU/HC or is contraindicated) and chronic pain or severe recurrent painful crises significantly affecting quality of life and not improving with medical treatment (HU/HC, analgesia)

			• Transfusions are not recommended for uncomplicated VOC
BSH, 2018 (Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease)[11]	May, 2018	UK	• Treatment with HU/HC is recommended for adults and children with: ○ ≥3 sickle cell-associated moderate to severe pain crisis in a 12-month period (Grade 1A) ○ Sickle cell pain that interferes with daily activities and quality of life (Grade 1C) • A history of severe and/or recurrent ACS (Grade 1A)
British Society for Haematology (BSH), 2016 (Guidelines on red cell transfusion in sickle cell disease Parts I and II)[83, 84]	November, 2016	UK	• [*With respect to the amelioration of disease*] Regular transfusion should be considered for patients failing HU/HC or for whom HU/HC is contraindicated or not acceptable (Grade 1B) • Transfusion is recommended and maybe life-saving in acute complications such as splenic sequestration, hepatic sequestration, aplastic crisis and severe ACS (Grade 1B) ○ Transfusion is not recommended in uncomplicated painful crises but should be considered if there is a substantial drop in Hb from baseline (e.g. >20 g/l or to Hb <50 g/l), haemodynamic compromise or concern about impending critical organ complications (Grade 1C)
NICE Clinical Guidance (CG143)[25]	June, 2012	UK	• VOC may require hospitalisation and patients presenting at a hospital with VOC should be treated as an acute medical emergency, be continuously assessed for possible acute complications, and offered appropriate analgesia within 30 minutes[b]
National Institutes of Health (NIH); National Heart, Lung and Blood Institute (NHLBI), 2014[82]	September, 2014	US	• Treatment with hydroxyurea is recommended for adults with: ○ ≥3 sickle cell-associated moderate to severe pain crises in a 12-month period (Strong Recommendation, High-Quality Evidence) ○ Sickle cell-associated pain that interferes with daily activities and quality of life (Strong Recommendation, Moderate-Quality Evidence)

			○ A history of severe and/or recurrent ACS (Strong Recommendation, Moderate-Quality Evidence) ○ Chronic blood transfusions are recommended for adults and children to prevent complications such as stroke in high risk patients (e.g. children)
[c]American Society of Haematology (ASH), 2014 (Hydroxyurea and transfusion therapy for the treatment of SCD)[93]	November, 2014	US	• Treatment with hydroxyurea is recommended for adults with: ○ ≥3 sickle cell-associated moderate to severe pain crises in a 12-month period (Strong Recommendation, High-Quality Evidence) ○ Sickle cell-associated pain that interferes with daily activities and quality of life (Strong Recommendation, Moderate-Quality Evidence) ○ A history of severe and/or recurrent ACS (Strong Recommendation, Moderate-Quality Evidence) ○ Severe symptomatic chronic anaemia that interferes with daily activities or quality of life (Strong Recommendation, Moderate-Quality Evidence) • Transfusion may be used to treat acute complications of SCD and to prevent chronic complications • Transfusion may also be used in the perioperative period in patients with SCD to prevent VOC, stroke, or ACS after surgery

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to evaluate levels of evidence and to assess the strength of recommendations in both the BSH and NIH/NHLBI guidelines.
Guidelines for the management of SCD from the German Association of the Scientific Medical Societies are also available online (AWMF; https://www.awmf.org/leitlinien/detail/ll/025-016.html), however, these are currently under revision and are no longer valid in the meantime.
[a] Paediatric guidelines only
[b] NICE CG143 is focussed on the management of VOC not their prevention
[c] Adapted from NHLBI evidence-based management of SCD: expert panel report, 2014
Abbreviations: ACS: acute chest syndrome; BSH: British Society for Haematology; ENERCA: European Network for Rare and Congenital Anaemia; Hb: haemoglobin; HSCT: haematopoietic stem cell transplantation; HC: hydroxycarbamide; HU: hydroxyurea; NHLBI: National Heart, Lung and Blood Institute; NICE: National Institute for Health and Care Excellence; NIH: National Institutes of Health; SCD: sickle cell disease; VOC: vaso-occlusive crises.
Source: BSH, 2016 (Guidelines on red cell transfusion in sickle cell disease. Part I: https://b-s-h.org.uk/guidelines/guidelines/red-cell-transfusion-in-sickle-cell-disease-part-I/;

Part 2: https://b-s-h.org.uk/guidelines/guidelines/red-cell-transfusion-in-sickle-cell-disease-part-ii/);[83, 84] BSH, 2018 (Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: https://b-s-h.org.uk/guidelines/guidelines/guidelines-for-the-use-of-hydroxycarbamide-in-children-and-adults-with-sickle-cell-disease/);[11] NICE CG143 (https://www.nice.org.uk/guidance/cg143);[25] Spanish Society of Paediatric Haematology and Oncology: SCD Clinical Practice Guidelines (http://www.sehop.org/wp-content/uploads/2019/03/Gu%C3%ADa-SEHOP-Falciforme-2019.pdf);[92] Workgroup for non-oncological haematology of the Netherlands Association for Haematology: SCD Treatment Guidelines (https://hematologienederland.nl/wp-content/uploads/2019/07/richtlijn_sikkelcelziekte_2017.pdf);[91] French guidelines for the management of adult sickle cell disease: 2015 update;[90] ENERCA, 2010 (https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.21865);[89] NIH. NHLBI, 2014 (https://www.nhlbi.nih.gov/health-topics/evidence-based-management-sickle-cell-disease);[82] ASH, 2014 (Hydroxyurea and transfusion therapy for the treatment of SCD).[93]

2.4 Comparators in the assessment

1. On the basis of the alternatives presented, identify the technologies to be used as comparator(s) for the assessment.

In line with the PICO provided in the project plan, best supportive care with or without HU/HC represents the comparator of interest for this assessment. For those patients for whom HU/HC is inappropriate or inadequate, alternative treatment options for the prevention of VOC are limited to hydration with IV fluids and keeping warm.[9, 26, 27, 64] Chronic blood transfusion may also be received by a small proportion of patients with SCD (~10%, as described above), however, this is typically for reasons other than the prevention of VOC e.g. as a preventative measure for patients at a high-risk of stroke, with only approximately 20% of planned transfusions being received for the prevention of VOC specifically.[15, 24, 86] Patients with SCD are also expected to receive pain relief medication, including NSAIDs, opioids and other analgesics, as symptomatic treatment of VOC.[9, 25-27]

In line with the anticipated licensed indication, crizanlizumab may be used as add-on therapy to HU/HC in patients who continue to experience VOC. As such, HU/HC is not expected to be replaced by crizanlizumab in clinical practice and would therefore not be considered as a standalone comparator as part of this assessment, but as a potential component of standard of care. HU/HC is the only currently licensed treatment for patients with SCD in the EU, and thus forms a major component of standard of care, and is also commonly prescribed in childhood for the majority of patients with SCD. It is therefore expected that patients would have at least been offered (if not actually received) treatment with HU/HC by the time that they are considered for treatment with crizanlizumab.

Additionally, due to the limitations around the small number eligible and treated patients as well as the risks involved in transplantation, HSCT is not considered to represent best supportive care for the majority of patients with SCD and, as such, has not been included as relevant comparator for the decision problem considered in this submission. Furthermore, treatment with crizanlizumab is not be expected to displace HSCT as a treatment option or necessarily alter the number of patients who would ultimately receive HSCT.

3 Current use of the technology

Summary of issues relating to current use of the technology

- Crizanlizumab is not currently licensed in any European countries. It is, however, undergoing health technology assessment (HTA) in the UK by the National Institute for Health and Care Excellence (NICE), with the first committee meeting provisionally scheduled for November 2020

3.1 Current use of the technology

1. Describe the experience of using the technology, for example the health conditions and populations, and the purposes for which the technology is currently used. Include whether the current use of the technology differs from that described in the (expected) authorisation.

Not applicable, as crizanlizumab is not currently licensed in any European countries.

2. Indicate the scale of current use of the technology, for example the number of people currently being treated with the technology, or the number of settings in which the technology is used.

Not applicable, as crizanlizumab is not currently licensed in any European countries.

3.2 Reimbursement and assessment status of the technology

1. Complete Table 5 with the reimbursement status of the technology in Europe.

Table 8: Overview of the reimbursement status of the technology in European countries

Country and issuing organisation	**Status of recommendation (positive/negative/ongoing/not assessed)**	**If positive, level of reimbursement[a]**
NICE, UK	Ongoing. The first committee meeting is provisionally scheduled for November 2020	NA
Include a reference to any publicly available guidance documents [a] For example full reimbursement or only partial reimbursement. If partial reimbursement give a percentage of reimbursement.		

Abbreviations: NA: not applicable; NICE: National Institute for Health and Care Excellence; UK: United Kingdom.

4 Investments and tools required

Summary of issues relating to the investments and tools required to introduce the technology

- Treatment with crizanlizumab should be initiated by physicians experienced in the management of SCD[12]
- Crizanlizumab will be available as a 10 mg/ml concentrate for solution for infusion. The total dose and required volume of crizanlizumab depend on the patient's body weight; 5 mg of crizanlizumab is administered per kg body weight. Crizanlizumab diluted solution must be administered through a sterile, non-pyrogenic 0.2 micron in-line filter by IV infusion over a period of 30 minutes[12]
- The diluted solution for infusion should be prepared by a healthcare professional using aseptic techniques[12]

4.1 Requirements to use the technology

1. If any special conditions are attached to the regulatory authorisation more information should be provided, including reference to the appropriate sections of associated documents (for example, the EPAR and SPC). Include:

    - conditions relating to settings for use, for example inpatient or outpatient, presence of resuscitation facilities
    - restrictions on professionals who can use or may prescribe the technology
    - conditions relating to clinical management, for example patient monitoring, diagnosis, management and concomitant treatments.

Treatment with crizanlizumab should be initiated by physicians experienced in the management of SCD.[12] The diluted solution for infusion should be prepared by a healthcare professional using aseptic techniques.[12]

Crizanlizumab is anticipated to be used in the secondary healthcare setting. The specific setting, however, may vary by country.

2. Describe the equipment required to use the technology.

Equipment to administer crizanlizumab via IV infusion would be required.[12]

3. Describe the supplies required to use the technology.

Crizanlizumab will be available as a 10 mg/ml concentrate for solution for infusion, supplied in a pack containing one vial of 10 ml and should be diluted before administration with either sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 5%.[12] Administration of crizanlizumab by intravenous infusion requires a sterile, non-pyrogenic 0.2 micron in-line filter.[12]

5 Clinical effectiveness and safety

Summary of the clinical effectiveness

- The SUSTAIN trial was a randomised, double-blind placebo-controlled phase II trial to determine the efficacy and safety of crizanlizumab for the prevention of recurrent VOC leading to healthcare visits (referred to as SCPC in the context of the trial) in patients with SCD aged 16–65 years and with a history of 2–10 VOC leading to healthcare visits in the previous 12 months. The SUSTAIN trial provides the primary source of evidence currently available for the use of crizanlizumab in the target population[3]
- In the SUSTAIN trial patients were permitted to receive concomitant medication that was consistent with standard of care, with 62.1% of patients in the trial receiving concomitant HU/HC at baseline.[3] The placebo arm of the SUSTAIN trial is considered to be a reasonable proxy for the comparator of this assessment i.e. supportive care with and without HU/HC (see Section 5.7 for more details) and results from pre-specified subgroup analyses by concomitant HU/HC use have been presented[3]

- The SUSTAIN trial met the primary endpoint, with crizanlizumab 5 mg/kg demonstrating a statistically significant and clinically meaningful reduction in the median annualised rate of VOC leading to healthcare visits compared with placebo (with an indicated 45.3% lower rate with crizanlizumab 5 mg/kg; Hodges-Lehmann median absolute difference of -1.01 [95% CI, -2.00, 0.00]; P = 0.010)[3, 32]
- Subgroup analyses also demonstrated improvements of the median annualised rate of VOC leading to healthcare visits with crizanlizumab 5 mg/kg (compared to placebo) across different pre-specified patient subgroups, including concomitant HU/HC use (yes or no), history of VOC leading to healthcare visits (2–4 or 5–10 crises in the 12 months prior to the study) and SCD genotype (HbSS or non-HbSS)[3]
- When compared to the placebo arm, crizanlizumab 5 mg/kg was also associated with a more than two-fold increase in the proportion of patients who remained free of VOC leading to healthcare visits at the end of the trial (35.8% versus 16.9%; OR, 2.85 [95% CI, 1.24, 6.56]) and a delay in the average time to first VOC leading to healthcare visits (4.07 versus 1.38 months; HR, 0.50 [95% CI, 0.33, 0.74])[3, 31, 32]
- The median annualised rate of uncomplicated VOC (i.e. VOC not classified as ASC, hepatic sequestration, splenic sequestration or priapism) was also lower in the crizanlizumab 5 mg/kg arm compared to placebo (1.08 versus 2.91; Hodges-Lehmann median absolute difference of -1.00 [95% CI, -1.98, 0.00])[3, 32]
- Crizanlizumab 5 mg/kg led to a 41.8% lower median annual rate of days hospitalised compared to placebo (4.00 versus 6.87 days; Hodges-Lehmann median absolute difference of 0.00 days hospitalised per year compared to placebo [95% CI, −4.36, 0.00]).[3, 32] Further analyses of SUSTAIN have shown that a higher proportion of patients were not hospitalised (i.e. zero days hospitalised) in the crizanlizumab 5 mg/kg arm versus placebo (46.3% versus 35.4%), and that the median time to first hospitalisation was more prolonged in the crizanlizumab 5 mg/kg arm versus placebo (6.34 months versus 3.22 months; HR, 0.683 [95% CI, 0.437, 1.066])[31]

Summary of safety

- Crizanlizumab is well tolerated with a favourable and well-manageable safety profile. The safety of crizanlizumab 5 mg/kg has been evaluated in the pooled safety analysis of 111 patients with SCD across two studies: SUSTAIN (n=66), and the SOLACE-adults single arm, open label PK/PD and safety study (n=45).[12] The median duration of exposure among the 111 patients in the crizanlizumab 5 mg/kg safety pool was 46 weeks (range, 4–58 weeks)[31]
- Use of crizanlizumab in combination with HU/HC for 75 (67.6%) patients did not result in any meaningful differences in safety profile[31]
- The most frequently reported adverse drug reactions (ADR, ≥10% of patients) in the crizanlizumab 5 mg/kg safety pool were nausea (16.2%), back pain (15.3%), pyrexia (14.4%) and arthralgia (14.4%). The majority of the ADRs were mild to moderate (grade 1 to 2). Severe events were observed for pyrexia and arthralgia (0.9% for each event)[31]
- Infusion related reactions were observed in two patients, and treatment-induced anti-crizanlizumab antibodies were transiently detected in one patient, among the 111 patients who received crizanlizumab 5 mg/kg (safety pool); there was no impact of anti-crizanlizumab antibody development on the PK, efficacy or safety of crizanlizumab

- The incidence of SAEs was similar across the crizanlizumab 5 mg/kg (25.8%) and placebo arms (27.4%) in SUSTAIN. Discontinuations due to adverse events were rare and occurred in 2.7% of the 111 patients treated with crizanlizumab 5 mg/kg (safety pool); no discontinuations due to ADRs were reported[31]
- No on-treatment deaths were reported in SOLACE-adults, and none of the 5 deaths reported in SUSTAIN had a suspected relationship to study drug[31]

5.1 Identification and selection of relevant studies

1. State the databases and trial registries searched and, when relevant, the platforms used to do this.

A systematic literature review (SLR) was conducted to identify RCTs of crizanlizumab and relevant comparators, as well as interventional non-RCTs and observational studies of crizanlizumab, for the prevention of VOC in SCD.

The SLR was originally conducted with electronic databases searched in August 2019. A subsequent update was conducted, with electronic databases searched in January 2020, in order to identify any additional evidence published since the original SLR searches were conducted. The following databases were searched:

- The MEDLINE databases and Embase were searched separately via the Ovid SP platform
- The Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Controlled Register of Trials (CENTRAL) were searched simultaneously via the Cochrane Library (Wiley Online) platform
- The Database of Abstracts of Reviews of Effects (DARE) was searched via the University of York's Centre for Reviews and Dissemination (CRD) website

Conference proceedings of major haematology conferences from the last two years (i.e. 2017 to 2019) were also hand-searched in September 2019. The SLR update also involved searching meetings of those conferences which had taken place since completion of the original SLR, namely the 2019 American Society of Hematology (ASH) Annual Meeting (December 2019), which was searched in January 2020. Across both the original SLR and the SLR update the following conferences were hand-searched:

- ASH Annual Meeting
- Annual Congress of the European Haematology Association (EHA)
- Annual Symposium of the Foundation for Sickle Cell Disease Research
- BSH Annual Scientific Meeting

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 querying the ClinicalTrials.gov website on 6th September 2019 (original SLR) and 14th February 2020 (SLR update), and hand-searching the bibliographies of any relevant SLRs and (network) meta-analyses identified during the course of the both the original SLR and the SLR update.

State the date the searches were done and any limits (for example date, language) placed on the searches.

Table 9 summarises the electronic databases searched on 13th August 2019 (original SLR) and 27th January 2020 (SLR update), from database inception.

Table 9: Information sources searched in the clinical SLR

Electronic databases	Interface
Original SLR (August 2019)	
MEDLINE, MEDLINE In-Process, MEDLINE Daily and MEDLINE EPub Ahead of Print (1946 to August 12, 2019)	Ovid SP
Embase (1974 to August 12, 2019)	Ovid SP
CDSR (Issue 8 of 12, August 2019)	Cochrane Library (Wiley Online)
CENTRAL (Issue 8 of 12, August 2019)	
DARE (Issue 2 of 4, April 2015)	The University of York's CRD platform
SLR update (January 2020)	
MEDLINE, MEDLINE In-Process, MEDLINE Daily and MEDLINE EPub Ahead of Print (1946 to January 24, 2020)	Ovid SP
Embase (1974 to 24th January 2020)	Ovid SP
CDSR (Issue 1 of 12, January 2020)	Cochrane Library (Wiley Online)
CENTRAL (Issue 1 of 12, January 2020)	
DARE (Issue 2 of 4, April 2015)	The University of York's CRD platform

Abbreviations: CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Controlled Register of Trials; CRD: Centre for Reviews and Dissemination; DARE: Database of Abstracts of Reviews of Effects.

2. Include as an appendix the search terms and strategies used to interrogate each database or registry.

Details of the search strategy for the SLR are presented Appendix A (Section 6.1)

3. In state the inclusion and exclusion criteria used to select studies and justify these.

The titles and abstracts of studies identified from the search strategy, where available, were reviewed according to the pre-specified inclusion/exclusion criteria presented in Table 10. These criteria were confirmed to also be in line with the assessment scope provided by EUnetHTA as part of the relevant project plan.

Table 10: Eligibility criteria for the clinical SLR

Domain	Inclusion criteria	Exclusion criteria
Population	Patients ≥16 years with SCD	Population did not include patients ≥16 years with SCD
Interventions	The following interventions for the prevention of vaso-occlusive crises:	Studies not investigating a relevant intervention specifically for the prevention of vaso-occlusive crises

Domain	Inclusion criteria	Exclusion criteria
	• 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)	
Comparators	Any or none (i.e. no restrictions regarding comparators for the eligible interventions were applied)	Not applicable
Outcomes	• Clinical and safety outcomes including but not limited to: ○ Sickle cell crises (number of events/rate of events/time to event) ○ Hospitalisation (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, Haemo-QoL-A, EQ-5D, or BPI	• 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 design	• For all interventions including crizanlizumab: ○ RCTs ○ Interventional non-RCTs (to include non-randomised and uncontrolled clinical studies) • In addition, for crizanlizumab only: ○ Observational studies • SLRs and (network) meta-analyses ○ These were considered relevant at the title/abstract review stage and hand	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

Domain	Inclusion criteria	Exclusion criteria
	searched for relevant primary studies, but were excluded during the full-text review stage unless they themselves presented primary research	
Publication type	• Peer-reviewed journal articles • Conference abstracts published in or after 2017	Conference abstracts published prior to 2017
Other considerations	Human subjects	Studies not on human subjects

Abbreviations: BPI: brief pain inventory; EQ-5D: EuroQol 5 dimensions; Haemo-QoL-A: Haemophilia-specific Quality of Life Questionnaire; HRQoL: health-related quality of life; HC: hydroxycarbamide; HSCT: haematopoietic stem cell transplantation; HU: hydroxyurea; RCT: randomised controlled trial; SF-36: Short Form 36-item questionnaire; SLR: systematic literature review.

4. Provide a flow chart showing the number of studies identified and excluded. The PRISMA statement can be used; the PRISMA flow chart is included below, as an example.

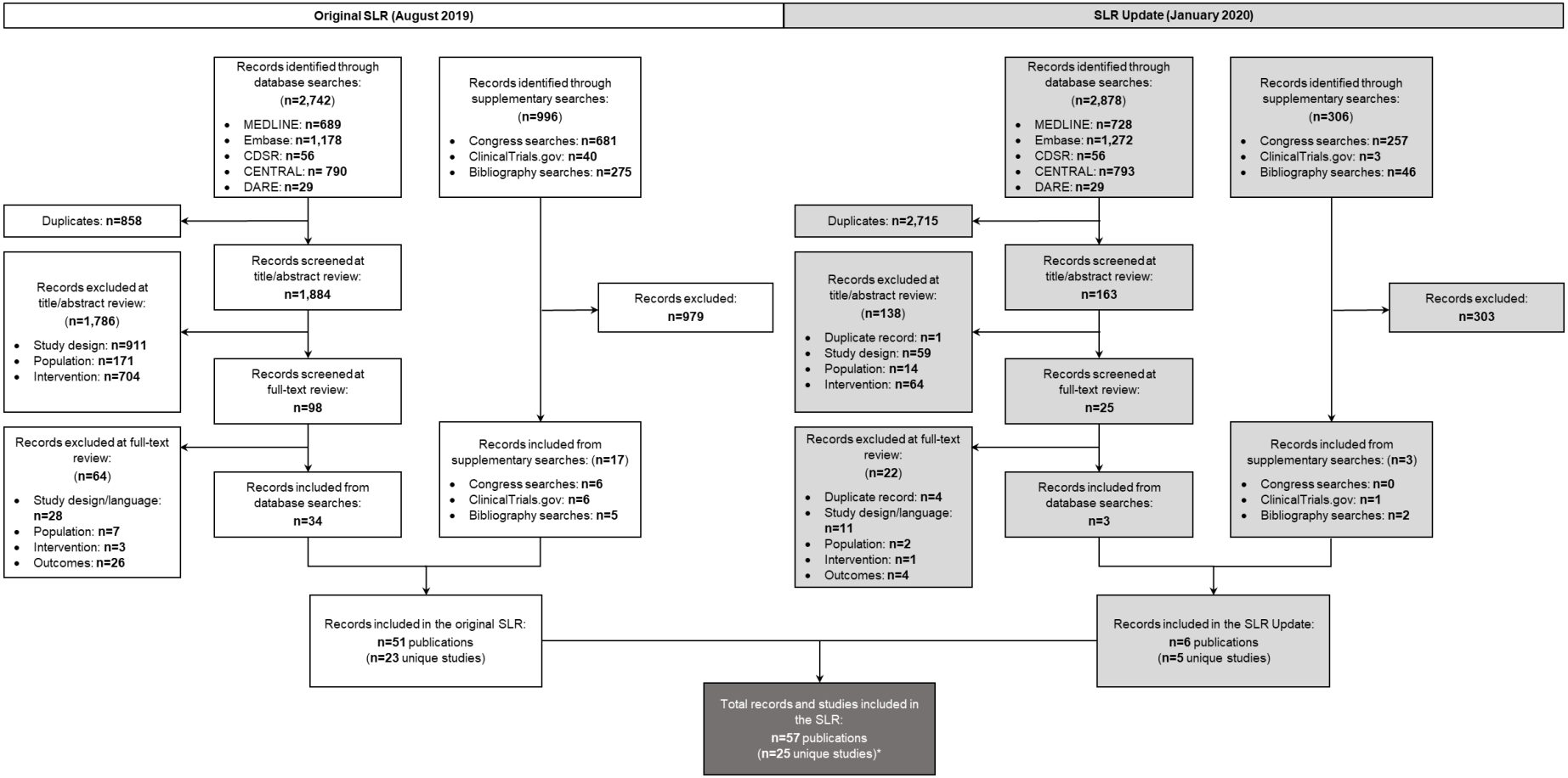
In the original SLR, a total of 2,742 records were retrieved by the electronic database searches. After deduplication of results, 1,884 unique records were suitable for review. After title and abstract review, 98 records were selected to be reviewed at the full-text stage.

In the SLR update, a total of 2,878 records were retrieved by the electronic database searches. After deduplication of results, 163 unique records were suitable for review. After title and abstract review, 25 records were selected to be reviewed at the full-text stage.

Supplementary searches of conferences, SLR bibliographies and clinical trials registries yielded 996 potentially relevant records in the original SLR, and 306 in the SLR update.

In total, across the original SLR and the SLR update, 57 publications reporting 25 unique studies were included in the SLR. This included 13 publications (two studies) investigating crizanlizumab, 20 publications (nine studies) for HU, seven publications (seven studies) for HSCT, two publications (two studies) for blood transfusion, five publications (two studies) for L-glutamine, five publications (two studies) for voxelotor and 5 publications of a retrospective cohort study of patients from the SUSTAIN trial, in which no patients actually received crizanlizumab. A PRISMA diagram showing the flow of records through each stage of the review process is presented in Figure 5.

Figure 5: PRISMA diagram of included and excluded studies for the clinical SLR



Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Controlled Register of Trials; DARE, Database of Abstracts of Reviews of Effects; SLR: systematic literature review.

*The number of unique studies included in the original SLR and SLR update do not sum because three of the studies were also identified in the original SLR.

5.2 Relevant studies

1. In Table 10 provide a list of the relevant studies identified.

The SLR identified the following studies related to crizanlizumab:

- SUSTAIN (A2201) was a randomised, double-blind placebo-controlled, multi-centre phase II trial to determine the efficacy and safety of crizanlizumab (5 mg/kg or 2.5 mg/kg) in patients with SCD aged 16 years and older who are experiencing recurrent VOC.[6] This trial is the primary source of evidence for this submission and is described in detail in Section 5.3
- SOLACE-adults (A2202) is an ongoing, open label pharmacokinetic/pharmacodynamic (PK/PD) study of crizanlizumab (5 mg/kg monthly following two loading doses in the first month of treatment) in patients with SCD aged 16–70 years who had experienced at least one VOC in the previous 12 months.[94, 95] The publication identified in the SLR related to a pooled safety analysis of the SUSTAIN trial and the SOLACE-adults study. No further results have been published from SOLACE-adults. Results of the pooled safety analysis of SUSTAIN and SOLACE are presented in Section 5.5.2 of this submission.

STAND (A2301) is an ongoing, placebo-controlled, double-blind, multicentre, confirmatory phase III study designed to assess the efficacy and safety of two doses of crizanlizumab (5 mg/kg and 7.5 mg/kg) compared with placebo in patients with SCD aged 12 years and older with history of VOC leading to healthcare visit.[17] As data from the STAND trial have not yet been reported (trial primary completion is expected in May 2022) this study was not identified in the SLR. Data from this trial are ultimately expected to support the conversion from a conditional to full marketing authorisation for crizanlizumab, as such further details are presented in Appendix B (Section 6.2).

SUCCESSOR (AUS02) was a multicentre, retrospective cohort study of patients aged ≥18 years with SCD who participated in the SUSTAIN trial at study sites in the US (N=48), assessing medical records for patients who completed SUSTAIN and were no longer on the study drug.[96] As a retrospective cohort study of patients who completed SUSTAIN, the publications reporting outcomes from SUCCESSOR were included as part of the SLR; however, as no patients in SUCCESSOR were administered crizanlizumab during the study period, this study does not provide evidence of the efficacy and safety of crizanlizumab, and has therefore not been considered as part of the evidence for this submission.

Although RCTs and interventional non-RCTs of HU/HC for the treatment of patients with SCD were identified in the SLR, HU/HC itself is not considered as a direct comparator for crizanlizumab in this submission. Instead, HU/HC is considered a potential component of standard of care with or without crizanlizumab. The placebo arm of the SUSTAIN trial, in which only a proportion of patients received HU/HC as concomitant medication, is thus considered to be more relevant for this assessment than the intervention arms of the clinical trials of HU/HC in which all patients received HU/HC as an investigational therapy and no patients would have received HU/HC prior to entry of the trial.

The SLR further identified two relevant studies which investigated the use of chronic blood transfusion as an intervention for patients with SCD:

- Koshy et al. (1988) was a prospective randomised control study which investigated outcomes including frequency of VOC in pregnant women who received either prophylactic transfusions, or transfusions only for medical or obstetric emergencies.[97] Because this study

was conducted exclusively in pregnant women, it was considered to be only of limited relevance to the population considered as part of the decision problem, i.e. all people with SCD aged 16 years and older. While still included in the SLR, this study was therefore not considered as part of the evidence for this submission

- Vichinsky et al. (2010) was a randomised trial of chronic blood transfusions versus standard of care in patients with abnormal neurocognitive function.[98] Only limited information on the study was included in the available conference abstract and so it is therefore difficult to assess how relevant this study is to the population considered as part of the decision problem. As information on the definition of VOC and the duration of the trial follow-up period was also not available as part of the abstract, it was not possible to calculate an annualised VOC rate that would be comparable to the results of the SUSTAIN trial. While still included in the SLR, this study was therefore not considered as part of the evidence for this submission

The SLR further identified four studies which investigated the use of L-glutamine or voxelotor as interventions for patients with SCD.[99-102] However, as L-glutamine and voxelotor have not received marketing authorisation from the EMA for patients with SCD, these studies have not been considered as part of the evidence for this submission. The SLR further identified seven ClinicalTrials.gov records which investigated the use of HSCT as an intervention for patients with SCD.[103-109] As the records only presented safety outcomes, full details have not been extracted.

A summary of the studies included in the SLR is presented in Table 11. A summary of electronic database records excluded at the full-text review stage of the original SLR and SLR update is presented in Appendix A (Section 6.1).

Table 11: List of relevant studies included in SLR

Study ID	Primary reference	Secondary reference(s)
Crizanlizumab		
SUSTAIN (A2201)	Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. New England Journal of Medicine 2017;376:429-439.[3]	Ataga KI, Kutlar A, Kanter J, et al. SUSTAIN: a multicenter, randomized, placebo-controlled, double-blind, 12-month study to assess safety and efficacy of selg1 with or without hydroxyurea therapy in sickle cell disease patients with sickle cell-related pain crises. Blood 2016;128.[110] Ataga KI, Kutlar A, Cancado R, et al. Crizanlizumab treatment is not associated with the development of proteinuria and hematuria in patients with sickle cell disease: A safety analysis from the sustain study. HemaSphere 2018;2 (Supplement 2):305-306.[111] Ataga KI, Kutlar A, DeBonnett L, et al. Crizanlizumab treatment is associated with clinically significant reductions in hospitalization in patients with sickle cell disease: Results from the SUSTAIN study. Blood. Conference: 61st Annual Meeting of the American Society of Hematology, ASH 2019;134.[112] Bailey M, Thompson M, Brown S. The impact of crizanlizumab on voc-related medical facility visits: PF715. HemaSphere 2019;3:312-313.[113] ClinicalTrials.gov. Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises.[114]

Study ID	Primary reference	Secondary reference(s)
		Kanter J, Kutlar A, Liles D, et al. Crizanlizumab 5.0 mg/kg increased the time to first on-treatment sickle cell pain crisis: A subgroup analysis of the phase II sustain study. Blood. Conference: 59th Annual Meeting of the American Society of Hematology, ASH 2017;130.[94] Kanter J, Liles DK, Smith-Whitley K, et al. Crizanlizumab 5.0 mg/kg exhibits a favorable safety profile in patients with sickle cell disease: Pooled data from two phase II studies. Blood. Conference: 61st Annual Meeting of the American Society of Hematology, ASH 2019;134.[115] [Also included as the primary publication for SOLACE-adults] Kutlar A, Kanter J, Liles D, et al. Crizanlizumab, A P-selectin inhibitor, increases the likelihood of not experiencing a sickle cell-related pain crisis while on treatment: results from the phase II SUSTAIN study. Haematologica 2017;102:166-.[116] Kutlar A, Kanter J, Liles D, et al. Crizanlizumab, a p-selectin inhibitor, increases the likelihood of not experiencing a sickle cell-related pain crisis while on treatment: results from the phase ii sustain study, In European Hematology Association, 2017.[116] Kutlar A, Kanter J, Liles DK, et al. Effect of crizanlizumab on pain crises in subgroups of patients with sickle cell disease: A

Study ID	Primary reference	Secondary reference(s)
		SUSTAIN study analysis. American Journal of Hematology 2019;94:55-61.[117] Liles DK, Cancado R, Kanter J, et al. Established prevention of vaso-occlusive crises with crizanlizumab is further improved in patients who follow the standard treatment regimen: Post-hoc analysis of the phase II SUSTAIN study. Blood. Conference: 60th Annual Meeting of the American Society of Hematology, ASH 2018;132.[118] Washko JK, Kutlar A, Liles D, et al. Crizanlizumab 5.0mg/kg increased the time to first on-treatment Sickle Cell Pain Crisis (SCPC) and the likelihood of not experiencing SCPC while on treatment: Subgroup analyses of the phase 2 sustain study. Pediatric Blood and Cancer 2018;65 (Supplement 1):S81. [119]
SOLACE-adults (A2202)	Kanter J, Liles DK, Smith-Whitley K, et al. Crizanlizumab 5.0 mg/kg exhibits a favorable safety profile in patients with sickle cell disease: Pooled data from two phase II studies. Blood. Conference: 61st Annual Meeting of the American Society of Hematology, ASH 2019;134.[115] [Also included as a secondary publication for SUSTAIN]	
Blood transfusions		
Koshy, 1988	Koshy M, Burd L, Wallace D, et al. Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperative study. New England journal of medicine 1988;319:1447-1452.[97]	
Vichinsky, 2010	Vichinsky E, Neumayr L, Gold JI, et al. A randomized trial of the safety and benefit of transfusion vs. standard care in the	

Study ID	Primary reference	Secondary reference(s)
	prevention of sickle cell-related complications in adults: a preliminary report from the phase II NHLBI comprehensive sickle cell centres (CSCC) study of neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adult patients with sickle cell disease. Blood 2010;116.[98]	
Haematopoietic stem cell transplantation		
NCT00004143	ClinicalTrials.gov. Allogeneic Mixed Chimerism Stem Cell Transplant Using Campath for Hemoglobinopathies & Bone Marrow Failure Syndromes.[103]	
NCT00153985	ClinicalTrials.gov. Allogeneic Stem Cell Transplantation Following Chemotherapy in Patients With Hemoglobinopathies.[104]	
NCT00176852	ClinicalTrials.gov. Stem Cell Transplant for Hemoglobinopathy.[105]	
Nur, 2019	Nur E, Gaartman A, van Tuijn C, et al. Matched sibling donor allogeneic stem cell transplantation with non-myeloablative conditioning preceded by azathioprine and hydroxyurea preconditioning in adult sickle cell patients: PB2302. HemaSphere 2019;3:1027-1028.[108]	
Saraf, 2016	Saraf SL, Oh AL, Patel PR, et al. Nonmyeloablative stem cell transplantation with alemtuzumab/low-dose irradiation to cure and improve the quality of life of adults with sickle cell disease. Biology of Blood and Marrow Transplantation 2016;22:441-448.[109]	
SCD-Haplo	ClinicalTrials.gov. SCD-Haplo: Phase II Study of HLA-Haploidentical SCT for Aggressive SCD.[106]	

Study ID	Primary reference	Secondary reference(s)
STRIDE	ClinicalTrials.gov. Bone Marrow Transplantation in Young Adults With Severe Sickle Cell Disease.[107]	
HU/HC		
Akingbola, 2017	Akingbola TS, Tayo B, Saraf SL, et al. Low fixed dose hydroxyurea for the treatment of adults with sickle cell disease in Nigeria. Blood. Conference: 59th Annual Meeting of the American Society of Hematology, ASH 2017;130.[120]	
Charache, 1992	Charache S, Dover GJ, Moore RD, et al. Hydroxyurea: effects on hemoglobin F production in patients with sickle cell anemia. Blood 1992;79:2555-65.[121]	
Kattamis, 2004	Kattamis A, Lagona E, Orfanou I, et al. Clinical response and adverse events in young patients with sickle cell disease treated with hydroxyurea. Pediatric Hematology & Oncology 2004;21:335-42.[122]	
LaSHS	Voskaridou E, Christoulas D, Bilalis A, et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: Results of a 17-year, single-center trial (LaSHS). Blood 2010;115:2354-2363.[123]	
Lima, 1997	Lima C, Arruda V, Costa F, et al. Minimal doses of hydroxyurea for sickle cell disease. Brazilian journal of medical and biological research 1997;30:933-940.[124]	
Loukopoulos, 2000	Loukopoulos D, Voskaridou E, Kalotychou V, et al. Reduction of the clinical severity of sickle cell/beta-thalassemia with hydroxyurea: The experience of a single center in Greece. Blood Cells, Molecules, and Diseases 2000;26:453-466.[125]	Voskaridou E, Kalotychou V, Loukopoulos D. Clinical and laboratory effects of long-term administration of hydroxyurea to patients with sickle-cell/beta-thalassaemia. British Journal of Haematology 1995;89:479-84. [126]
Multicenter Study of Hydroxyurea	Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in Sickle cell	Ballas S, Marcolina M, Dover G, et al. Erythropoietic activity in patients with sickle cell anaemia before and after treatment

Study ID	Primary reference	Secondary reference(s)
	anemia. New England Journal of Medicine 1995;332:1317-1322.[30]	with hydroxyurea. British journal of haematology 1999;105:491-496.[127] Ballas SK, Barton FB, Waclawiw MA, et al. Hydroxyurea and sickle cell anemia: Effect on quality of life. Health and Quality of Life Outcomes 2006;4 (no pagination).[128] Ballas SK, Bauserman RL, McCarthy WF, et al. Hydroxyurea and acute painful crises in sickle cell anemia: Effects on hospital length of stay and opioid utilization during hospitalization, outpatient acute care contacts, and at home. Journal of Pain and Symptom Management 2010;40:870-882.[129] Charache S. Experimental therapy of sickle cell disease. Use of hydroxyurea. The American journal of pediatric hematology/oncology 1994;16:62-66.[130] Charache S, Terrin ML, Moore RD, et al. Design of the multicenter study of hydroxyurea in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea. Controlled clinical trials 1995;16:432-446.[131] Charache S, Barton FB, Moore RD, et al. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Medicine 1996;75:300-326.[132]

Study ID	Primary reference	Secondary reference(s)
		Darbari DS, Nouraie M, Taylor JG, et al. Alpha-thalassaemia and response to hydroxyurea in sickle cell anaemia. European Journal of Haematology 2014;92:341-345.[133] Moore RD, Charache S, Terrin ML, Barton FB, Ballas SK, Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Cost-effectiveness of hydroxyurea in sickle cell anemia. American journal of hematology. 2000 May;64(1):26-31.[134] Smith WR, Ballas SK, McCarthy WF, et al. The association between hydroxyurea treatment and pain intensity, analgesic use, and utilization in ambulatory sickle cell anemia patients. Pain medicine (malden, mass.) 2011;12:697-705.[135] Steinberg MH, Lu Z-H, Barton FB, et al. Fetal hemoglobin in sickle cell anemia: determinants of response to hydroxyurea. Blood 1997;89:1078-1088.[136]
ClinicalTrials.gov (NCT02225132)	ClinicalTrials.gov. Assessment of Algorithm-Based Hydroxyurea Dosing on Fetal Hemoglobin Response, Acute Complications, and Organ Function in People With Sickle Cell Disease.[137]	
Phase 2 Study of Montelukast for the Treatment of Sickle Cell Anemia (NCT01960413)	ClinicalTrials.gov. Phase 2 Study of Montelukast for the Treatment of Sickle Cell Anemia.[138]	

Study ID	Primary reference	Secondary reference(s)
L-glutamine		
Niihara, 2014	Niihara Y, Macan H, Eckman JR, Koh H, Cooper ML. L-Glutamine therapy reduces hospitalization for sickle cell anemia and sickle β0-thalassemia patients at six months: a phase II randomized trial. Clin Pharmacol Biopharm. 2014;3(116):2.[99]	
Phase 3 Study of L-Glutamine Therapy (NCT01179217)	Niihara Y, Viswanathan K, Miller ST, et al. Phase 3 study of l-glutamine therapy in sickle cell anemia and sickle β0 - thalassemia subgroup analyses show consistent clinical improvement. Blood 2016;128:1318-1318.[102]	Nct. A Phase III Safety and Efficacy Study of L-Glutamine to Treat Sickle Cell Disease or Sickle βo-thalassemia. Https://clinicaltrials.gov/show/nct01179217 2010.[139] Niihara Y, Majumdar S, Razon R, et al. Phase 3 study of l-glutamine in sickle cell disease: Analyses of time to first and second crisis and average cumulative recurrent events. Blood. Conference: 59th Annual Meeting of the American Society of Hematology, ASH 2017;130.[140] Niihara Y, Miller ST, Kanter J, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. New England Journal of Medicine 2018;379:226-235.[141]
Voxelotor		
Blyden, 2018	Blyden G, Bridges K and Bronte L. Compassionate-use voxelotor (GBT440) for patients with severe sickle cell disease (SCD) and life-threatening comorbidities. HemaSphere. 2018; 2 (Supplement 2):305.[100]	
Parallel Group Voxelotor Study	Lehrer-Graiwer J, Howard J, Hemmaway CJ, et al. GBT440, a potent anti-sickling hemoglobin modifier reduces hemolysis, improves anemia and nearly eliminates sickle cells in	Lehrer-Graiwer J, Howard J, Hemmaway CJ, et al. Long-term dosing in sickle cell disease subjects with GBT440, a Novel HbS polymerization inhibitor. Blood 2016;128.[142]

Study ID	Primary reference	Secondary reference(s)
	peripheral blood of patients with sickle cell disease. Blood 2015;126:542.[101]	Howard J, Hemmaway CJ, Telfer P, et al. A phase 1/2 ascending dose study and open-label extension study of voxelotor in patients with sickle cell disease. Blood 2019;133:1865-1875.[143] Howard J, Hemmaway C, Telfer P, et al. Long-Term Dosing in Sickle Cell Disease Subjects with GBT440, A novel HbS polymerization inhibitor, In Annual Symposium of the Foundation for Sickle Cell Disease Research, 2017.[144]
Other		
SUCCESSOR[a] (AUS02)	Shah N, Boccia R, Kraft WK, et al. A multicenter retrospective noninterventional follow-up study in patients with sickle cell pain crisis who previously participated in the SUSTAIN trial in the United States successor study. Blood. Conference: 60th Annual Meeting of the American Society of Hematology, ASH 2018;132.[145]	Liles D, Shah N, Scullin B, et al. Successor: a multicenter retrospective noninterventional follow-up study in patients with sickle cell pain crises who previously participated in the SUSTAIN trial in the United States: S853. HemaSphere 2019;3:380-381.[96] Shah N, Boccia R, Kraft WK, et al. Pro3 Successor Study: Treatment and Health Care Resource Utilization by Sickle Cell Patients Who Participated in the Sustain Study in the United States. Value in Health 2019;22 (Supplement 2):S335.[146] Shah N, Boccia R, Kraft WK, et al. Successor study: Baseline demographics of the retrospective, noninterventional follow-up study in a subset of patients with sickle cell pain crises who previously participated in SUSTAIN in the United States,

Study ID	Primary reference	Secondary reference(s)
		In Annual Symposium of the Foundation for Sickle Cell Disease Research, 2019.[147] Shah N, Boccia R, Kraft W, et al. Rate of sickle cell pain crises in patients who previously participated in the SUSTAIN trial in the United States: the successor study. Journal of managed care and specialty pharmacy 2019;25:S36-.[148]

[a] SUCCESSOR was a retrospective cohort study of patients who completed SUSTAIN. No patients received treatment with crizanlizumab during the SUCCESSOR study period.

5.3 Main characteristics of studies

1. In Table 12, describe the main characteristics of the studies.

SUSTAIN was a randomised, double-blind placebo-controlled, multi-centre, phase II trial to determine the efficacy and safety of crizanlizumab as a treatment for patients with SCD aged 16 years and older who are experiencing recurrent VOC.[3] The trial consisted of a 30-day screening phase, a 52-week treatment phase, and a 6-week follow-up evaluation phase.[3] Patients eligible for inclusion in the trial were patients with SCD aged 16–65 years who had experienced 2–10 VOC leading to healthcare visits in the 12 months prior to enrolment in the trial (i.e. had recurrent VOC).[3]

Concomitant medication consistent with the standard care for patients with SCD was allowed in the SUSTAIN trial. Specifically, enrolment of patients treated with concomitant HU/HC was permitted in all of the treatment arms provided that prior to the beginning of the study, HU/HC had been prescribed for at least six months, with a stable dose for at least three months.[3] Patients who were receiving chronic blood transfusion (either exchange or top-up) were excluded from the study in order to minimise confounding from the possible impact that transfusion may have on outcomes, rather than because of any safety concerns related to the use of crizanlizumab in patients receiving transfusions. Patients were also excluded if they received chronic anticoagulant therapy (other than aspirin).[31]

Once enrolled, patients were randomised by an interactive web- or voice-response system in a ratio of 1:1:1 to one of three treatment arms: crizanlizumab 2.5 mg/kg (N=66); crizanlizumab 5 mg/kg (N=67), or placebo (N=65), all of which were administered intravenously 14 times over a period of 52 weeks.[3] Randomisation was performed centrally on the basis of a block design with stratification according to the number of VOC leading to healthcare visits in the previous year (2–4 or 5–10) and by concomitant HU/HC use (yes or no).[3] 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. Therefore, information from the crizanlizumab 2.5 mg/kg is only included where necessary in the context of the overall SUSTAIN trial population.

The primary endpoint of the trial was the annualised rate of VOC leading to healthcare visits and the trial was designed with 90% power to detect a clinically meaningful treatment difference in this outcome (assumed as 40% relative reduction versus placebo). In SUSTAIN, VOC leading to healthcare visits, which were described as sickle cell-related pain crises (SCPC), were defined as an acute episode of pain with no other cause than a vaso-occlusive event that required a medical facility visit and treatment with oral or parenteral opioids, or parenteral NSAIDs. ACS, hepatic sequestration, splenic sequestration and priapism (requiring a healthcare visit), by definition, were also considered VOC.[3] Secondary endpoints included the annualised rate of days hospitalised, time to first and second VOC leading to healthcare visits, annualised rate of uncomplicated crises (defined as crises other than ACS, hepatic sequestration, splenic sequestration or priapism), annualised rate of ACS, and patient-reported outcomes (PRO) including the Brief Pain Inventory (BPI) questionnaire and the SF-36 v2.0 questionnaire.[3, 31] A summary of the main characteristics of SUSTAIN (NCT01895361) is presented in Table 12.

Table 12: Characteristics of studies

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N, enrolled)	Primary outcome measure and follow-up time point	Secondary and exploratory outcome measures and follow-up time points
SUSTAIN (NCT01895361)	To determine the efficacy and safety of crizanlizumab in patients with SCD aged 16 years and older	Double-blind, randomised (1:1:1), placebo-controlled, multi-centre phase II trial	• 16 to 65 years of age • Confirmed medical history or diagnosis of SCD (including HbSS, HbSC, HbSβ^0-thalassemia or HbSβ+-thalassemia patients) • 2–10 VOC leading to healthcare visits within the 12 months before enrolment • Patients receiving HU/HC must have been prescribed	• Crizanlizumab 2.5 mg/kg (N=66) • Crizanlizumab 5 mg/kg (N=67) • Placebo (N=65)	• Annualised rate of VOC leading to healthcare visits, which was calculated as follows: total number of crises x 365 ÷ (end date − date of randomisation + 1)[a]	• The annualised rate of days hospitalised • The times to first and second crises • The annualised rate of uncomplicated crises (defined as crises other than ACS, hepatic sequestration, splenic sequestration, or priapism) • Annualised rate of ACS • Number of patients free from VOC leading to healthcare visits (post-hoc analysis) • BPI questionnaire • SF-36 v2.0 questionnaire

			HU/HC for the preceding six months and be dose-stabilised for at least three months • Patients who were undergoing long-term red-cell transfusion therapy were not eligible			• Changes in clinical laboratory parameters; biomarker analyses; pharmacokinetic and pharmacodynamic analyses (not reported here) • Safety – frequency and severity of AEs

[a] In SUSTAIN, VOC leading to healthcare visits, which were described as SCPC, were defined as acute episodes of pain, with no medically determined cause other than a vaso-occlusive event that resulted in a visit to a medical facility and treatment oral/parenteral narcotic agents or parenteral NSAIDs. ACS, hepatic sequestration, splenic sequestration, and priapism were also considered to be crisis events. All crises that were identified by trial investigators were adjudicated in a blinded fashion by an independent crisis-review committee, which comprised of three independent haematologists.

Abbreviations: ACS: acute chest syndrome; AE: adverse event; BPI: Brief Pain Inventory; Hb: haemoglobin; HbS: homozygous haemoglobin; HC: hydroxycarbamide; HU: hydroxyurea; SCD: sickle cell disease; SCPC: sickle cell-related pain crises; VOC: vaso-occlusive crises; SF-36 v2: Short Form 36-item questionnaire version 2.

Sources: Ataga et al. (2017);[3] Novartis – Data on File: Additional Study Information.[31]

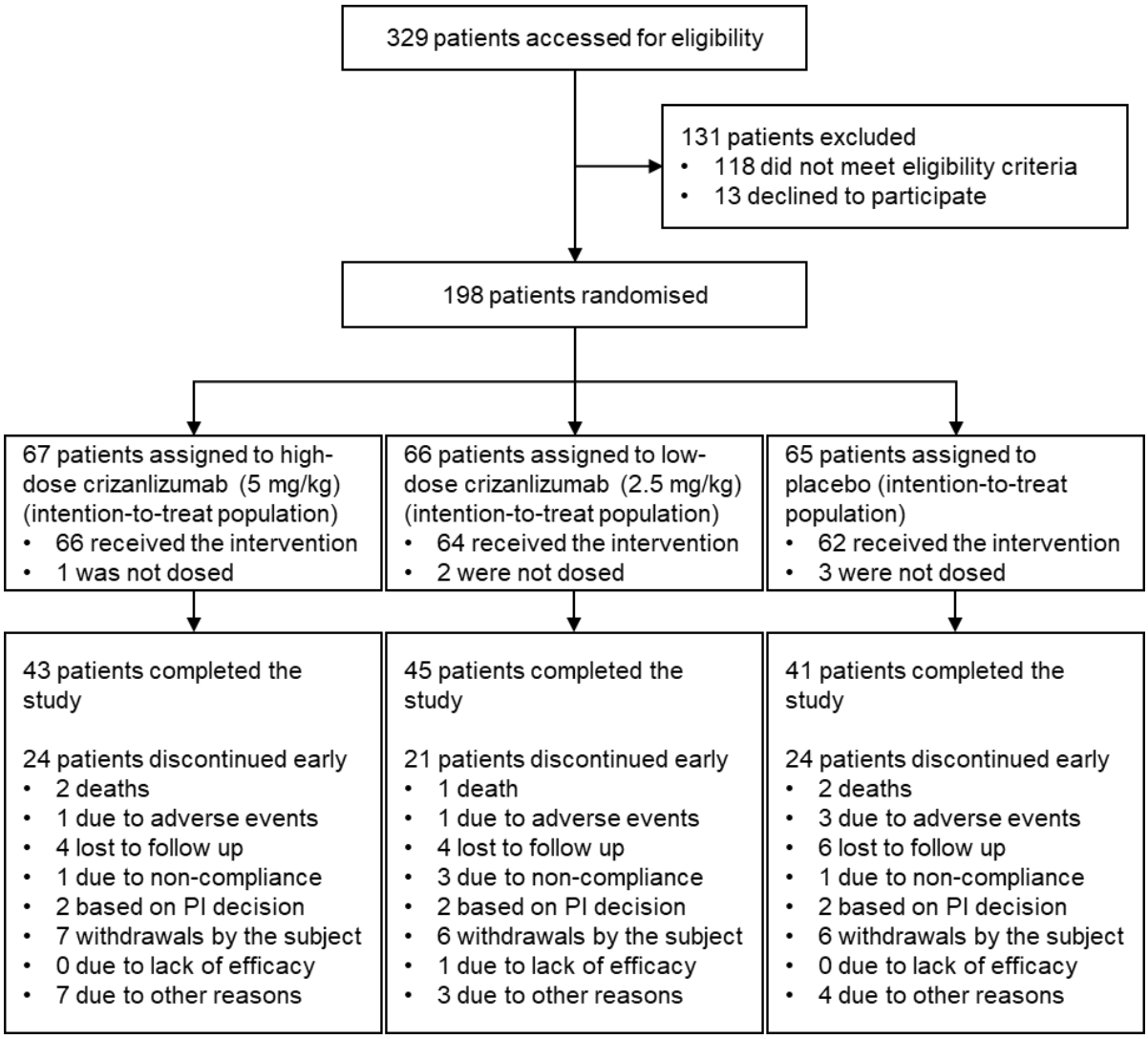
2. For each study provide a flow diagram of the numbers of patients moving through the trial.

5.3.1 Patient disposition

Of the 198 patients randomised to one of the three treatment arms of the SUSTAIN trial, 129 patients completed the study, with a similar dropout rate seen across all three treatment arms: 43/67 (64.2%), 45/66 (68.2%), and 41/65 (63.1%) patients in the crizanlizumab 5 mg/kg arm, crizanlizumab 2.5 mg/kg arm and the placebo arm, respectively, completed the study.[3] This rate of discontinuation seen in the SUSTAIN trial also appears similar to rates reported in other recent placebo-controlled trials in patients with SCD.[141]

One patient in the crizanlizumab 5 mg/kg arm and three patients in the placebo arm did not receive a single dose of study treatment, and were consequently excluded from the safety population (see Table 13 for definitions of the analysis sets used in the SUSTAIN trial).[3] The per-protocol (PP) population included 40/67 (59.7%) and 41/65 (63.1%) patients in the crizanlizumab 5 mg/kg arm and the placebo arm, respectively.[3] Figure 6 presents a CONSORT diagram detailing the flow of participants in the double-blind, randomised, placebo controlled SUSTAIN trial.

Figure 6: CONSORT diagram showing patient flow and disposition in the SUSTAIN trial



Source: Adapted from Ataga et al. (2017) – Figure S1.[3]

3. For each study provide a comparison of patients (including demographic, clinical and social information [if applicable]) in treatment arms at baseline.

5.3.2 Demographic and baseline characteristics

The baseline characteristics of the patients randomised to either the crizanlizumab 5 mg/kg or placebo treatment arms in the SUSTAIN trial are presented in Table 13.

Baseline characteristics were generally similar across the crizanlizumab 5 mg/kg and placebo treatment arms.[3] The median age of randomised patients was 29 years in the crizanlizumab 5 mg/kg arm (range, 16–63) and 26 years (range, 16–56) in the placebo arm, and the vast majority of patients reported their race as 'Black' (91.9%).[3] HbSS was the most common genotype of patients included in the trial (71.2%).[3] With regards to the stratification factors, 62.1% of patients were receiving concomitant HU/HC and 62.6% of patients had 2–4 VOC leading to healthcare visits in the last 12 months.[3]

Table 13: Demographic and other baseline characteristics in the intention-to-treat (ITT) population of the SUSTAIN trial

Characteristic	Crizanlizumab, 5 mg/kg, N=67	Placebo, N=65
Age – years		
Median	29	26
Range	16–63	16–56
Sex – n (%)		
Male	32 (48)	27 (42)
Female	35 (52)	38 (58)
Race – n (%)		
Black	60 (90)	60 (92)
White	4 (6)	3 (5)
Other	3 (4)	2(3)
SCD genotype – n (%)		
HbSS	47 (70)	47 (72)
Other	20 (30)	18 (28)
Concomitant HU/HC use – n (%)		
Yes	42 (63)	40 (62)
No	25 (37)	25 (38)
VOC leading to healthcare visits during previous 12 months – n (%)		
2–4 crises	42 (63)	41 (63)
5–10 crises	25 (37)	24 (37)

Abbreviations: HbSS: homozygous sickle haemoglobin; HC: hydroxycarbamide; HU: hydroxyurea; ITT: intention to treat; SCD: sickle cell disease; VOC: vaso-occlusive crises.
Sources: Ataga et al. (2017) – Table 1.[3]

5.3.3 Concomitant medications

Concomitant medications used by ≥20% of the patients within either of the crizanlizumab 5 mg/kg or placebo treatment arms are presented in Table 14. In addition to HU/HC, the concomitant medications most used in the SUSTAIN trial (across all treatment arms) were folic acid (73.7%) as well as medications intended for pain relief, such as morphine (46.0%) and ibuprofen (42.4%).[31] Generally, concomitant medication use was relatively balanced with ≤10% difference for most medications between both the crizanlizumab 5 mg/kg and placebo arms.[31]

Table 14: Concomitant medications used by ≥20% of patients within the crizanlizumab 5 mg/kg or placebo arm (ITT population)

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)
Zofran	18 (26.9)	22 (33.8)

[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: HC: hydroxycarbamide; HU: hydroxyurea; ITT: intention-to-treat; WHO: World Health Organisation.
Source: Novartis – Data on File: Additional Study Information.[31]

Patients were excluded from the SUSTAIN trial if they were on a chronic transfusion program or if planning on undergoing an exchange transfusion during the duration of the study, due to the potentially confounding effect of transfusions on the primary efficacy outcome. However, patients were still allowed to receive ad-hoc transfusions for the management of acute complications, blood transfusions did therefore occur infrequently in SUSTAIN.[31] Overall, the number and percentage of patients receiving occasional transfusions were balanced across the placebo (62 transfusions in 26 [40.0%] patients) and crizanlizumab 5 mg/kg (56 transfusions in 25 [37.3%]

patients) arms.[31] This represents an average of 0.84 and 0.95 transfusions per patient in the crizanlizumab 5 mg/kg and placebo arms, respectively.[31]

5.4 Individual study results (clinical outcomes)

1. Describe the relevant endpoints, including the definition of the endpoint, and method of analysis.

5.4.1 Relevant endpoints

The key clinical endpoints assessed in the SUSTAIN trial were as follows (see Table 16 for full definitions of endpoints):

- Primary endpoint:
  - Annualised rate of VOC leading to healthcare visits
- Secondary and exploratory endpoints:
  - The annualised rate of days hospitalised (key secondary endpoint)
  - The time to first VOC leading to healthcare visits
  - The time to second VOC leading to healthcare visits
  - The annualised rate of uncomplicated VOC leading to healthcare visits (defined as crises other than ACS, hepatic sequestration, splenic sequestration, or priapism)
  - Number and percentage of patients free from VOC leading to healthcare visits (post-hoc analysis)
  - HRQoL – BPI and SF-36 v2.0

While patient deaths were recorded as part of SUSTAIN, only few deaths (5 across all treatment arms, see Section 5.5.2) occurred during the 52-week trial duration. The trial design did therefore not allow for the detection of differences in mortality between the treatment arms. However, supplementary long-term evidence for the association between VOC rates and mortality was available from analyses of the HES database and is presented as part of this submission (see Section 2.1.2).

5.4.2 Methods of analysis

The analysis sets used in the analysis of the SUSTAIN trial are presented in Table 15.

Table 15: Analyses sets used in the analysis of outcomes of the SUSTAIN trial

Analysis set	Description
ITT population	The ITT population is made up of all patients who were randomised The ITT population was analysed according to the randomised treatment arm
PP population	The PP population is made up of all ITT patients who received at least 12 of the 14 planned study drug doses, completed a visit at least 14 days after final dose of study drug, and had no major protocol violations that impacted the efficacy assessments The PP population was documented prior to database lock The PP population was analysed according to the randomised treatment arm
Safety population	The safety population is made up of all patients who received at least one dose of study drug The safety population was analysed by actual treatment received

Abbreviations: ITT: intention-to-treat; PP: per-protocol.
Source: Novartis – Data on File: Additional Study Information.[31]

The statistical analyses used in the SUSTAIN trial for the primary endpoint, alongside sample size calculations and methods for handling missing data, are presented in Table 16.

A hierarchical testing procedure was followed in the analysis of the SUSTAIN trial, with the anticipation that high-dose (5 mg/kg) crizanlizumab would be more efficacious than low-dose (2.5 mg/kg) crizanlizumab. For the primary endpoint, α = 0.05 was utilised to test high dose versus placebo, and if significant, low dose versus placebo was tested. This controlled the overall alpha level for the study at 0.05 for the primary efficacy endpoint. The primary endpoint also 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 1 dose was 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 significant. If both doses were successful for the primary endpoint, then for the key secondary endpoint, α = 0.05 was be utilised to test high dose versus placebo, and if significant, low dose versus placebo was to be tested.

There were no adjustments for other secondary efficacy analyses.

Table 16: Methods for data collection and analysis in SUSTAIN (NCT01895361)

Endpoint	Definition	Method of analysis
Annualised rate of VOC leading to healthcare visits	Calculated as the total number of crises x 365 ÷ (end date − date of randomisation + 1), where the end date is the last dose date + 14 days VOC leading to healthcare visits were defined as acute episodes of pain, with no	A stratified Wilcoxon rank sum test, with randomisation stratification factors of HU/HC therapy and VOC history as strata, was used to test the null hypothesis that the distribution of annualised rates of VOC leading to healthcare visits in patients

	medically defined cause other than a vaso-occlusive event, that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral NSAID ACS, hepatic sequestration, splenic sequestration and priapism (requiring a healthcare visit), were also considered VOC, by definition While this definition of VOC did not include stroke, the incidence of ischaemic stroke was recorded as adverse event only very few events occurred during the 52-week trial duration (see Section 5.5.2). It can therefore be expected that the inclusion of stroke in the definition of VOC would only have a negligible impact on this endpoint	treated with crizanlizumab and placebo are identical Medians, median differences, and 95% confidence intervals (CIs) for the median differences were estimated using Hodges-Lehmann method, and the following hierarchical testing procedure was followed: $\alpha = 0.05$ was utilised to test crizanlizumab 5 mg/kg versus placebo, and if significant, to test crizanlizumab 2.5 mg/kg versus placebo The primary analysis utilised the ITT principle and included all patients who were randomised to treatment A PP analysis was also conducted for the annualised rate of VOC leading to healthcare visits
Annualised rate of days hospitalised	Calculated as the total number of days hospitalised × 365/(end date – date of randomisation + 1), where the end date is the last dose date + 14 days	The annualised rate of days hospitalised was calculated similarly to the primary efficacy variable. The same statistical methods used for the primary efficacy endpoint were utilised
Time to first VOC leading to healthcare visits	Defined as months from date of randomisation to first VOC leading to healthcare visits 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 respectively	Time to first VOC leading to healthcare visits was analysed using the Kaplan-Meier method. Differences between the active treatment arms and placebo with respect to the time to VOC leading to healthcare visits were carried out using the log-rank test. HRs and corresponding 95% CI were estimated using Cox regression analyses with HU/HC therapy, categorised VOC history, and treatment as covariates

Time to second VOC leading to healthcare visits	Defined as months from date of randomisation to second VOC leading to healthcare visits A patient with fewer than two VOC leading to healthcare visits before withdrawal or completion of the study was considered censored at the time of the end date respectively	Time to second VOC leading to healthcare visits was analysed using the Kaplan-Meier method. Differences between the active treatment arms and placebo with respect to the time to VOC leading to healthcare visits were carried out using the log-rank test. HRs and corresponding 95% CI were estimated using Cox regression analyses with HU/HC therapy, categorised VOC history, and treatment as covariates
Annualised rate of uncomplicated VOC leading to healthcare visits	Uncomplicated VOC leading to healthcare visits were defined as crises other than ACS, hepatic sequestration, splenic sequestration or priapism	The annualised rate of uncomplicated VOC leading to healthcare visits were calculated similarly to the primary efficacy variable. The same statistical methods used for the primary efficacy endpoint were utilised
Number and percentage of patients free from VOC leading to healthcare visit	To be considered free from VOC leading to healthcare visit, patients needed to have an annualised rate of VOC leading to healthcare visit (as defined above) equal to zero	The proportion of patients free from VOC leading to healthcare visit was analysed by a logistic regression model adjusted for HU/HC therapy and categorised VOC history. The OR for treatment effect and corresponding 95% CI was extracted from that model

Abbreviations: ACS: acute chest syndrome; CI: confidence interval; HC: hydroxycarbamide; HU: hydroxyurea; HR: hazard ratio; ITT: intention-to-treat; NR: not reported; NSAID: non-steroidal anti-inflammatory drugs; OR: odds ratio; PP: per-protocol; VOC: vaso-occlusive crises.
Source: Novartis – Data on File: Additional Study Information.[31]

2. Provide a summary of the study results for each relevant comparison and outcome.

5.4.3 Primary efficacy endpoint (ITT and per-protocol [PP] populations)

Annualised rate of VOC leading to healthcare visits

The SUSTAIN trial met the primary endpoint, demonstrating a statistically significant and clinically meaningful reduction in the annualised rate of VOC leading to healthcare visit with crizanlizumab 5 mg/kg compared with placebo.[3]

At the end of the treatment phase, the median annualised rate of VOC leading to healthcare visits in the crizanlizumab 5 mg/kg arm was 1.63 (interquartile range, 0.00–3.97), as compared with 2.98 (interquartile range, 1.25–5.87) in the placebo arm (indicating a 45.3% lower rate with crizanlizumab 5 mg/kg; Hodges-Lehmann median absolute difference of -1.01 [95% CI, -2.00, 0.00]; P = 0.010) (Table 17).[3, 32]

The primary endpoint findings were supported by a sensitivity analysis of the annualised rate of VOC leading to healthcare visits among the 125 patients in the PP population, which only included those patients who had received at least 12 of the 14 planned study drug doses, completed a visit at least 14 days after final dose of study drug, and had no major protocol violations that impacted the efficacy assessments. The median annualised rate of VOC leading to healthcare visits in the PP population was 1.04 (range, 0.00–3.42) in the crizanlizumab 5 mg/kg arm, as compared to 2.18 (range, 1.96–4.96) in the placebo arm (indicating a 52.3% lower rate with crizanlizumab 5 mg/kg, Hodges-Lehmann median absolute difference of -1.02 [95% CI, -2.00, -0.03]; P = 0.02).[3, 31]

Stroke was not included as part of the definition of VOC in the SUSTAIN trial. However, ischemic 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).[32] Given the rarity of these events, the inclusion of stroke in the definition of VOC would be expected to have a minimal impact on the annualised rate of VOC in each arm.

Table 17: Annualised rates of VOC leading to healthcare visits in the SUSTAIN trial (ITT and PP populations)

	Crizanlizumab, 5 mg/kg	Placebo
ITT population, N	67	65
Median rate per year (IQR)	1.63 (0.00–3.97)	2.98 (1.25–5.87)
Difference from placebo, %	-45.3	-
Hodges-Lehmann median rate per year[a]	2.00	3.49
Hodges-Lehmann median rate per year difference from placebo (95% CI)[b]	-1.01 (-2.00, 0.00)	-
P-value[b]	0.010	-
PP population, N	40	41
Median rate per year (IQR)	1.04 (0.00–3.42)	2.18 (1.96–4.96)
Difference from placebo, %	-52.3	-
Hodges-Lehmann median rate per year difference from placebo (95% CI)[b]	-1.02 (-2.00, -0.03)	-
P-value	0.02	-

[a] The Hodges-Lehmann median is a non-parametric estimator of the location parameter.
[b] Median differences and confidence intervals were estimated using Hodges-Lehmann method. P-values were from a Stratified Wilcoxon Rank Sum Test
Abbreviations: CI: confidence interval; IQR: inter-quartile range; ITT: intention-to-treat; PP: per-protocol; VOC: vaso-occlusive crises.
Source: Ataga et al. (2017) – Table 2;[3] Novartis Clinical Trials Results Website: SUSTAIN Technical Result Summary;[32] Novartis – Data on File: Additional Study Information.[31]

In a subsequent post-hoc analysis of the SUSTAIN trial, analyses were also conducted to determine the number of VOC events across all medical facilities, and by medical facility type.[113] Crizanlizumab 5 mg/kg was shown to be associated with a reduction in the event rate for VOC leading to a medical facility visit compared to placebo (2.3 versus 3.67 events per person year; incident rate ratio [IRR] of VOC leading to medical facility visit, 0.63 [95% CI, 0.5, 0.79];).[113] The reduction in VOC leading to medical facility visits with crizanlizumab 5 mg/kg as compared to placebo was largely driven by a reduction in visits to emergency care units (IRR, 0.55 [95% CI, 0.35, 0.87];), and specialised SCD crisis centres (IRR, 0.34 [95% CI, 0.18, 0.62];), as well as a trend towards a decrease in hospital inpatient admissions (IRR, 0.76 [95% CI, 0.56, 1.05];).[113]

5.4.4 Secondary and exploratory efficacy outcomes (ITT population only)

A summary of the results from the secondary efficacy outcomes of the SUSTAIN trial are presented in Table 18, and are described in further detail below.

Table 18: Secondary efficacy endpoints in the SUSTAIN trial (ITT population)

Outcome	Crizanlizumab, 5 mg/kg, N=67	Placebo, N=65
Annualised rate of days hospitalised (key secondary endpoint)		
Median rate per year (IQR)	4.00 (0.00–25.72)	6.87 (0.00–28.30)
Difference from placebo, %	-41.8	-
Hodges-Lehmann median rate per year[a]	12.48	13.00
Hodges-Lehmann median rate per year difference from placebo (95% CI)[b]	0.00 (-4.36, 0.00)	-
P-value[c]	0.450	-
Time to first VOC leading to healthcare visits		
Median time to first crisis (IQR), months	4.07 (1.31–NR)[b]	1.38 (0.39–4.90)
HR (95% CI)	0.50 (0.33, 0.74)	-
Time to second VOC leading to healthcare visits		
Median time to second crisis (IQR), months	10.32 (4.47–NR)[b]	5.09 (2.96–11.01)
HR (95% CI)	0.53 (0.33, 0.87)	-
Annualised rate of uncomplicated VOC leading to healthcare visits		
Median rate per year (IQR)	1.08 (0.00–3.96)	2.91 (1.00–5.00)
Difference from placebo, %	-62.9	-
Hodges-Lehmann median rate per year[b]	1.97	3.00
Hodges-Lehmann median rate per year difference from placebo (95% CI)[c]	-1.00 (-1.98, 0.00)	-
VOC free patients (post-hoc analysis)		
Number (%) of patients free of VOC leading to healthcare visits	24 (35.8)	11 (16.9)
OR (95% CI)	2.85 (1.24, 6.56)	-

[a] The Hodges-Lehmann median is a non-parametric estimator of the location parameter. [b] Median differences and confidence intervals were estimated using Hodges-Lehmann method. [c] P-value is for the comparison between the active-treatment group and the placebo group and were calculated with the use of a stratified Wilcoxon rank-sum test.

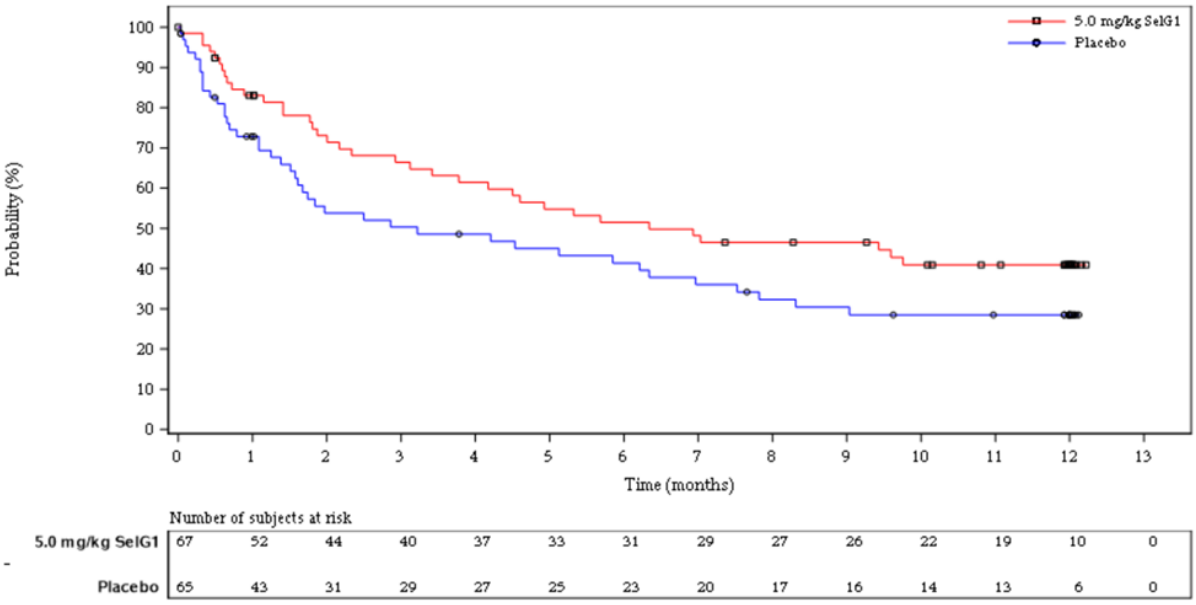
Abbreviations: CI: confidence intervals; HR: hazard ratio; IQR: inter-quartile range; ITT: intention-to-treat; OR: odds ratio; VOC: vaso-occlusive crises.

Source: Ataga et al. (2017) – Table 3;[3] Novartis – Data on File: Additional Study Information;[31] Novartis Clinical Trials Results Website: SUSTAIN Technical Result Summary.[32]

Annualised rate of days hospitalised (key secondary endpoint)

Crizanlizumab 5 mg/kg led to a 41.8% lower median annual rate of days hospitalised compared to placebo (4.00 versus 6.87 days; Hodges-Lehmann median absolute difference of 0.00 days hospitalised per year compared to placebo [95% CI, −4.36, 0.00; P = 0.450]).[3] This numerical but statistically non-significant reduction in the annualised rate of hospitalisation should however be considered clinically relevant, considering that VOC tend to be the primary cause of hospitalisation amongst patients with SCD, and that the lack of statistical significance between the treatment arms for this endpoint is likely due to the variability and skewed nature of the data.[32] For example, the full range in the rate of annual days hospitalised was 0.0–130.7 in the crizanlizumab 5 mg/kg arm and 0.0–307.4 in the placebo arm, meaning that a small proportion of patients in each group were hospitalised for a much longer period of time than average.[31] Further post-hoc analyses of SUSTAIN have shown that a higher proportion of patients were not hospitalised (i.e. zero days hospitalised) in the crizanlizumab 5 mg/kg arm versus placebo (46.3% versus 35.4%), and that the median time to first hospitalisation was more prolonged in the crizanlizumab 5 mg/kg arm versus placebo (6.34 months versus 3.22 months; HR, 0.683 [95% CI, 0.437, 1.066]; see Figure 7 for the Kaplan-Meier plot).[31]

Figure 7: Kaplan-Meier estimates of time to first hospitalisation (ITT population)



SelG1 = crizanlizumab
Abbreviations: ITT: intention-to-treat.
Source: Novartis – Data on File: Additional Study Information.[31]

The analyses described above included all hospitalisation days, and not just hospitalisation days due to VOC. Exploratory analyses of SUSTAIN were also conducted to determine the annualised rate of days with VOC leading healthcare visits (see below).

Annualised rate of days with VOC leading to healthcare visits (exploratory analysis)

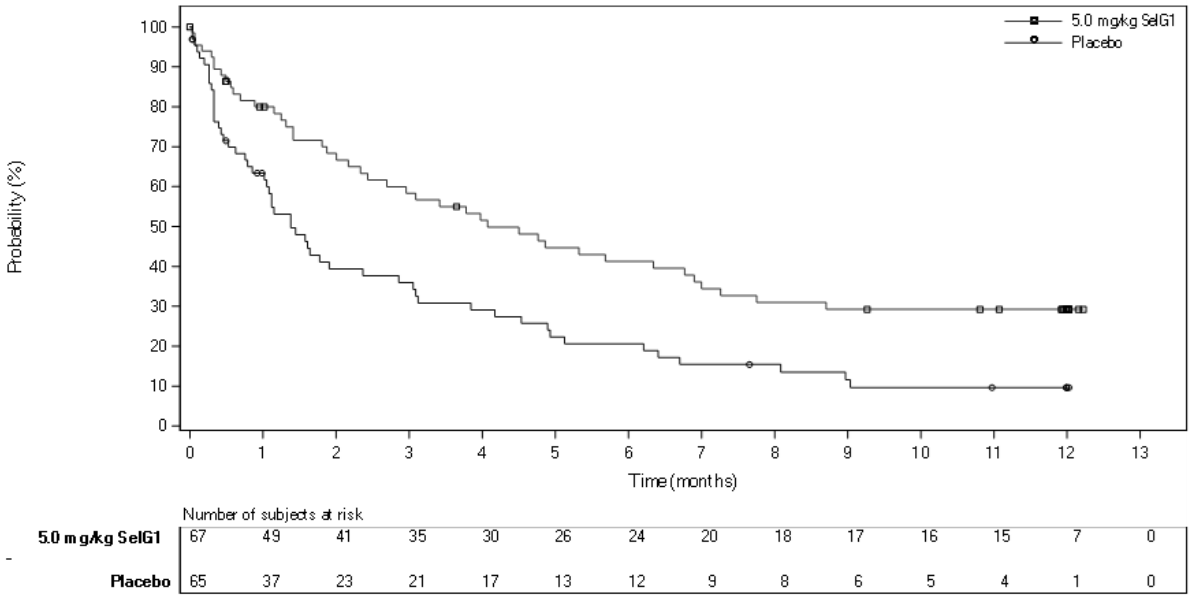
The annualised rate of days with VOC leading to healthcare visits was assessed as an exploratory outcome in the SUSTAIN trial and was defined as the total number of days with VOC leading to healthcare visits by the patient from randomisation, analysed using the same method for the primary efficacy analysis to determine an annualised rate.[31] In the crizanlizumab 5 mg/kg arm, the median annualised rate of days with VOC leading to healthcare visits (9.79) was lower

than in the placebo arm (13.92), although the difference was not statistically significant (P = 0.092).[31]

Time to first and second crisis

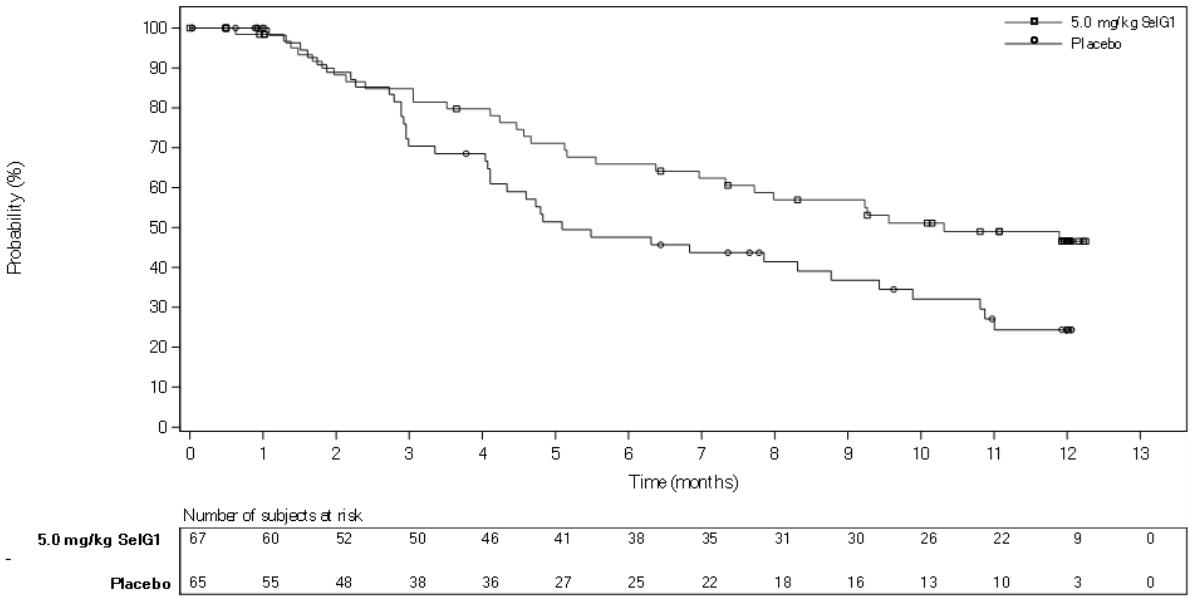
When compared with placebo, crizanlizumab 5 mg/kg demonstrated an estimated 50% risk reduction in the median time to first VOC leading to healthcare visits (HR, 0.50 [95% CI, 0.33, 0.74]) and an estimated 47% risk reduction in the median time to second VOC leading to healthcare visits (HR, 0.53 [95% CI, 0.33, 0.87]).[3, 32] Based on Kaplan-Meier estimates, treatment with crizanlizumab 5 mg/kg was associated with longer median time to first and second VOC leading to health visits compared with placebo (4.07 versus 1.38 months and 10.32 versus 5.09 months, respectively).[3] Kaplan-Meier plots for each of these outcomes are presented in Figure 8 and Figure 9.

Figure 8: Kaplan-Meier estimates of time to first VOC leading to healthcare visits (ITT population)



SelG1 = crizanlizumab
Abbreviations: ITT: intention-to-treat; VOC: vaso-occlusive crises.
Source: Crizanlizumab D181 SmPC.[12]

Figure 9: Kaplan-Meier estimates of time to second VOC leading to healthcare visits (ITT population)



SelG1 = crizanlizumab
Abbreviations: ITT: intention-to-treat; VOC: vaso-occlusive crises.
Source: Novartis – Data on File: Additional Study Information.[31]

VOC free patients (post-hoc analysis)

There was a two-fold increase in the proportion of patients free from VOC leading to healthcare visits in the crizanlizumab 5 mg/kg arm compared with placebo (35.8% versus 16.9%; OR, 2.85 [95% CI, 1.24, 6.56]).[3, 31]

Uncomplicated crises and type of VOC leading to healthcare visits

Uncomplicated crises were defined as VOC leading to healthcare visits other than the ACS, hepatic sequestration, splenic sequestration, or priapism.[3] 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 versus 2.91; Hodges-Lehmann median absolute difference of -1.00 [95% CI, -1.98, 0.00]).[3] Other complications, such as hepatic sequestration, splenic sequestration, and priapism, were also rare (median annualised rate, 0.00 in all treatment arms).[3]

A breakdown of treatment-emergent VOC leading to healthcare visits that occurred in the trial by event category (from the safety population) is provided in Table 19. The low incidence of ACS and other complications observed in SUSTAIN may be due to the limited (52-week) duration of the trial.[3]

Table 19: Treatment-emergent VOC leading to healthcare visits by event (safety population)[a]

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

[a] Treatment-emergent VOC are defined as all VOC which start (or increase in severity) after the date of first dose of study medication. All treatment-emergent VOC were adjudicated by the CRC.
[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 CRC subsequently indicated that four events which met the criteria for VOC should be given the event classification of "death".
Abbreviations: ACS: acute chest syndrome; CRC: Crisis Review Committee; VOC: vaso-occlusive crises.
Source: Novartis – Data on File: Additional Study Information.[31]

Patient-reported outcomes

In the SUSTAIN trial, the BPI and SF-36 v2.0 questionnaires (both 1-week recall) were administered to patients at each treatment visit, i.e. at Days 1 and 15, and then every 4 weeks from Week 6, and at Week 52 and the Week 58 follow-up visit. Results from these questionnaires are presented in Table 20 (SF-36 physical health domain), Table 21 (SF-36 mental health domain), Table 22 (BPI pain severity domain), and Table 23 (BPI pain interference domain).

Changes in the pain-severity domain and pain interference domain of the BPI questionnaire were small and there were no statistically significant changes from baseline in the least squares mean over the course of the trial.[3] No significant differences between treatment arms were reported for either domain of the BPI.[32] In addition, there were no statistically significant differences observed between the crizanlizumab 5 mg/kg arm versus the placebo arm in the least squares mean change from baseline at Week 52 or the Week 58 follow-up visit in any of the SF-36 scales or domains.[31] The lack of significant difference observed in the SF-36 v2.0 scores between treatment arms indicates that treatment with crizanlizumab (including its administration via intravenous infusion) did not result any detrimental impact on HRQoL due to toxicity or side effects.[31]

Table 20: Treatment comparisons in change from baseline in physical health domain from SF-36 (ITT population)

	Treatment group		Treatment group comparison (active – placebo)
	Crizanlizumab, 5 mg/kg, N=67	**Placebo, N=65**	**Crizanlizumab, 5 mg/kg, N=67**
Baseline, n	63	65	-
Mean (SD)	39.369 (10.1090)	40.186 (8.6707)	-
Day 15, n	61	59	-
Mean (SD)	40.043 (9.9135)	38.516 (8.9416)	-
Day 15 CfB, n	59	59	-
Mean (SD)	0.137 (4.9797)	-1.457 (6.4952)	-
LS mean (95% CI)	0.348 (-1.114, 1.810)	-1.384 (-2.849, 0.082)	1.732 (-0.299, 3.763)
P-value	0.639	0.064	0.094
Week 14, n	55	48	-
Mean (SD)	38.836 (10.5972)	39.496 (11.2849)	-
Week 14 CfB, n	53	48	-
Mean (SD)	-1.169 (5.9755)	-1.090 (7.3194)	-
LS mean (95% CI)	-0.935 (-2.940, 1.069)	-0.664 (-2.752, 1.424)	-0.272 (-3.136, 2.592)
P-value	0.358	0.531	0.852
Week 26, n	48	46	-
Mean (SD)	40.478 (10.1347)	40.545 (9.1943)	-
Week 26 CfB, n	46	46	-
Mean (SD)	0.737 (7.8805)	0.256 (7.4647)	-
LS mean (95% CI)	0.564 (-1.458, 2.586)	0.053 (-1.987, 2.093)	0.511 (-2.330, 3.352)
P-value	0.582	0.959	0.723
Week 38, n	46	42	-

	Treatment group		Treatment group comparison (active – placebo)
	Crizanlizumab, 5 mg/kg, N=67	**Placebo, N=65**	**Crizanlizumab, 5 mg/kg, N=67**
Mean (SD)	41.534 (10.9681)	40.605 (10.3769)	-
Week 38 CfB, n	45	42	-
Mean (SD)	1.626 (8.1914)	-0.154 (8.4164)	-
LS mean (95% CI)	1.571 (-0.706, 3.848)	0.368 (-1.981, 2.716)	1.203 (-2.039, 4.445)
P-value	0.175	0.757	0.464
Week 52, n	36	34	-
Mean (SD)	41.901 (11.0729)	41.392 (11.0879)	-
Week 52 CfB, n	35	34	-
Mean (SD)	2.688 (8.1424)	0.327 (7.7844)	-
LS mean (95% CI)	2.013 (-0.362, 4.389)	0.412 (-2.005, 2.829)	1.601 (-1.762, 4.965)
P-value	0.096	0.737	0.348
Week 58 follow-up, n	47	46	-
Mean (SD)	40.854 (10.3975)	41.128 (9.3069)	-
Week 58 follow-up[a] CfB, n	47	46	-
Mean (SD)	1.058 (8.3775)	0.426 (8.2605)	-
LS mean (95% CI)	1.009 (-1.273, 3.290)	0.335 (-1.982, 2.652)	0.674 (-2.551, 3.899)
P-value	0.384	0.776	0.680

[a] For patients who discontinue crizanlizumab or placebo, assessments six weeks or more after final dose are considered in the Week 58 Follow-up windowed visit.
Abbreviations: CfB: change from baseline; CI: confidence Interval; ITT: intention to treat; LS: least squares; SD: standard deviation; SF-36: Short Form 36-item questionnaire.
Source: Novartis – Data on File: Additional Study Information.[31]

Table 21: Treatment comparisons in change from baseline in mental health domain from SF-36 (ITT population)

	Treatment group		Treatment group comparison (active – placebo)
	Crizanlizumab, 5 mg/kg, N=67	**Placebo, N=65**	**Crizanlizumab, 5 mg/kg, N=67**
Baseline, n	63	65	-
Mean (SD)	46.460 (11.1014)	43.938 (14.8107)	-
Day 15, n	61	59	-
Mean (SD)	48.549 (10.1299)	46.397 (13.4165)	-
Day 15 CfB, n	59	59	-
Mean (SD)	2.206 (9.1040)	2.628 (11.0797)	-
LS mean (95% CI)	2.102 (-0.097, 4.301)	1.612 (-0.612, 3.837)	0.490 (-2.587, 3.566)
P-value	0.061	0.154	0.754
Week 14, n	55	48	-
Mean (SD)	47.856 (11.7499)	49.343 (13.3241)	-
Week 14 CfB, n	53	48	-
Mean (SD)	1.229 (12.1501)	2.282 (9.8767)	-
LS mean (95% CI)	1.361 (-1.389, 4.112)	2.678 (-0.215, 5.571)	-1.317 (-5.267, 2.633)
P-value	0.330	0.069	0.511
Week 26, n	48	46	-
Mean (SD)	47.396 (13.1434)	47.697 (11.3960)	-
Week 26 CfB, n	46	46	-
Mean (SD)	1.268 (12.4105)	2.438 (11.8645)	-
LS mean (95% CI)	1.071 (-1.890, 4.031)	1.901 (-1.094, 4.896)	-0.830 (-4.998, 3.338)
P-value	0.476	0.212	0.694
Week 38, n	46	42	-

	Treatment group		Treatment group comparison (active – placebo)
	Crizanlizumab, 5 mg/kg, N=67	**Placebo, N=65**	**Crizanlizumab, 5 mg/kg, N=67**
Mean (SD)	50.089 (12.3488)	45.323 (14.5010)	-
Week 38 CfB, n	45	42	-
Mean (SD)	1.886 (11.1175)	0.270 (13.5659)	-
LS mean (95% CI)	1.893 (-1.095, 4.881)	-0.524 (-3.621, 2.573)	2.417 (-1.841, 6.675)
P-value	0.212	0.738	0.264
Week 52, n	36	34	-
Mean (SD)	47.458 (12.6146)	46.929 (13.9156)	-
Week 52 CfB, n	35	34	-
Mean (SD)	-0.847 (9.6358)	1.441 (10.9061)	-
LS mean (95% CI)	0.157 (-3.251, 3.566)	0.609 (-2.858, 4.075)	-0.451 (-5.281, 4.378)
P-value	0.927	0.729	0.854
Week 58 follow-up, n	47	46	-
Mean (SD)	45.410 (12.7382)	46.047 (12.4552)	-
Week 58 follow-up[a] CfB, n	47	46	-
Mean (SD)	-0.425 (10.4659)	0.995 (11.3632)	-
LS mean (95% CI)	-0.505 (-3.385, 2.376)	0.711 (-2.217, 3.638)	-1.215 (-5.281, 2.851)
P-value	0.730	0.632	0.556

[a] For patients who discontinue crizanlizumab or placebo, assessments six weeks or more after final dose are considered in the Week 58 Follow-up windowed visit.
Abbreviations: CfB: change from baseline; CI: confidence Interval; ITT: intention to treat; LS: least squares; SD: standard deviation; SF-36: Short Form 36-item questionnaire.
Source: Novartis – Data on File: Additional Study Information.[31]

Table 22: Treatment comparisons in change from baseline in pain severity domain[a] (ITT population)

	Treatment group		Treatment group comparison (active – placebo)
	Crizanlizumab, 5 mg/kg, N=67	**Placebo, N=65**	**Crizanlizumab, 5 mg/kg, N=67**
Baseline, n	48	55	-
Mean (SD)	4.363 (2.1176)	4.129 (2.0076)	-
Day 15, n	46	52	-
Mean (SD)	4.241 (2.4058)	4.615 (2.0433)	-
Day 15 CfB, n	38	47	-
Mean (SD)	-0.123 (1.3419)	0.355 (1.7298)	-
LS mean (95% CI)	-0.116 (-0.591, 0.358)	0.221 (-0.211, 0.654)	-0.338 (-0.974, 0.298)
P-value	0.628	0.313	0.295
Week 14, n	42	37	-
Mean (SD)	4.595 (1.8983)	4.196 (2.0918)	-
Week 14 CfB, n	32	33	-
Mean (SD)	-0.146 (1.1520)	-0.152 (2.0728)	-
LS mean (95% CI)	-0.026 (-0.514, 0.463)	-0.297(-0.774, 0.180)	0.272 (0.404, 0.948)
P-value	0.918	0.219	0.427
Week 26, n	33	33	-
Mean (SD)	4.232 (2.0443)	3.811 (1.9616)	-
Week 26 CfB, n	27	32	-
Mean (SD)	-0.377 (1.2460)	-0.563 (2.3751)	-
LS mean (95% CI)	-0.200 (-0.821, 0.422)	-0.456 (-1.047, 0.135)	0.256 (-0.596, 1.108)
P-value	0.526	0.129	0.552
Week 38, n	33	33	-

	Treatment group		Treatment group comparison (active – placebo)
	Crizanlizumab, 5 mg/kg, N=67	**Placebo, N=65**	**Crizanlizumab, 5 mg/kg, N=67**
Mean (SD)	4.242 (1.7848)	4.576 (1.8087)	-
Week 38 CfB, n	25	29	-
Mean (SD)	-0.267 (1.4079)	0.333 (1.8430)	-
LS mean (95% CI)	-0.271 (-0.810, 0.268)	0.073 (-0.443, 0.590)	-0.344 (-1.082, 0.394)
P-value	0.321	0.779	0.357
Week 52, n	22	24	-
Mean (SD)	4.216 (1.9060)	3.854 (2.2589)	-
Week 52 CfB, n	18	22	-
Mean (SD)	-0.634 (1.8501)	-0.310 (1.9508)	-
LS mean (95% CI)	-0.478 (-1.142, 0.186)	-0.261 (-0.876, 0.354)	-0.217 (-1.117, 0.682)
P-value	0.156	0.402	0.632
Week 58 follow-up, n	34	35	-
Mean (SD)	4.385 (2.1072)	4.221 (1.8429)	-
Week 58 follow-up[b] CfB, n	27	30	-
Mean (SD)	-0.145 (1.2309)	-0.444 (1.8626)	-
LS mean (95% CI)	-0.079 (-0.599, 0.442)	-0.095 (-0.601, 0.412)	0.016 (-0.705, 0.736)
P-value	0.765	0.712	0.965

[a] BPI severity is calculated as the average of non-missing responses to pain severity questions 12-15.[b] For patients who discontinue crizanlizumab or placebo, assessments six weeks or more after final dose are considered in the Week 58 Follow-up windowed visit.
Abbreviations: CfB: change from baseline; CI: confidence Interval; ITT: intention to treat; LS: least squares; SD: standard deviation.
Source: Novartis Clinical Trials Results Website: SUSTAIN Technical Result Summary;[32] Novartis – Data on File: Additional Study Information.[31]

Table 23: Treatment comparisons in change from baseline in pain interference domain[a] (ITT population)

	Treatment group		Treatment group comparison (active – placebo)
	Crizanlizumab, 5 mg/kg, N=67	**Placebo, N=65**	**Crizanlizumab, 5 mg/kg, N=67**
Baseline, n	48	55	-
Mean (SD)	4.643 (2.5726)	4.995 (2.9470)	-
Day 15, n	46	52	-
Mean (SD)	3.810 (2.8626)	4.697 (2.5645)	-
Day 15 CfB, n	38	47	-
Mean (SD)	-0.674 (2.2868)	-0.816 (2.3556)	-
LS mean (95% CI)	-0.932 (-1.580, -0.284)	-0.791 (-1.381, -0.202)	-0.140 (-1.010, 0.729)
P- value	0.005	0.009	0.750
Week 14, n	42	37	-
Mean (SD)	4.764 (2.8445)	4.984 (2.9371)	-
Week 14 CfB, n	32	33	-
Mean (SD)	-0.213 (2.3988)	-0.039 (3.0412)	-
LS mean (95% CI)	-0.433 (-1.269, 0.403)	-0.103 (-0.929, 0.723)	-0.329 (-1.500, 0.841)
P- value	0.307	0.805	0.578
Week 26, n	33	33	-
Mean (SD)	4.596 (2.4385)	4.567 (2.4648)	-
Week 26 CfB, n	27	32	-
Mean (SD)	-0.583 (2.2844)	-0.821 (3.1561)	-
LS mean (95% CI)	-0.685 (-1.476, 0.106)	-0.719 (-1.459, 0.020)	0.034 (-1.040, 1.109)
P- value	0.089	0.057	0.950
Week 38, n	33	33	-

	Treatment group		Treatment group comparison (active – placebo)
	Crizanlizumab, 5 mg/kg, N=67	**Placebo, N=65**	**Crizanlizumab, 5 mg/kg, N=67**
Mean (SD)	4.065 (2.2431)	4.909 (2.5332)	-
Week 38 CfB, n	25	29	-
Mean (SD)	-0.886 (2.7720)	-0.221 (3.1076)	-
LS mean (95% CI)	-0.636 (-1.428, 0.157)	-0.279 (-1.032, 0.474)	-0.357 (-1.441, 0.727)
P- value	0.115	0.463	0.515
Week 52, n	22	24	-
Mean (SD)	4.663 (2.5129)	4.386 (2.8779)	-
Week 52 CfB, n	18	22	-
Mean (SD)	-1.014 (2.0989)	-0.819 (2.8490)	-
LS mean (95% CI)	-0.662 (-1.615, 0.290)	-0.796 (-1.673, 0.081)	0.134 (-1.154, 1.422)
P- value	0.170	0.075	0.837
Week 58 follow-up, n	34	35	-
Mean (SD)	4.269 (2.4446)	4.639 (2.4845)	-
Week 58 follow-up[b] CfB, n	27	30	-
Mean (SD)	-0.476 (2.3473)	-0.802 (2.5785)	-
LS mean (95% CI)	-0.538 (-1.254, 0.178)	-0.671 (-1.360, 0.019)	0.133 (-0.854, 1.120)
P- value	0.139	0.057	0.790

[a] BPI interference is calculated as the average of non-missing responses to pain interference questions 23a-23g.[b] For patients who discontinue crizanlizumab or placebo, assessments six weeks or more after final dose are considered in the Week 58 Follow-up windowed visit.
Abbreviations: CfB: change from baseline; CI: confidence Interval; ITT: intention to treat; LS: least squares; SD: standard deviation.
Source: Novartis Clinical Trials Results Website: SUSTAIN Technical Result Summary;[32] Novartis – Data on File: Additional Study Information.[31]

5.4.5 Subgroup analysis

Pre-specified subgroup analyses of the annualised rates of VOC leading to healthcare visits in the ITT population were performed according to concomitant HU/HC use (yes or no), history of VOC leading to healthcare visits (2–4 or 5–10 crises in the 12 months prior to the study) and SCD genotype (HbSS or non-HbSS).[3]

The demographic and baseline characteristics of patients by treatment arm in the SUSTAIN trial according to history of VOC leading to healthcare visits, SCD genotype and concomitant HU/HC use are presented in Table 24, Table 25 and Table 26, respectively.

Table 24: Patient demographics and baseline characteristics by history of VOC leading to healthcare visits and treatment arm in the SUSTAIN trial

Characteristic	2–4 crises		5–10 crises	
	Crizanlizumab, 5 mg/kg, N=42	Placebo, N=41	Crizanlizumab, 5 mg/kg, N=25	Placebo, N=24
Age – years				
Median	28.5	27	31	26
Range	16–63	16–56	17–55	18–51
Sex – n (%)				
Male	20 (47.6)	18 (43.9)	12 (48.0)	9 (37.5)
Female	22 (52.4)	23 (56.1)	13 (52.0)	15 (62.5)
Race – n (%)				
Black/African American	39 (92.9)	39 (95.1)	21 (84.0)	21 (87.5)
SCD genotype – n (%)				
HbSS	31 (73.8)	29 (70.7)	16 (64.0)	18 (75.0)
HbSC	5 (11.9)	5 (12.2)	4 (16.0)	3 (12.5)
HbSβ^0-thalassemia	2 (4.8)	6 (14.6)	1 (4.0)	1 (4.2)
HbSβ^+-thalassemia	3 (7.1)	0	4 (16.0)	1 (4.2)
Other	1 (2.4)	1 (2.4)	0	1 (4.2)
Concomitant HU/HC use – n (%)				
Yes	25 (59.5)	24 (58.5)	17 (68.0)	16 (66.7)
No	17 (40.5)	17 (41.5)	8 (32.0)	8 (33.3)
VOC leading to healthcare visits during previous 12 months – n (%)				
2–4 crises	42 (100)	41 (100)	NA	NA
5–10 crises	NA	NA	25 (100)	24 (100)

Abbreviations: HbS: homozygous haemoglobin; HbSS: homozygous sickle haemoglobin; HC: hydroxycarbamide; HU: hydroxyurea; ITT: intention to treat; NA: not applicable; SCD: sickle cell disease; VOC: vaso-occlusive crises.
Sources: Kutlar et al. (2019).[149]

Table 25: Patient demographics and baseline characteristics by SCD genotype and treatment arm in the SUSTAIN trial

Characteristic	HbSS		Non-HbSS	
	Crizanlizumab, 5 mg/kg, N=47	Placebo, N=47	Crizanlizumab, 5 mg/kg, N=20	Placebo, N=18
Age – years				
Median	30	26	27.5	31.5
Range	18–63	16–56	16–62	18–54
Sex – n (%)				
Male	23 (48.9)	20 (42.6)	9 (45.0)	7 (38.9)
Female	24 (51.1)	27 (57.4)	11 (55.0)	11 (61.1)
Race – n (%)				
Black/African American	44 (93.6)	42 (89.4)	16 (80.0)	18 (100)
SCD genotype – n (%)				
HbSS	47 (100)	47 (100)	NA	NA
HbSC	NA	NA	9 (45.0)	8 (44.4)
HbSβ^0-thalassemia	NA	NA	3 (15.0)	7 (38.9)
HbSβ^+-thalassemia	NA	NA	7 (35.0)	1 (5.6)
Other	NA	NA	1 (5.0)	2 (11.1)
Concomitant HU/HC use – n (%)				
Yes	34 (72.3)	31 (66.0)	8 (40.0)	9 (50.0)
No	13 (27.7)	16 (34.0)	12 (60.0)	9 (50.0)
VOC leading to healthcare visits during previous 12 months – n (%)				
2–4 crises	31 (66.0)	29 (61.7)	11 (55.0)	12 (66.7)
5–10 crises	16 (34.0)	18 (38.3)	9 (45.0)	6 (33.3)

Abbreviations: HbS: homozygous haemoglobin; HbSS: homozygous sickle haemoglobin; HC: hydroxycarbamide; HU: hydroxyurea; ITT: intention to treat; NA: not applicable; SCD: sickle cell disease; VOC: vaso-occlusive crises.
Sources: Kutlar et al. (2019).[149]

Table 26: Patient demographics and baseline characteristics by concomitant HU/HC use and treatment arm in the SUSTAIN trial

Characteristic	HU/HC: Yes		HU/HC: No	
	Crizanlizumab, 5 mg/kg, N=42	Placebo, N=40	Crizanlizumab, 5 mg/kg, N=25	Placebo, N=25
Age – years				
Median	29.5	26	28	28
Range	16–63	16–56	17–54	18–50
Sex – n (%)				
Male	22 (52.4)	18 (45.0)	10 (40.0)	9 (36.0)
Female	20 (47.6)	22 (55.0)	15 (60.0)	16 (64.0)
Race – n (%)				
Black/African American	38 (90.5)	35 (87.5)	22 (88.0)	25 (100)
SCD genotype – n (%)				
HbSS	34 (81.0)	31 (77.5)	13 (52.0)	16 (64.0)
HbSC	2 (4.8)	4 (10.0)	7 (28.0)	4 (16.0)
HbSβ^0-thalassemia	2 (4.8)	4 (10.0)	1 (4.0)	3 (12.0)
HbSβ^+-thalassemia	3 (7.1)	0	4 (16.0)	1 (4.0)
Other	1 (2.4)	1 (2.5)	0	1 (4.0)
Concomitant HU/HC use – n (%)				
Yes	42 (100)	40 (100)	NA	NA
No	NA	NA	25 (100)	25 (100)
VOC leading to healthcare visits during previous 12 months – n (%)				
2–4 crises	25 (59.5)	24 (60.0)	17 (68.0)	17 (68.0)
5–10 crises	17 (40.5)	16 (40.0)	8 (32.0)	8 (32.0)

Abbreviations: HbS: homozygous haemoglobin; HbSS: homozygous sickle haemoglobin; HC: hydroxycarbamide; HU: hydroxyurea; ITT: intention to treat; NA: not applicable; SCD: sickle cell disease; VOC: vaso-occlusive crises.
Sources: Kutlar et al. (2019).[149]

Across all subgroups, crizanlizumab 5 mg/kg was associated with a lower median annualised rate of VOC leading to healthcare visits compared to placebo (Table 27).[3] As SUSTAIN was not powered to detect differences between treatment arms in the pre-specified subgroups, the results of the statistical tests in these subgroup analyses should be interpreted with caution. However, the results do suggest that crizanlizumab is efficacious regardless of concomitant HU/HC use, as well as SCD genotype and history of VOC leading to healthcare visits.

In addition, post-hoc analyses were also performed for selected secondary outcomes (including the time to first VOC leading to healthcare visits and the proportion of patients free of VOC leading to healthcare visits) comparing the crizanlizumab 5 mg/kg and placebo arms (see Table 28, Figure 10 and Figure 11).[117]

Table 27: Prespecified subgroup analyses from the ITT population in the SUSTAIN trial

	Crizanlizumab (5 mg/kg)	Placebo
According to concomitant HU/HC use		
Yes	n=42	n=40
Median annualised rate of VOC leading to healthcare visits (IQR)	2.43 (0.00–4.01)	3.58 (1.31–6.23)
Difference from placebo – %	-32.1	-
Hodges-Lehmann median annual rate of VOC leading to healthcare visits[a]	2.55	4.00
Hodges-Lehmann median difference from placebo (95% CI; p-value)[b]	-1.01 (-2.44, 0.00; 0.084)	-
No	n=25	n=25
Median annualised rate of VOC leading to healthcare visits (IQR)	1.00 (0.00–2.00)	2.00 (1.63–3.90)
Difference from placebo – %	-50.0	-
Hodges-Lehmann median annual rate of VOC leading to healthcare visits[a]	1.47	2.51
Hodges-Lehmann median difference from placebo (95% CI; p-value)[b]	-1.02 (-2.00, 0.00; 0.046)	-
According to number of VOC leading to healthcare visits in previous 12 months		
2–4 VOC leading to healthcare visits	n=42	n=41
Median annualised rate of VOC leading to healthcare visits (IQR)	1.14 (0.00–2.00)	2.00 (2.00–3.90)
Difference from placebo – %	-43.0	-
Hodges-Lehmann median annual rate of VOC leading to healthcare visits[a]	1.98	2.12
Hodges-Lehmann median difference from placebo (95% CI; p-value)[b]	-0.05 (-1.56, 0.01; 0.279)	-
5–10 VOC leading to healthcare visits	n=25	n=24
Median annualised rate of VOC leading to healthcare visits (IQR)	1.97 (0.00–3.98)	5.32 (2.01–11.05)

	Crizanlizumab (5 mg/kg)	Placebo
Difference from placebo – %	-63.0	-
Hodges-Lehmann median annual rate of VOC leading to healthcare visits[a]	2.51	6.08
Hodges-Lehmann median difference from placebo (95% CI; p-value)[b]	-2.74 (-5.00, -0.83; 0.005)	-
According the SCD genotype (HbSS versus non-HbSS)		
HbSS	n=47	n=47
Median annualised rate of VOC leading to healthcare visits (IQR)	1.97 (0.00–3.96)	3.01 (1.01–6.00)
Difference from placebo – %	-34.6	-
Hodges-Lehmann median annual rate of VOC leading to healthcare visits[a]	2.01	3.73
Hodges-Lehmann median difference from placebo (95% CI; p-value)[b]	-1.01 (-2.18, 0.00; 0.060)	-
Non-HbSS	n=20	n=18
Median annualised rate of VOC leading to healthcare visits (IQR)	0.99 (0.00–4.01)	2.00 (1.86–5.00)
Difference from placebo – %	-50.5	-
Hodges-Lehmann median annual rate of VOC leading to healthcare visits[a]	1.99	2.99
Hodges-Lehmann median difference from placebo (95% CI; p-value)[b]	-1.01 (-2.01, 0.00; 0.223)	-
According the SCD genotype (other genotype categories)		
HbSC	n=9	n=8
Median annualised rate of VOC leading to healthcare visits (range)	1.00 (0.0–4.0)	3.50 (0.0–10.1)

	Crizanlizumab (5 mg/kg)	Placebo
Difference from placebo – %	-71.4	-
Hodges-Lehmann median annual rate of VOC leading to healthcare visits[a]	0.99	4.13
Hodges-Lehmann median difference from placebo (95% CI)[b]	-2.00 (-7.87, -0.01)	-
HbSS or HbSβ^0-thalassemia	n=50	n=54
Median annualised rate of VOC leading to healthcare visits (range)	1.97 (0.0–24.3)	2.99 (0.0–24.3)
Difference from placebo – %	-34.1	-
Hodges-Lehmann median annual rate of VOC leading to healthcare visits[a]	2.01	3.33
Hodges-Lehmann median difference from placebo (95% CI)[b]	-1.00 (-1.98, 0.00)	-
HbSC or HbSβ$^+$-thalassemia or other	n=17	n=11
Median annualised rate of VOC leading to healthcare visits (range)	0.98 (0.0–15.2)	2.01 (0.0–11.4)
Difference from placebo – %	-51.2	-
Hodges-Lehmann median annual rate of VOC leading to healthcare visits[a]	0.99	4.13
Hodges-Lehmann median difference from placebo (95% CI)[b]	-1.97 (-5.00, 0.00)	-

[a] The Hodges-Lehmann median is a non-parametric estimator of the location parameter.
[b] Median differences and confidence intervals were estimated using Hodges-Lehmann method. P-values were from a Stratified Wilcoxon Rank Sum Test, with HC/HU therapy (yes, no) and categorised crises history (2 to 4, 5 to 10) as reported in the Integrated Interactive Voice/Web Response System as the strata.
Abbreviations: CI: confidence interval; HbSS: homozygous sickle haemoglobin; HC: hydroxycarbamide; HU: hydroxyurea; IQR: inter-quartile range; ITT: intention-to-treat; SCD: sickle cell disease; VOC: vaso-occlusive crises.
Source: Ataga et al. (2017) – Table 2;[3] Novartis – Data on File: Additional Study Information.[31]

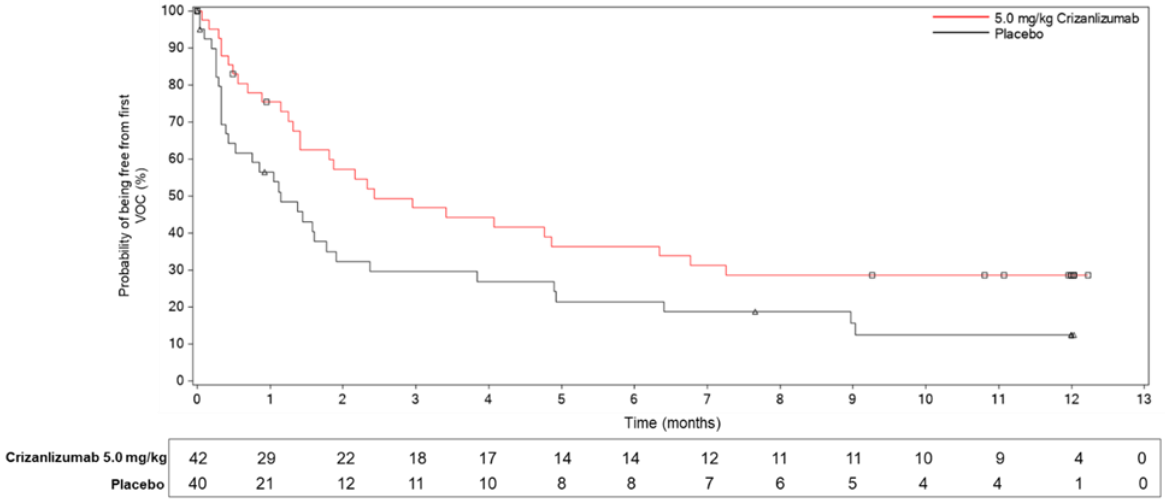
Table 28: Post-hoc subgroup analyses for selected secondary outcomes from the SUSTAIN trial

	Crizanlizumab (5 mg/kg)	Placebo
According to concomitant HU/HC use		
Yes	n=42	n =40
Proportion of patients free of VOC leading to healthcare visits (%)	33.3	17.5
Median time to first VOC leading to healthcare visits (months; IQR)	2.43 (1.15–NR)	1.15 (0.33–4.90)
No	n=25	n=25
Proportion of patients free of VOC leading to healthcare visits (%)	40.0	16.0
Median time to first VOC leading to healthcare visits (months; IQR)	5.68 (3.09–NR)	2.86 (0.79–4.53)
According to number of VOC leading to healthcare visits in previous 12 months		
2–4 VOC leading to healthcare visits	n=42	n=41
Proportion of patients free of VOC leading to healthcare visits (%)	40.5	24.4
Median time to first VOC leading to healthcare visits (months; IQR)	4.76 (1.81–NR)	1.61 (0.62–6.70)
5–10 VOC leading to healthcare visits	n=25	n=24
Proportion of patients free of VOC leading to healthcare visits (%)	28.0	4.2
Median time to first VOC leading to healthcare visits (months; IQR)	2.43 (1.25–7.75)	1.03 (0.30–2.97)
According the SCD genotype		
HbSS	n=47	n=47
Proportion of patients free of VOC leading to healthcare visits (%)	31.9	17.0
Median time to first VOC leading to healthcare visits (months; IQR)	4.07 (1.31–NR)	1.12 (0.33–4.17)

	Crizanlizumab (5 mg/kg)	Placebo
Non-HbSS	n=20	n=18
Proportion of patients free of VOC leading to healthcare visits (%)	45.0	16.7
Median time to first VOC leading to healthcare visits (months; IQR)	6.90 (1.41–NR)	3.09 (1.12–6.21)

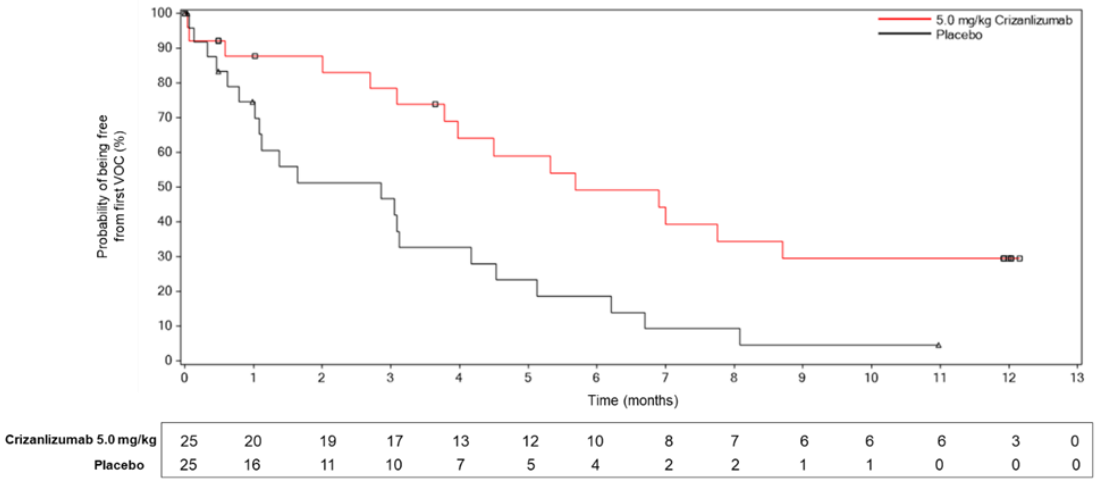
Abbreviations: Hb: haemoglobin; HC: hydroxycarbamide; HU: hydroxyurea; IQR: interquartile range; NR: not reported; SCD: sickle cell disease; VOC: vaso-occlusive crises.
Source: Kutlar et al. (2019) – Tables 1 and 2.[117]

Figure 10: Kaplan Meier curve of time to first VOC – patients treated with HU/HC



Abbreviations: HC: hydroxycarbamide; HU: hydroxyurea; VOC: vaso-occlusive crises.
Source: Novartis – Data on File: Additional Study Information.[31]

Figure 11: Kaplan Meier curve of time to first VOC – patients not treated with HU/HC



Abbreviations: HC: hydroxycarbamide; HU: hydroxyurea; VOC: vaso-occlusive crises.
Source: Novartis – Data on File: Additional Study Information.[31]

5.5 Individual study results (safety outcomes)

1. Describe the relevant endpoints, including the definition of the endpoint and methods of analysis.

Crizanlizumab is well tolerated, with a favourable and well-manageable safety profile. The safety of crizanlizumab 5 mg/kg has been evaluated in 111 patients with SCD (any genotype including HbSS, HbSC, HbS β^0-thalassemia, HbS β^+-thalassemia) in two studies: the pivotal study, SUSTAIN, a 52-week, randomised, double-blind, placebo-controlled study (n=66 at crizanlizumab 5 mg/kg), and the SOLACE-adults single arm, open label PK/PD and safety study (n=45 at crizanlizumab 5 mg/kg).[31]

The key safety endpoints assessed in the pooled safety analysis were as follows:

- Treatment exposure
- AEs
- SAEs
- ADRs (see Appendix C [Section 6.3] for definition of ADRs)

Safety endpoints were analysed based on the SUSTAIN safety population (as described in Section 5.4.2), and the crizanlizumab 5 mg/kg safety pool comprised of 111 patients exposed to the recommended crizanlizumab dose of 5 mg/kg in SUSTAIN and SOLACE-adults.[31] Only descriptive analyses of safety were performed (i.e. no formal between-treatment statistical analyses). AEs were summarised by Medical Dictionary for Regulatory Activities (MedDRA) and according to preferred term. Patients with multiple occurrences of the same AE or a continuing AE were counted once, and only the maximum severity level was provided.

2. For the technology, and the comparator, tabulate the total number of adverse events, frequency of occurrence (as a %), absolute and relative risk and 95% CI reported in each of the clinical studies. Categorise the adverse events by frequency, severity and system organ class.

5.5.1 Treatment exposure

Among the 111 patients in the crizanlizumab 5 mg/kg safety pool, the median duration of exposure was 46 weeks (range, 4–58 weeks). In the Safety set of the SUSTAIN trial, the median duration of exposure in the placebo arm (n=62) and crizanlizumab 5 mg/kg arm (n=66) was 54.0 weeks (range, 4–58) and 53.9 weeks (range, 4–57), respectively.[31] The duration of exposure to study drug in the crizanlizumab 5 mg/kg and placebo arms of the SUSTAIN trial is therefore not expected to impact any of the outcomes or safety assessments of the study.

5.5.2 Safety analysis

An overview of AEs in SUSTAIN and the crizanlizumab 5 mg/kg safety pool are presented in Table 29. Overall, crizanlizumab was well tolerated and the incidence of SAEs was similar across the crizanlizumab 5 mg/kg and placebo arms of SUSTAIN. SAEs in the SUSTAIN trial were reported by 17 patients (25.8%) in the crizanlizumab 5 mg/kg treatment arm and 17 patients (27.4%) in the placebo arm.[31]

In the crizanlizumab 5 mg/kg safety pool, the proportion of patients experiencing SAEs was 21.6%. Discontinuations due to adverse events were rare and occurred in 3 (2.7%) of the 111 patients treated with crizanlizumab 5 mg/kg; no discontinuations due to ADRs were reported.[31] Among the 111 patients exposed to the recommended dose of 5 mg/kg, 75 (67.6%) patients were treated in combination with HU/HC. Crizanlizumab given to patients already taking HU/HC did not result in any meaningful differences in the safety profile (Table 30).[31]

Table 29: Overview of AEs in SUSTAIN and the crizanlizumab 5 mg/kg safety pool

Patients, n (%)[a]	SUSTAIN				Safety pool	
	Crizanlizumab, 5 mg/kg, N=66		Placebo, N=62		Crizanlizumab, 5 mg/kg, N=111	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	57 (86.4)	12 (18.2)	55 (88.7)	12 (19.4)	94 (84.7)	26 (23.4)
Treatment-related AE[b]	27 (40.9)	4 (6.1)	15 (24.2)	3 (4.8)	36 (32.4)	5 (4.5)[c]
Any SAE	17 (25.8)	7 (10.6)	17 (27.4)	8 (12.9)	24 (21.6)	12 (10.8)
Treatment-related SAE[b]	6 (9.1)	3 (4.5)	2 (3.2)	1 (1.6)	6 (5.4)	3 (2.7)
Fatal SAE[d]	2 (3.0)	2 (3.0)	2 (3.2)	2 (3.2)	2 (1.8)	2 (1.8)
Any AE leading to discontinuation	2 (3.0)	1 (1.5)	3 (4.8)	2 (3.2)	3 (2.7)	2 (1.8)
Treatment-related AE leading to discontinuation[b]	1 (1.5)	0	2 (3.2)	1 (1.6)	1 (0.9)	0

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. [b] Treatment-related is defined as any investigator assessment of possibly drug related, probably drug related, or definitely drug related. [c] 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. [d] None of the fatal SAEs was treatment-related.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: Novartis – Data on File: Additional Study Information.[31]

Table 30: Overview of AEs by concomitant HU/HC use in SUSTAIN and the crizanlizumab 5 mg/kg safety pool

Patients, n (%)[a]	SUSTAIN				Safety pool	
	Crizanlizumab, 5 mg/kg, N=66 No use of HU/HC, n=24 Use of HU/HC, n=42		Placebo, N=62 No use of HU/HC, n=23 Use of HU/HC, n=39		Crizanlizumab, 5 mg/kg, N=111 No use of HU/HC, n=36 Use of HU/HC, n=75	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any AE						
No use of HU/HC	21 (87.5)	5 (20.8)	21 (91.3)	5 (21.7)	31 (86.1)	10 (27.8)
Use of HU/HC	36 (85.7)	7 (16.7)	34 (87.2)	7 (17.9)	63 (84.0)	16 (21.3)
Any SAE						
No use of HU/HC	8 (33.3)	3 (12.5)	7 (30.4)	4 (17.4)	11 (30.6)	6 (16.7)
Use of HU/HC	9 (21.4)	4 (9.5)	10 (25.6)	4 (10.3)	13 (17.3)	6 (8.0)
Any AE leading to discontinuation						
No use of HU/HC	2 (8.3)	1 (4.2)	1 (4.3)	0	3 (8.3)	2 (5.6)
Use of HU/HC	0	0	2 (5.1)	2 (5.1)	0	0

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
Abbreviations: AE: adverse event; HC: hydroxycarbamide; HU: hydroxyurea; SAE: serious adverse event.
Source: Novartis – Data on File: Additional Study Information.[31]

Common AEs (≥5% in the safety pool) in SUSTAIN and the crizanlizumab 5 mg/kg safety pool are provided in Table 31. At least one AE was reported in 94 patients (84.7%) in the safety pool; the most frequently reported (≥10% of patients) AEs were headache (19.8%), nausea (16.2%), back pain (15.3%), arthralgia (14.4%), pyrexia (14.4%), pain in extremity (13.5%), and upper respiratory tract infections (11.7%). In SUSTAIN, with the exception of arthralgia, no AE in the crizanlizumab 5 mg/kg arm was reported with an absolute difference ≥10% compared with the placebo arm.[31]

Table 31: Common AEs (≥5% in the safety pool) by preferred term

Patients, n (%)	SUSTAIN		Safety pool
	Crizanlizumab, 5 mg/kg, N=66	Placebo, N=62	Crizanlizumab, 5 mg/kg, N=111
Patients with at least one event	57 (86.4)	55 (88.7)	94 (84.7)
Headache	11 (16.7)	10 (16.1)	22 (19.8)
Nausea	12 (18.2)	7 (11.3)	18 (16.2)
Back pain	10 (15.2)	7 (11.3)	17 (15.3)
Arthralgia	12 (18.2)	5 (8.1)	16 (14.4)
Pyrexia	7 (10.6)	4 (6.5)	16 (14.4)
Pain in extremity	11 (16.7)	10 (16.1)	15 (13.5)
Upper respiratory tract infection	7 (10.6)	6 (9.7)	13 (11.7)
Urinary tract infection	9 (13.6)	7 (11.3)	11 (9.9)
Diarrhoea	7 (10.6)	2 (3.2)	9 (8.1)
Musculoskeletal pain	8 (12.1)	6 (9.7)	9 (8.1)
Fatigue	5 (7.6)	2 (3.2)	8 (7.2)
Pruritus	5 (7.6)	3 (4.8)	8 (7.2)
Hypokalaemia	1 (1.5)	5 (8.1)	7 (6.3)
Cough	4 (6.1)	7 (11.3)	6 (5.4)
Vomiting	5 (7.6)	3 (4.8)	6 (5.4)

AEs were coded with the use of preferred terms from the Medical Dictionary for Regulatory Activities.
Abbreviations: AE: adverse event.
Source: Novartis – Data on File: Additional Study Information.[31]

Adverse drug reactions in the target indication

AEs as reported in the clinical studies in the crizanlizumab-development program were selected as candidates for further evaluation for their relationship with treatment with crizanlizumab. Details of how these ADRs were selected are provided in Appendix C (Section 6.3).

The most frequently reported ADRs (≥10% of patients) in the crizanlizumab 5 mg/kg safety pool were nausea (16.2%), back pain (15.3%), pyrexia (14.4%) and arthralgia (14.4%).[12] The majority of the ADRs were mild to moderate (grade 1 to 2), with severe events (grade ≥3) observed for pyrexia and arthralgia (1 case [0.9%] each).[31]

An overview of ADRs in SUSTAIN and the crizanlizumab 5 mg/kg safety pool is presented in Table 32. Within each system organ class, the adverse reactions were ranked by order of decreasing frequency in the crizanlizumab 5 mg/kg safety pool. In addition, the corresponding frequency category for each ADR is based on the frequency in the crizanlizumab 5 mg/kg safety pool and the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000).[31]

Table 32: Overview of ADRs (by system organ class)

	SUSTAIN		Safety pool	Frequency[a]
	Crizanlizumab, 5 mg/kg, N=66	Placebo, N=62	Crizanlizumab, 5 mg/kg, N=111	
Gastrointestinal disorders, n (%)				
Nausea	12 (18.2)	7 (11.3)	18 (16.2)	Very common
Abdominal pain[b]	8 (12.1)	3 (4.8)	10 (9.0)	Common
Diarrhoea	7 (10.6)	2 (3.2)	9 (8.1)	Common
Vomiting	5 (7.6)	3 (4.8)	6 (5.4)	Common
General disorders and administration site conditions, n (%)				
Pyrexia	7 (10.6)	4 (6.5)	16 (14.4)	Very common
Infusion site reaction[b]	1 (1.5)	1 (1.6)	3 (2.7)	Common
Injury, poisoning and procedural complications, n (%)				
Infusion-related reaction	2 (3.0)	0	2 (1.8)	Common
Musculoskeletal and connective tissue disorders, n (%)				
Back pain	10 (15.2)	7 (11.3)	17 (15.3)	Very common
Arthralgia	12 (18.2)	5 (8.1)	16 (14.4)	Very common
Musculoskeletal chest pain	5 (7.6)	0	5 (4.5)	Common
Myalgia	5 (7.6)	0	5 (4.5)	Common
Respiratory, thoracic and mediastinal disorders, n (%)				
Oropharyngeal pain	4 (6.1)	1 (1.6)	4 (3.6)	Common
Skin and subcutaneous tissue disorders, n (%)				
Pruritus[b]	5 (7.6)	3 (4.8)	8 (7.2)	Common

[a] Frequency from the safety pool

[b] The following groupings contain the following MedDRA preferred terms:

- Abdominal pain: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, and abdominal tenderness
- Infusion site reaction: infusion site extravasation, infusion site pain, and infusion site swelling
- Pruritus: pruritus and vulvovaginal pruritus

Source: Novartis – Data on File: Additional Study Information.[31]

Immunogenicity and infusion-related reactions

As with other mAbs, there is a potential for infusion-related reactions and immunogenicity. Infusion related reactions were observed in two patients (1.8%) treated with crizanlizumab 5 mg/kg, neither of which was serious or required discontinuation. Treatment-induced anti-crizanlizumab antibodies were transiently detected in one patient (0.9%) among the 111 patients who received crizanlizumab 5 mg/kg; there was no impact of anti-crizanlizumab antibody development on the PK, efficacy or safety of crizanlizumab.[31]

Deaths and life-threatening events

A total of five patients died during the SUSTAIN trial, including two patients in the crizanlizumab 5 mg/kg arm (one patient due to sickle cell anaemia with VOC, and one patient from endocarditis and sepsis) and two in the placebo arm (one patient from right ventricular failure, and one from VOC, ischemic stroke, coma, sepsis, and venous thrombosis of the right lower limb).[31] No on-treatment deaths were reported in SOLACE-adults, and none of the deaths reported in SUSTAIN had a suspected relationship to crizanlizumab.[31]

Three additional single-occurrence AEs in SUSTAIN that were considered to be both serious and life-threatening, but that did not result in death, included sepsis (in the placebo arm), anaemia, and intracranial haemorrhage (both in the crizanlizumab 2.5 mg/kg arm).[3] With regards to the incidence of stroke in the SUSTAIN trial, ischaemic stroke, as a serious complication related to SCD, was reported as a TEAE in one patient (in the placebo arm) and intracranial haemorrhage was reported in one patient (in the crizanlizumab 2.5 mg arm).[31]

5.6 Conclusions

1. Provide a general interpretation of the evidence base considering the benefits associated with the technology relative to those of the comparators.

Crizanlizumab is a humanised mAb with a novel, selective and well described mechanism of action, which was designed to specifically target a key component of the pathogenesis of vaso-occlusion and VOC – P-selectin-mediated multi-cellular adhesion.[12] In recognition of this novel mechanism of action, the WHO created a new ATC fourth-level code (B06AX – Other haematological agents) and assigned the B06AX01 ATC code to crizanlizumab.

The SUSTAIN trial is the primary and most relevant source of data currently available for the safety and efficacy of crizanlizumab for the indication under consideration.[3] In the SUSTAIN trial, crizanlizumab 5 mg/kg (which is the expected licensed dose) was effective in improving outcomes related to the frequency and time to VOC leading to healthcare visits during the 52-week trial.[3] Specifically, crizanlizumab 5 mg/kg was associated with a statistically significant improvement in the median annualised rate of VOC leading to healthcare visits (1.63 [0.00–3.97] versus 2.98 [1.25–5.87] in the placebo arm; indicating a 45.3% reduction; Hodges-Lehmann median absolute difference of -1.01 [95% CI, -2.00, 0.00]; P = 0.010).[3, 32] Treatment with crizanlizumab 5 mg/kg was associated with a three-fold longer median time to first VOC compared with placebo (4.07 versus 1.38 months, HR, 0.50 [95% CI, 0.33, 0.74]) and a two-fold increase in the proportion of patients free from VOC leading to healthcare visit compared to placebo (35.8% versus 16.9% OR, 2.85 [95% CI, 1.24, 6.56]).[3, 31, 32]

While SUSTAIN was not specifically designed or statistically powered to demonstrate benefit in the pre-specified subgroups, crizanlizumab 5 mg/kg demonstrated improvements in the median annualised rate of VOC leading to healthcare visits versus placebo across different patient subgroups based on concomitant HU/HC use (yes or no), history of VOC leading to healthcare visits (2–4 or 5–10 crises in the previous year) or SCD genotype (HbSS or non-HbSS).[3] Crizanlizumab would therefore be a valuable treatment option for all patients with recurrent VOC, regardless of SCD genotype, and has been shown to be effective in those patients with particularly severe disease (5–10 crises in the previous year), who would represent a patient population with a high level of clinical need. Importantly, treatment with crizanlizumab was shown to be effective at reducing the frequency of VOC as both an add-on therapy to HU/HC

(concomitant HU/HC: yes) and as a monotherapy for those patients not receiving HU/HC (concomitant HU/HC: no). Furthermore, safety results from the SUSTAIN trial demonstrate that treatment with crizanlizumab is well tolerated, either as add-on therapy in patients receiving concomitant HU/HC or as a monotherapy, with a similar incidence of SAEs across the active treatment and placebo arms.[3]

The significant benefits of crizanlizumab demonstrated in the SUSTAIN trial with regards to the annualised rate of VOC leading to healthcare visits can also be expected to translate into additional, longer-term benefits that are not directly shown in the 52-week SUSTAIN trial, including hospitalisation-related resource use, HRQoL, occurrence of serious complications and mortality.[3] SUSTAIN demonstrated that treatment with crizanlizumab 5 mg/kg was associated with a significant reduction in the annualised rate of VOC leading to a medical facility visit compared to placebo and a clinically relevant reduction in the annual number of days hospitalised (see Section 5.4.3), indicating the potential for a substantial reduction in healthcare resource utilisation for patients treated with crizanlizumab.[113] A post-hoc analysis of SUSTAIN demonstrated that the reduction in VOC leading to medical facility visits with crizanlizumab 5 mg/kg compared with placebo was largely driven by a reduction in visits to emergency care units and specialised SCD crisis centres.[113]

The 52-week duration of the SUSTAIN trial did not however allow for the detection of differences in mortality and other relatively rare events, such as ACS and other SCD-related complications. Indeed, only few deaths (5 across all treatment arms) and complications (see Table 19) occurred in the SUSTAIN trial.[3] Any interventional trial designed to detect differences in mortality, even when considering an increased risk of death within the SCD patient population, would require a significantly long follow-up period and would therefore not be feasible to implement in practice. Long-term evidence for the association between the frequency of VOC and SCD-related complications and mortality is however available from the analyses of the HES database which demonstrated an increased risk of death and SCD-related complications (such as ACS), with increasing frequency of VOC leading to healthcare visits in the previous 12 months.[13, 15] The findings from the HES database analysis with regards to the relationship between VOC and mortality is consistent with the study by Platt et al. (1991), which was conducted prior to the introduction of HU/HC, and also showed an increased risk of death for patients with SCD with an average of ≥3 VOC per year.[65] Patients with a higher annual rate of VOC therefore still tend to have worse survival outcomes compared to those with fewer VOC, and mortality rates have been shown to be reduced amongst patients with SCD who received currently available therapies that reduce the frequency of VOC.[33-36] Further long-term evidence (for up to five years) for the use of crizanlizumab in patients with SCD aged 12 years and older will also be available from the currently ongoing STAND phase III trial (see Section 6.2).[17]

Statistically significant differences between treatment arms and changes from baseline in HRQoL outcomes (BPI and SF-36; see Section 5.4.4) were not reported in the SUSTAIN trial.[3] However, given the unpredictable timing and acute nature of VOC it is possible that the HRQoL measured at the time of the treatment visits missed or did not fully capture the expected impact of VOC on patient HRQoL and assessments of pain. Tellingly, 1,024 (93.1%) of the SF-36 questionnaires that were administered in the SUSTAIN trial were not completed within a 7-day window of a VOC, and only 59 individual patients did complete a SF-36 questionnaire within a 7-day window of a VOC, meaning that the detrimental impact of VOC on HRQoL is unlikely to have been captured by the data collected in SUSTAIN.[31] Other published studies have however demonstrated the negative impact of individual VOC on HRQoL for patients with SCD.[4] Furthermore, evidence of the long-term impact of recurrent VOC on HRQoL is provided by the

analyses of the LEGACY registry in which patients with SCD with ≥3 VOC in the previous 12 months were reported to experience significantly lower HRQoL across all subscales of the SF-36 compared to patients with fewer VOC.[14] HRQoL data in LEGACY were collected at specific time intervals (every six months) over a three-year period, and not on the occurrence of specific events. LEGACY is therefore considered to provide a broader picture of patient HRQoL that would include the impact of recurrent VOC on chronic pain and other chronic complications, as well as patient's general wellbeing.[14]

In conclusion, the SUSTAIN trial demonstrates that crizanlizumab in addition to standard of care is associated with a significant reduction in the rate of VOC leading to healthcare visits compared to standard of care alone. The avoidance of each and every VOC is an important to patients with SCD as:

- Each VOC induces severe pain, increases morbidity, decreases HRQoL, and can result in organ damage/failure, stroke and/or death
- Every VOC leads to ischemia/tissue damage
- Every VOC is a debilitating/traumatising experience for the patient
- Every VOC can potentially necessitate hospitalisation and use of strong analgesics (i.e. opioids), and typically requires complex work-up/health care utilisation
- Every VOC has impact on daily activity of life (work, school, etc.)

2. Provide a general interpretation of the evidence base considering the harms associated with the technology relative to those of the comparators.

Treatment with crizanlizumab is well tolerated with a favorable and well-manageable safety profile. In the SUSTAIN trial, the incidence of SAEs was similar across the crizanlizumab 5 mg/kg (25.8%) and placebo arms (27.4%).[3]

The most frequently reported ADRs (≥10% of patients) in the crizanlizumab 5 mg/kg safety pool (n=111; median duration of exposure 46 weeks) were nausea, back pain, pyrexia and arthralgia.[31] The majority of the ADRs were mild to moderate (grade 1 to 2). Severe events were observed for pyrexia and arthralgia (0.9% for each event). No discontinuations due to ADRs were reported with crizanlizumab 5 mg/kg. The use of crizanlizumab in combination with HU/HC did not result in any meaningful differences in the safety profile of crizanlizumab.[31]

These safety results demonstrate that treatment with crizanlizumab is well tolerated, either as an add-on therapy for patients receiving concomitant HU/HC or as a monotherapy for patients not receiving HU/HC (i.e. for whom HU/HC is inappropriate or inadequate).[3]

5.7 Strengths and limitations

1. Summarise the internal validity of the evidence base, taking into account the study quality, the validity of the endpoints used as well as the overall level of evidence. Include a statement about the consistency of the results in the evidence base.

The evidence presented in this submission for the safety and efficacy of crizanlizumab has been derived from a SLR, which identified SUSTAIN as the only RCT for crizanlizumab for which data are currently available.[3]

SUSTAIN is a high-quality study (i.e. randomised, double-blind) and data from SUSTAIN has been used as the basis of the conditional marketing authorisation application submitted to the EMA. A central allocation method was used to conceal treatment allocation, with patients assigned by an interactive web- or voice-response system.[12] Randomisation was performed centrally on the basis of a block design with stratification according to the number of VOC leading to healthcare visits in the previous year (2–4 or 5–10) and by concomitant HU/HC use (yes or no).[3] Treatment groups were similar at the outset of the study in terms of prognostic factors, and there were no significant between-group differences in the main baseline characteristics reported from the trial (age, sex, race, genotype, HU/HC use, number of crises in previous 12 months).[3] There were also no unexpected imbalances in drop-outs between groups and reasons for drop-outs appear to be similar across treatment groups.[3] Further, the population enrolled into the SUSTAIN trial can be considered representative of the patients with SCD in Europe (see Table 33).

The study endpoints of the SUSTAIN trial are clinically meaningful and representative of unmet medical needs of patients with SCD, for which currently available therapies provide insufficient disease control. The primary endpoint of the SUSTAIN trial (i.e. annualised rate of VOC leading to healthcare visits) is highly relevant for patients with SCD and clinicians. VOC were defined as acute episodes of pain, with no medically defined cause other than a vaso-occlusive event, that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral NSAID, with certain complications associated with SCD (ACS, hepatic sequestration, splenic sequestration, and priapism) also considered to be VOC events by definition.[3] The definition of VOC used is therefore broad and takes into consideration how patients would actually present in clinical practice. Given that the experience of pain crises is subjective, it is also important that the definition of VOC used in the SUSTAIN trial was measurable, hence the requirement for a medical facility visit and receipt of specific interventions for VOC. Furthermore, all the crises that were identified by trial investigators were adjudicated in a blinded fashion by an independent crisis-review committee, consisting of three haematologists with expertise in SCD.[12] However, due to the definition used, not all VOC experienced by patients (i.e. those that do not result in a medical facility visit) were captured in the trial, and the potential impact of treatment on VOC that are managed at home has not been assessed. As shown in the SWAY study, the proportion of VOC managed at home is not insignificant (24%) and it is not necessarily the case that the VOC that are managed at home are ‘less severe’ VOC that do not require medical attention.[58] Instead patients may manage VOC themselves at home because of perceptions about the care they may receive and to avoid the stigma attached to seeking pain relief at hospital (e.g. with opioids), when they are otherwise looking fit and healthy.

While SUSTAIN was designed to detect a meaningful treatment difference in the annualised rate of VOC, which was assumed as 40% relative reduction versus placebo, there is no definition of a minimal clinically important difference for this outcome available. However, feedback from patients and also clinicians indicates that the avoidance of each and every single VOC is clinically relevant and meaningful with regards to patients HRQoL. Further to this, results of the HES database analysis suggest that ≥1 VOC requiring a medical facility visit are already associated with an increased mortality in patients with SCD.[113]

Due to the duration of the trial, differences in long-term outcomes, such as mortality, or relatively uncommon complications, such as ACS, could not be detected. Furthermore, given the unpredictable timing and acute nature of VOC, it is possible that the HRQoL measured at the time of the treatment visits missed or did not fully capture the detrimental impact of VOC on patient HRQoL and assessments of pain. For example, in the SUSTAIN trial, only 76 (6.9%) SF-

36 questionnaires that were administered were completed within a 7-day window of a VOC leading to healthcare visits.[3, 12, 31, 110] To establish the impact of treatment with crizanlizumab beyond VOC rates (e.g. on HRQoL or mortality and SCD-related complications), other sources of evidence, such as the HES database analysis and the LEGACY registry study (see Section 2.1.2), that explore the relationship between VOC and these outcomes need to be considered.

2. Provide a brief statement of the relevance of the evidence base to the scope of the assessment.

The trial population of SUSTAIN, which included patients with SCD aged 16–65 years who had experienced 2–10 VOC leading to healthcare visits in the 12 months prior to enrolment, is consistent with the expected licensed indication for crizanlizumab and the project plan for this assessment.[3] Additionally, as shown in Table 33, the SUSTAIN study population is considered to be representative of the European SCD population with respect to key baseline characteristics, such as genotype, race/ethnicity, and age.

Table 33: Comparison of the SUSTAIN trial population with European SCD population

Characteristic	SUSTAIN	Europe (epidemiology data)
All genotypes included in SUSTAIN	HbSS (71.2%), HbSC (16.2%), HbS β^0-thalassemia (6.1%) HbS β^+-thalassemia (5.1%) Others (1.5%)	HbSS 60-90% HbSC 4-25% (HbSC higher in studies in the UK)
Ethnicity/Race	Black/African American: 91.9%	African/Sub-Saharan African or Caribbean: 89% (England); 94% (France); 35.6% (Italy)[a]
	White: 4.5%	Caucasian: <0.5% (England), NR (France); 64.4% (Italy)[a]
	Other: 3.5%	Other/Not stated: 13% (England); 6% (France); 0% (Italy)[a]
HU/HC use	62.1% patients received HU/HC 37.9% did not receive HU/HC	HU/HC use: 14–40% (5 studies in more than 10,000 patients in total)
Age (years)	Mean (±SD): 30.1 (10.33) Median: 28.0 Range: 16 - 63	Median range[b]: 24.5 – 39.6 (Italy[c], Netherlands, France, UK)

[a] High proportion among Caucasian population in Italy may be due to higher prevalence among South (Sicily) as well as additional migration from non-African countries. [b] Medians obtained from studies where subjects of all ages or adults >16 years of age were considered. Sweden was not included as available data refer to the immigrant population only and have been collected over a much longer period, compared to the other studies (i.e. 23 years), which is likely to result in big changes in the age distribution of the analysed population. [c] Only patients

with SCD with HU/HC exposure were considered.
Abbreviations: Hb: haemoglobin; HbS: homozygous haemoglobin; NR: not reported; SCD: sickle cell disease; SD: standard deviation.
Sources: Rigano et al. (2018);[150] Cela et al. (2017);[42] Colombatti et al. (2018);[151] Voskaridou et al. (2012);[76] Couque et al. (2016);[152] Le et al. (2015);[153] Telfer et al. (2007);[154] De Luna (2018);[155] Cecchini (2014);[156] Hemminki (2015);[79] AlJuburi (2013);[157] AlJuburi (2012);[158] NHR report 2018/19;[44] Van Tuijn (2017);[159] van Beers (2008).[6]

In the SUSTAIN trial, which included sites in the USA (51 sites), Brazil (8), and Jamaica (1), medications consistent with the standard care of patients with SCD were allowed during this study.[31] The clinical management of SCD does not differ substantially between these countries and clinical practice in Europe. For example, HU/HC, as the only treatment authorised in the EU for the prevention of VOC, is recommended for use in patients with SCD experiencing multiple VOC in a 12-month period or experiencing VOC which impacts daily activity or HRQoL, by the US (NHLBI) and across Europe, including the UK, Spain and Netherlands.[11, 82, 91, 92] Similarly, the NHLBI, ENERCA and BSH guidance recommends that chronic blood transfusions should be used primarily for prevention of complications such as stroke in high risk patients, particularly children.[82, 11, 89] In the Netherlands, chronic blood transfusions are recommended only in exceptional cases in patients with very frequent VOC or other serious complications who do not respond to HU/HC.[91] Because of the similarity in the clinical guidance provided by the NHLBI and European sources, the standard of care received by patients in the SUSTAIN trial is expected to be generalisable to European clinical practice. The efficacy of crizanlizumab as an add-on to standard of care that is more directly related to European treatment practices will be provided by the ongoing STAND phase III trial, which includes patients across Europe (e.g. Belgium, France, Germany, Greece, Italy, Netherlands, Spain, UK).

The enrolment of patients treated with concomitant HU/HC in the SUSTAIN trial is consistent with the expected licensed indication and expected use of crizanlizumab in clinical practice (i.e. either as an add-on therapy to HU/HC for patients who continue to experience VOC with HU/HC alone, or as a monotherapy for those patients for whom HU/HC is inappropriate or inadequate).[3] The use of HU/HC in European clinical practice is however likely to be lower than the proportion observed in SUSTAIN – 61.5% of patients in the placebo arm compared with approximately 23% in the international SWAY study (which included patients from a number of European countries).[3, 24] Pre-specified subgroup analyses were conducted to assess the efficacy of crizanlizumab in patients treated with or without concomitant HU/HC in the SUSTAIN trial (see Section 5.4.5). These subgroup analyses, and the analysis of the ITT population, demonstrated that crizanlizumab is effective at reducing the frequency of VOC regardless of concomitant HU/HC use.

Patients with chronic blood transfusions were excluded from the SUSTAIN trial. Whilst the use of chronic blood transfusions for the prevention of recurrent VOC is supported in clinical treatment guidelines, estimates suggest that less than 10% of patients with SCD are being regularly transfused and that less than one in five (17%) elective transfusions are for the prevention of recurrent VOC specifically.[44, 83, 84, 86] Further to this, as also demonstrated by the results of the SLR, there are limited relevant data for the efficacy of 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. Other concomitant medications used in the SUSTAIN arm (e.g. folic acid, opioids and anti-inflammatory drugs) were consistent with the ongoing treatments reported by patients in the international SWAY study.[24]

The placebo arm of the SUSTAIN trial can therefore be considered generalisable to expected clinical practice in Europe and therefore a reasonable proxy for the comparator of interest for this assessment. In conclusion, evidence from the SUSTAIN trial is considered to be directly relevant to the scope of the assessment, in terms of the population, intervention and comparator included in the trial.

6 Appendices

6.1 Appendix A: Identification and selection of relevant studies

6.1.1 SLR search strategy

Search terms were identical for both the original SLR and the SLR update, with the results of the update deduplicated against the original search results and novel records retained for screening.

Table 34: Search terms for the MEDLINE, MEDLINE In-Process, MEDLINE Daily and MEDLINE ePub Ahead of Print databases (searched via the Ovid SP platform)

Interface: Ovid SP **Date searched: original SLR, 13th August 2019; SLR update, 27th January 2020** **Records retrieved: original SLR, 689; SLR update, 728**				
Term group	**#**	**Search terms**	**Results (original SLR)**	**Results (SLR update)**
Disease area: sickle cell disease	1	exp anemia, sickle cell/	21,482	21,910
	2	exp pain/	378,747	387,268
	3	acute disease/	208,520	210,553
	4	(pain$ or acute$ or cris$ or episode$).ti,ab,kf.	1,950,612	2,002,699
	5	or/2-4	2,112,287	2,166,117
	6	1 and 5	5,485	5,651
	7	(sickl$ adj10 (pain$ or acute$ or cris$ or episode$)).ti,ab,kf.	3,711	3,815
	8	6 or 7	6,195	6,367
Intervention: crizanlizumab	9	(crizanlizumab$ or SEG101 or SelG1).mp.	13	20
Study design: RCTs and interventional non-RCTs	10	randomized controlled trials as topic/	125,695	130,260
	11	randomized controlled trial/	487,079	499,323
	12	random allocation/	99,981	102,005
	13	double blind method/	152,627	155,934
	14	single blind method/	27,156	28,022
	15	clinical trial/	517,404	521,104
	16	clinical trial, phase ii.pt.	30,969	31,974
	17	clinical trial, phase iii.pt.	15,358	16,204
	18	clinical trial, phase iv.pt.	1,737	1,824
	19	controlled clinical trial.pt.	93,207	93,539
	20	randomized controlled trial.pt.	487,079	499,323
	21	multicenter study.pt.	254,656	265,445

Interface: Ovid SP **Date searched: original SLR, 13th August 2019; SLR update, 27th January 2020** **Records retrieved: original SLR, 689; SLR update, 728**				
Term group	**#**	**Search terms**	**Results (original SLR)**	**Results (SLR update)**
	22	clinical trial.pt.	517,404	521,104
	23	exp clinical trials as topic/	328,941	336,065
	24	(clinical adj trial$).ti,ab,kf.	345,941	359,921
	25	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kf.	165,593	169,184
	26	placebos/	34,427	34,707
	27	placebo$.ti,ab,kf.	207,370	212,117
	28	(allocat$ adj2 random$).ti,ab,kf.	32,673	33,771
	29	((single arm or single-arm or uncontrolled) adj3 (study or studies or trial$)).ti,ab,kf.	9,861	10,352
	30	(Open-label adj (trial$ or stud$)).ti,ab,kf.	10,698	10,959
	31	((Non-blinded or unblinded) adj (trial$ or stud$)).ti,ab,kf.	665	674
	32	or/10-31	1,561,039	1,603,631
Study design: Observational studies	33	exp Epidemiologic studies/	2,345,692	2,429,231
	34	exp case control studies/	1,010,732	1,051,616
	35	exp Cohort Studies/	1,885,168	1,950,156
	36	Case control.ti,ab,kf.	118,367	122,323
	37	(cohort adj (study or studies)).ti,ab,kf.	184,672	196,574
	38	cohort analy$.ti,ab,kf.	7,940	8,406
	39	(follow up adj (study or studies)).ti,ab,kf.	48,701	49,711
	40	(observational adj (study or studies)).ti,ab,kf.	95,779	101,534
	41	Longitudinal$.ti,ab,kf.	244,698	254,688
	42	retrospective$.ti,ab,kf.	675,800	707,110
	43	Cross sectional.ti,ab,kf.	318,932	335,596
	44	Cross-sectional studies/	300,768	316,530
	45	exp Longitudinal Studies/	125,583	130,712
	46	exp Follow-Up Studies/	619,432	632,650
	47	exp Prospective Studies/	509,919	527,352
	48	exp Retrospective Studies/	763,059	796,347

Interface: Ovid SP **Date searched: original SLR, 13th August 2019; SLR update, 27th January 2020** **Records retrieved: original SLR, 689; SLR update, 728**				
Term group	**#**	**Search terms**	**Results (original SLR)**	**Results (SLR update)**
	49	(Prospective adj (study or studies)).ti,ab,kf.	166,162	170,627
	50	(evaluation adj (study or studies)).ti,ab,kf.	5,412	5,599
	51	(epidemiologic adj (study or studies)).ti,ab,kf.	25,828	26,289
	52	(chart adj3 review).ti,ab,kf.	36,769	38,293
	53	(registry or registries).ti,ab,kf.	115,470	121,549
	54	(medical record$ or real world or population based or survey$ or questionnaire$ or medicare or medicaid or marketscan).ti,ab,kf.	1,230,053	1,275,629
	55	(real-world adj (evidence or stud$ or outcome$)).ti,ab,kf.	2,168	2,594
	56	or/33-55	3,762,707	3,893,743
Exclusion terms	57	exp animals/ not exp humans/	4,607,932	4,667,177
	58	comment/ or editorial/ or case reports/	3,160,312	3,238,090
	59	(case stud$ or case report$).ti.	277,451	286,133
	60	historical article/	353,259	356,385
	61	or/57-60	8,091,500	8,231,207
Combined	62	8 and 32	715	754
	63	8 and 9 and 56	0	0
	64	62 or 63	715	754
Final	65	64 not 61	**689**	**728**

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to August 12, 2019

Table 35: Search terms for Embase (searched via the Ovid SP platform)

Interface: Ovid SP **Date searched: original SLR, 13th August 2019; SLR update, 27th January 2020** **Records retrieved: original SLR, 1,178; SLR update, 1,272**				
Term group	**#**	**Search terms**	**Results (original SLR)**	**Results (SLR update)**
	1	exp sickle cell anemia/	34,493	35,594
	2	exp pain/	1,241,095	1,275,114

Interface: Ovid SP **Date searched: original SLR, 13th August 2019; SLR update, 27th January 2020** **Records retrieved: original SLR, 1,178; SLR update, 1,272**				
Term group	**#**	**Search terms**	**Results (original SLR)**	**Results (SLR update)**
Disease area: sickle cell disease	3	acute disease/	87,812	88,953
	4	(pain$ or acute$ or cris$ or episode$).ti,ab,kw.	2,725,135	2,802,342
	5	or/2-4	3,278,928	3,367,899
	6	1 and 5	12,207	12,759
	7	(sickl$ adj10 (pain$ or acute$ or cris$ or episode$)).ti,ab,kw.	5,728	5,954
	8	6 or 7	12,595	13,165
Intervention: crizanlizumab	9	(crizanlizumab$ or SEG101 or SelG1).mp.	51	73
Study design: RCTs and interventional non-RCTs	10	randomized controlled trials as topic/	101,050	108,933
	11	randomized controlled trial/	564,363	588,257
	12	clinical trial/	961,627	963,038
	13	controlled clinical trial/	464,406	463,509
	14	multicenter study/	225,377	241,482
	15	exp randomization/	83,875	86,029
	16	single blind procedure/	36,198	37,754
	17	double blind procedure/	164,187	169,106
	18	crossover procedure/	60,253	62,029
	19	placebo/	339,761	346,489
	20	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	112,643	119,879
	21	(single blind$ or double blind$ or ((treble or triple) adj blind$)).ti,ab,kw.	223,975	229,349
	22	placebo$.ti,ab,kw.	295,300	303,008
	23	(allocat$ adj2 random$).ti,ab,kw.	40,700	42,020
	24	randomi?ed controlled trial$.ti,ab,kw.	215,941	227,559
	25	rct.ti,ab,kw.	35,213	37,482
	26	((single arm or single-arm) adj3 (study or studies or trial$)).ti,ab,kw.	9,679	10,659
	27	(Open-label adj (trial$ or stud$)).ti,ab,kw.	18,182	18,858
	28	(Non-blinded adj (trial$ or stud$)).ti,ab,kw.	274	275

Interface: Ovid SP **Date searched: original SLR, 13th August 2019; SLR update, 27th January 2020** **Records retrieved: original SLR, 1,178; SLR update, 1,272**				
Term group	**#**	**Search terms**	**Results (original SLR)**	**Results (SLR update)**
	29	or/10-28	1,876,247	1,931,457
Study design: observational studies	30	exp Epidemiologic studies/	3,195,956	3,307,725
	31	exp case control study/	162,385	169,224
	32	exp cohort analysis/	495,436	544,670
	33	Case control.ti,ab,kw.	155,205	160,289
	34	(cohort adj (study or studies)).ti,ab,kw.	271,933	290,008
	35	cohort analy$.ti,ab,kw.	11,613	12,413
	36	(follow up adj (study or studies)).ti,ab,kw.	63,891	65,296
	37	(observational adj (study or studies)).ti,ab,kw.	150,980	160,276
	38	Longitudinal$.ti,ab,kw.	329,715	344,900
	39	retrospective$.ti,ab,kw.	1,121,970	1,179,037
	40	Cross sectional.ti,ab,kw.	418,505	441,097
	41	Cross-sectional study/	311,570	332,957
	42	exp Longitudinal Study/	129,200	135,467
	43	exp follow up/	1,439,307	1,495,583
	44	exp Prospective Study/	542,108	577,237
	45	exp Retrospective Study/	809,399	872,270
	46	exp Observational Study/	175,436	187,702
	47	(Prospective adj (study or studies)).ti,ab,kw.	247,863	255,462
	48	(evaluation adj (study or studies)).ti,ab,kw.	7,790	8,047
	49	(epidemiologic adj (study or studies)).ti,ab,kw.	32,789	33,379
	50	(chart adj3 review).ti,ab,kw.	74,279	78,459
	51	(registry or registries).ti,ab,kw.	195,457	205,920
	52	(medical record$ or real world or population based or survey$ or questionnaire$ or medicare or medicaid or marketscan).ti,ab,kw.	1,696,125	1,767,408
	53	(real-world adj (evidence or stud$ or outcome$)).ti,ab,kw.	5,019	6,057

Interface: Ovid SP **Date searched: original SLR, 13th August 2019; SLR update, 27th January 2020** **Records retrieved: original SLR, 1,178; SLR update, 1,272**				
Term group	**#**	**Search terms**	**Results (original SLR)**	**Results (SLR update)**
	54	or/30-53	6,785,608	7,045,579
Exclusion terms	55	("conference abstract" or "conference review").pt.	3,529,823	3,696,649
	56	limit 55 to yr="1974-2016"	2,642,410	2,637,078
	57	exp animals/ not exp humans/	4,496,478	4,572,986
	58	(case stud$ or case report$).ti.	339,954	348,965
	59	editorial.pt.	627,400	641,261
	60	case study/	63,335	66,633
	61	or/56-60	7,859,336	7,956,727
Combined	62	8 and 29	1,526	1,623
	63	8 and 9 and 54	15	23
	64	62 or 63	1,531	1,629
Final	65	64 not 61	**1,178**	**1,272**

Database(s): Embase 1974 to August 12, 2019

Table 36: Search terms for CDSR and CENTRAL (searched simultaneously via the Cochrane Library Wiley Online platform)

Interface: Cochrane Library Wiley Online platform **Date searched: original SLR, 13th August 2019; SLR update, 27th January 2020** **Records retrieved: original SLR, 846; SLR update, 849**				
Term group	**#**	**Search terms**	**Results (original SLR)**	**Results (SLR update)**
Disease area: sickle cell disease	1	[mh "Anemia, Sickle Cell"]	656	674
	2	[mh pain]	44,889	45,940
	3	[mh ^"acute disease"]	9,318	9,384
	4	pain* or acute* or cris* or episode*:ti,ab,kw	310,166	321,890
	5	{OR #2-#4}	314,613	326,384
	6	#1 AND #5	393	402
	7	(sickl* NEAR/10 (pain* or acute* or cris* or episode*)):ti,ab,kw	725	723

Interface: Cochrane Library Wiley Online platform Date searched: original SLR, 13th August 2019; SLR update, 27th January 2020 Records retrieved: original SLR, 846; SLR update, 849				
Term group	**#**	**Search terms**	**Results (original SLR)**	**Results (SLR update)**
	8	#6 OR #7	846	849
	9	#8 in Cochrane Reviews, Cochrane Protocols, Trials	846	849

Database(s): Cochrane Database of Systematic Reviews [Issue 8 of 12, August 2019], Cochrane Central Register of Controlled Trials [Issue 8 of 12, August 2019]

Table 37: Search terms for DARE (searched via the University of York's CRD platform)

Interface: University of York's CRD platform Date searched: original SLR, 13th August 2019; SLR update, 27th January 2020 Records retrieved: original SLR, 29; SLR update, 29				
Term group	**#**	**Search terms**	**Results (original SLR)**	**Results (SLR update)**
Disease area: sickle cell disease	1	MeSH DESCRIPTOR Anemia, Sickle Cell EXPLODE ALL TREES	41	41
	2	MeSH DESCRIPTOR Pain EXPLODE ALL TREES	3,117	3,117
	3	MeSH DESCRIPTOR Acute Disease	961	961
	4	((pain* or acute* or cris* or episode*))	14,186	14,186
	5	(#2 or #3 or #4)	14,454	14,454
	6	(#1 and #5)	15	15
	7	(((sickl* adj9 (pain* or acute* or cris* or episode*)) or ((pain* or acute* or cris* or episode*) adj9 sickl*)))	35	35
	8	(#6 or #7)	39	39
	9	(#8) IN DARE	29	29

Database(s): Database of Abstracts of Reviews of Effects [Issue 2 of 4, April 2015]

Table 38: Search strategy for the conference proceedings

Conference	Year	Source	Search strategy	Results
American Society of Hematology (ASH) Annual Meeting	2017	http://www.bloodjournal.org/content/130/suppl_1?sso-checked=true	Search each term individually in the 'search this issue' search bar: Sickle cell crisis	216 identified; 0 included

Conference	Year	Source	Search strategy	Results
			Sickle cell crises Vaso occlusive	
	2018	http://www.bloodjournal.org/content/132/suppl_1	Search each term individually in the 'search this issue' search bar: Sickle cell crisis Sickle cell crises Vaso occlusive	239 identified; 0 included
	2019	https://ashpublications.org/blood/issue/134/Supplement_1	Search each term individually in the 'search this issue' search bar: Sickle cell crisis Sickle cell crises Vaso occlusive	257 identified; 0 included
Annual Congress of the European Haematology Association (EHA)	2017	https://library.ehaweb.org/eha/#!*menu=16*browseby=9*sortby=1*trend=4016	Type the first keyword into the search box, click advanced search, select the relevant meeting and search. Click display by content types and review the abstracts, eposters and slide presentations. Repeat for each keyword: Sickle cell crisis Sickle cell crises Vaso occlusive	17 identified; 1 included
	2018			30 identified; 0 included
	2019			31 identified; 3 included
Annual Symposium of the Foundation for Sickle Cell Disease Research	2017	https://11thfoundationforsickleecell2017.sched.com/	Ctrl-F for each search term in the pdf: Crisis Crises Vaso occlusive Vaso-occlusive	42 identified; 0 included
	2019	https://fscdr.org/wp-content/uploads/2019/06/FINAL-JOURNAL.pdf		50 identified; 1 included

Conference	Year	Source	Search strategy	Results
British Society for Haematology (BSH) Annual Scientific Meeting	2017	https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.14613	Ctrl-F for each search term in the pdf: Crisis Crises Vaso occlusive Vaso-occlusive	12 identified; 0 included
	2018	https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.15226		17 identified; 0 included
	2019	https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.15854		27 identified; 0 included

Abbreviations: ASH: Annual meeting of the American Society of Hematology; BSH: British Society for Haematology; EHA: The European Hematology Association Congress.

Table 39: Search strategy for ClinicalTrials.gov

Condition	Other terms	Phases	Study results	Recruitment status	Results
Sickle Cell Disease	pain OR acute OR crisis OR crises OR episode OR vasoocclusive OR vaso occlusive	II, III or IV	"Studies With Results"	All	Original SLR: 40 identified; 6 included SLR update: 3 identified; 1 included

6.1.2 Excluded records

Table 40: Electronic database records excluded at the full-text review stage of the clinical SLR

#	Full reference	Reason for exclusion
Original SLR (August 2019)		
1.	Akingbola TS, Tayo B, Ezekekwu CA, et al. Maximum tolerated dose versus fixed low-dose hydroxyurea for treatment of adults with sickle cell anemia-retrospective comparison of two studies. Blood. Conference: 60th Annual Meeting of the American Society of Hematology, ASH 2018;132.	Publication or study design not relevant
2.	Al-Jam'a AH, Al-Dabbous IA. Hydroxyurea in sickle cell disease patients from Eastern Saudi Arabia. Saudi Medical Journal 2002;23:277-281.	Study does not report an outcome of relevance
3.	Ataga KI, Hoppe CC, Ware RE, et al. Novel trial design to evaluate oral voxelotor for the treatment of sickle cell disease: The phase 3	Study does not report an

#	Full reference	Reason for exclusion
	hemoglobin oxygen affinity modulation to inhibit sickle hemoglobin polymerization (HOPE) trial. HemaSphere 2018;2 (Supplement 2):670.	outcome of relevance
4.	Ballas SK, McCarthy WF, Guo N, et al. Early detection of responders to hydroxyurea therapy. American journal of hematology. 2010;85:6.	Study population not relevant
5.	Braga LB, Ferreira AC, Guimaraes M, et al. Clinical and laboratory effects of hydroxyurea in children and adolescents with sickle cell anemia: a Portuguese hospital study. Hemoglobin 2005;29:171-80.	Study does not report an outcome of relevance
6.	Brown C, Hoppe C, Inati A, et al. Results from a phase 2a study (GBT440-007) evaluating adolescents with sickle cell disease treated with multiple doses of voxelotor (GBT440), a hbs polymerization inhibitor. HemaSphere 2018;2 (Supplement 2):304-305.	Study does not report an outcome of relevance
7.	Charache S. Pharmacological modification of hemoglobin F expression in sickle cell anemia: an update on hydroxyurea studies. Experientia 1993;49:126-32.	Publication or study design not relevant
8.	Cho G, Hambleton IR. Regular long-term red blood cell transfusions for managing chronic chest complications in sickle cell disease. Cochrane database of systematic reviews (Online) 2011;9:CD008360.	Publication or study design not relevant
9.	Cho G, Hambleton IR. Regular long-term red blood cell transfusions for managing chronic chest complications in sickle cell disease. Cochrane Database of Systematic Reviews 2014;2014 (1) (no pagination).	Publication or study design not relevant
10.	Daltro GC, Fortuna V, De Souza ES, et al. Efficacy of autologous stem cell-based therapy for osteonecrosis of the femoral head in sickle cell disease: A five-year follow-up study. Stem Cell Research and Therapy 2015;6 (1) (no pagination).	Study does not report an outcome of relevance
11.	Davies S, Olujohungbe A. Hydroxyurea for sickle cell disease. Cochrane Database of Systematic Reviews 2001:CD002202.	Publication or study design not relevant
12.	de Montalembert M, Belloy M, Bernaudin F, et al. Three-year follow-up of hydroxyurea treatment in severely ill children with sickle cell disease. The French Study Group on Sickle Cell Disease. Journal of Pediatric Hematology/Oncology 1997;19:313-8.	Study does not report an outcome of relevance
13.	Economou M, Teli A, Papadopoulou E, et al. Long-term use of hydroxyurea in children and adolescents with sickle /beta thalassemia. Haematologica 2017;102 (Supplement 2):850.	Study does not report an outcome of relevance
14.	Elira Dokekias A, Ngolet Ossini L, Atipo Tsiba FO, et al. Blood transfusion assessment to 112 homozygous sickle-cell disease	Intervention not relevant

#	Full reference	Reason for exclusion
	patients in university hospital of Brazzaville. [French]. Transfusion Clinique et Biologique 2009;16:464-470.	
15.	Elira Dokekias A, Okandze Elenga JP, Ndinga J, et al. [Evaluation of clinical response by hydroxyurea in 132 patients with major sickle cell anemia]. Tunisie Medicale 2005;83:32-7.	Publication or study design not relevant
16.	Elsabbagh EM, Abunar O, Habbal A, et al. Alternative-donor hematopoietic stem cell transplantation for sickle cell disease in pediatric patients: A systematic review and meta-analysis. Blood. Conference: 60th Annual Meeting of the American Society of Hematology, ASH 2018;132.	Publication or study design not relevant
17.	Fortin PM, Hopewell S, Estcourt LJ. Red blood cell transfusion to treat or prevent complications in sickle cell disease: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2018;8:CD012082.	Publication or study design not relevant
18.	Goldberg MA, Brugnara C, Dover GJ, et al. Hydroxyurea and erythropoietin therapy in sickle cell anemia. Seminars in oncology 1992;19:74-81.	Study population not relevant
19.	Guilcher GMT, Monagel DA, Nettel-Aguirre A, et al. Nonmyeloablative Matched Sibling Donor Hematopoietic Cell Transplantation in Children and Adolescents with Sickle Cell Disease. Biology of Blood & Marrow Transplantation 2019;25:1179-1186.	Publication or study design not relevant
20.	Guthrie T. Hydroxyurea for sickle cell. P and t 1995;20:497-498.	Publication or study design not relevant
21.	Heeney M, Rees D, De Montalembert M, et al. Crizanlizumab dose confirmation in pediatric patients with sickle cell disease: Solace-kids design. Pediatric Blood and Cancer 2019;66 (Supplement 2):S240-S241.	Study does not report an outcome of relevance
22.	Hoppe C, Ataga K, Ware R, et al. Novel trial design to evaluate oral voxelotor for the treatment of sickle cell disease: Protocol of the phase 3 hemoglobin oxygen affinity modulation to inhibit sickle hemoglobin polymerization (hope) trial (GBT440-031). Pediatric Blood and Cancer 2018;65 (Supplement 1):S122.	Study does not report an outcome of relevance
23.	Hoppe C, Inati A, Brown C, et al. Initial results from a cohort in a phase 2A study (GBT440-007) evaluating adolescents with sickle cell disease treated with multiple doses of voxelotor, a sickle hemoglobin polymerization inhibitor. Pediatric Blood and Cancer 2018;65 (Supplement 1):S91-S92.	Study population not relevant
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6.2 Appendix B: Additional information for the STAND trial

STAND is an ongoing, placebo-controlled, double-blind, multicentre, confirmatory phase III study designed to assess the efficacy and safety of two doses of crizanlizumab (5 mg/kg and 7.5 mg/kg) compared with placebo in patients with SCD aged 12 years and older with history of VOC leading to healthcare visit.[17] The study is currently in the recruitment stage and the estimated study completion data December 2027.

As currently designed, the study will include patients aged 12 years and older with confirmed diagnosis of SCD (all genotypes are eligible) who have experienced ≥2 VOC leading to healthcare visit in the 12 months prior to screening visit. Subjects may receive HU/HC and/or L-glutamine as a standard of care.[17] Two-hundred and forty patients will be randomised in a 1:1:1 ratio to either 5.0 mg/kg or 7.5 mg/kg of crizanlizumab or placebo.[17]

Following randomisation, patients will receive their first dose of investigational treatment (crizanlizumab or placebo) via IV administration on Week 1 Day 1, followed by a second dose 14 days later (Week 3 Day 1), and then investigational treatment administration will take place every 4 weeks for a total on-study treatment period of up to 5 years. Following conduct of the primary analysis, once all randomised subjects have reached one year of investigational treatment or discontinued within year one, unblinding and change from placebo to crizanlizumab or to an alternative dose of crizanlizumab will be permitted for each individual patient. Patients will receive investigational treatment for 5 years or until unacceptable toxicity, death, are lost to follow-up or discontinued from the investigational treatment for any other reasons at the discretion of the investigator or the patient.

The primary endpoint of the trial is annualised rate of VOC events leading to healthcare visit over the first year post-randomisation. The key secondary endpoint is the rate of all VOC leading to healthcare visit and treated at home (based on documentation by health care provider following contact with subject) (time frame: 1 year, 5 years).[17] Other secondary endpoints include:

- Annualised rate of VOC managed at home (time frame: 1 year)
- Duration of VOC leading to healthcare visit (time frame: 1 year)
- Number and percentage of subjects free from VOC leading to healthcare visit (time frame: 1 year)
- The time to first and second VOC calculated respectively as the time from date of randomisation until the first and the second VOC leading to healthcare visit over the first year post-randomisation
- Annualised rate of visits to clinic, ER and hospitalisations, both overall and VOC-related over the first year post randomisation

Exploratory objectives include the assessment of quality of life in each group and the assessment of SCD-related organ/function damage.

6.3 Appendix C: Additional information on adverse drug reactions

AEs as reported in the clinical studies in the crizanlizumab-development program were selected as candidates for further evaluation for their relationship with treatment with crizanlizumab for the purpose of the labelling document. Of note, this evaluation of relationship done by Novartis was not equivalent to the individual relationship to study drug that investigators have mentioned for each individual AE on a case by case basis.

The selection of the ADRs was done in a staggered approach. The first step was the selection of AEs as candidates for the further ADR-evaluation. This was done separately for the studies involving healthy subjects (Studies A2101 and A2102) and for each of the studies including patients (SUSTAIN and SOLACE-adults). All AEs which fulfilled the criteria to be ADR candidates were then further evaluated for relatedness to treatment with crizanlizumab. Finally, the frequency for each AE which was defined as an ADR was calculated based on the pooled data from the crizanlizumab 5 mg/kg arms of SUSTAIN and SOLACE-adults.

For the healthy subjects in Studies A2101 and A2102, all AEs were reviewed and screened for ADR candidates, considering AE incidence, any grade 3/4 AE, AEs leading to discontinuation, or any AEs suspected by the Investigator to be drug related. The selection of ADR-candidate was done with a qualitative approach with specific attention to whether the AEs were atypical for healthy subjects studies.

The concepts for selection of ADR-candidates from SUSTAIN and SOLACE-adults were:

For SUSTAIN:

- AE occurring with ≥ 2% frequency in at least one of the active arms AND
- Risk ratio in any of the arms vs. placebo of 1.5 (increase of 50% or more events over placebo)

For SOLACE-adults:

- AEs occurring with ≥ 2% frequency

In addition to this, the clinical database was searched for events which are on the list of ‘Designated Medical Events’ and furthermore, the Novartis Argus safety database was searched for AEs and SAEs which should be included into the evaluation of ADR-candidates based on their medical relevance.

The AEs identified as ADR candidates were assessed by using the criteria as described by Bradford-Hill.

Aspects of this evaluation included the following factors:

- Considering the limited number of patients in the clinical development program, the ADR candidates were evaluated at the event level for potential relatedness to treatment with crizanlizumab. Aspects that were specifically considered were: timing with respect to treatment with crizanlizumab, de-challenge and re-challenge effect, including time from drug discontinuation to symptom resolution, and reasons for drug discontinuation in clinical trials.
- The frequency and consistency of reporting across studies was considered. Based on the larger number of patients and the placebo-controlled design, AE-candidates were primarily

evaluated based on data from SUSTAIN, and data from SOLACE-adults were used to validate these ADR candidates in the framework of the assessment for consistency.

- The comparisons of AE frequencies between the active treatment group(s) vs. placebo form a major part of the assessment of whether or not an AE is considered an ADR.
- The dose response, i.e. the dose-dependency or the pattern related to exposure was considered for assessment whether an AE is an ADR; for dose-response, the 2 dosages in SUSTAIN were considered.
- Further aspects were considered, e.g. consistency of the event with drug pharmacology; if the AE is rare and typically considered as drug-related (e.g. Stevens-Johnson Syndrome); knowledge of the frequency of the event in the patient population with SCD; consistency across different safety variables (e.g. AEs and laboratory data).

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