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Crizanlizumab for adults with sickle-cell disease: a systematic review and network meta-analysis

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Running title: Crizanlizumab for adults with sickle-cell disease

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ABSTRACT

Objectives: Treatment options for preventing vaso occlusive crises (VOC) among patients with sickle cell disease (SCD) are limited, especially if hydroxyurea treatment has failed or is contraindicated. A systematic literature review (SLR) and network meta-analysis (NMA) were conducted to evaluate the efficacy and safety of crizanlizumab for older adolescent and adult (≥16 years old) SCD patients.

Methods: The SLR included randomized controlled trials (RCT) and uncontrolled studies. Bayesian NMA of VOC, all-cause hospitalization days, and adverse events were conducted.

Results: The SLR identified 51 studies and 9 RCTs on 14 treatments that met the NMA inclusion criteria. The NMA found crizanlizumab 5.0 mg/kg was associated with a reduction in VOC (hazard ratio 0.55, 95% credible interval (0.43, 0.69); Bayesian probability of superiority >0.99), all-cause hospitalization days (0.58 (0.50, 0.68); >0.99), and no evidence of difference on adverse events (0.91 (0.59, 1.43); 0.66) or serious adverse events (0.93 (0.47, 1.87); 0.59) compared with placebo. The hazard ratio for reduction in VOC for crizanlizumab relative to L-glutamine was 0.67 (0.50, 0.88); >0.99). These results were sensitive to assumptions regarding whether patient age is an effect modifier.

Conclusions: This NMA provides preliminary evidence comparing the efficacy of crizanlizumab with other treatments for VOC prevention.

PATIENT AND PUBLIC INVOLVEMENT

- No patient or public involvement in this study.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This SLR was comprehensive in terms of outcomes and interventions and was focused on the target population of crizanlizumab.
- To include a diverse range of outcome summaries, a shared parameter Bayesian NMA was employed, as recommended by NICE.
- Risk of bias was assessed using the best practice Cochrane collaboration tool.
- It was not possible to adjust for differences in statistical analysis across RCTs.
- The strength of comparisons on outcomes other than crisis were weak, and crisis may not be the key outcome for patients.

INTRODUCTION

Sickle Cell Disease (SCD) affects approximately 100,000 people in the US.[1] The disease is caused by an autosomal-recessive single gene defect in the beta chain of hemoglobin (HbA), which results in sickle cell hemoglobin (HbS). Sickled cells break down prematurely, and are associated with varying degrees of anemia. Interactions of red blood cells, white blood cells, platelets and endothelial cells are an important contributor to the pathophysiology of sickle cell disease.[2-7] For instance, endothelial cells lining the vasculature are activated and have increased expression of adhesion molecules in SCD patients; this plays a central role in the development of vaso-occlusion.[3 8 9] Ultimately, obstruction of small blood capillaries cause painful crises, damage to major organs, and increased vulnerability to severe infections. Over the past several decades, life expectancy has improved, however, the disease continues to be associated with early mortality and high morbidity.[10] The aim of treatment is to aid disease and chronic pain management, reduce severity and/or prevent complications, and manage acute pain during crises.[11]

There is no widely available cure for SCD and few effective treatments. Hydroxyurea and L-glutamine (Endari), the only two FDA-approved drugs for SCD, are indicated for the prevention of VOCs.[12] In a two-year pediatric study, per patient health care costs for children on hydroxyurea were $9450, compared with $13716 for those who did not receive this treatment.[13] Despite the National Heart, Lung, and Blood Institute's (NHLBI) recommendations, hydroxyurea is not regularly prescribed and adherence to the therapy is poor.[14] Further, there are no current clinical guidelines outlining when to integrate L-glutamine into care. Regular blood transfusions can also be used as a preventive measure, but they may also lead to abnormally high levels of iron in the blood, which can cause long-term organ damage and reactions due to a mismatch between the donors and recipients.[14]

Crizanlizumab is a new drug for the prevention of vaso-occlusive crises. A phase II multicenter, randomized, placebo-controlled, double-blind, 12-month study was completed to evaluate crizanlizumab 5.0 mg/kg and 2.5 mg/kg versus placebo.[15] This study found that the median rate of crises per year was 1.63 with crizanlizumab 5.0 mg/kg versus 2.98 with placebo (indicating a 45.3% lower rate with high-dose crizanlizumab 5.0 mg/kg, *P=0.01*). The median time to the first crisis was also significantly longer with high-dose crizanlizumab 5.0 mg/kg than with placebo (4.07 vs. 1.38 months, *P=0.001*), as was the median time to the second crisis (10.32 vs. 5.09 months, *P=0.02*). In addition, the median rate of uncomplicated crises per year was 1.08 with crizanlizumab 5.0 mg/kg, as compared with 2.91 with placebo (indicating a 62.9% lower rate with crizanlizumab 5.0 mg/kg, *P=0.02*).

The comparative efficacy and safety of crizanlizumab has been evaluated against placebo, however head-to-head randomized controlled trial (RCT) evidence is lacking for comparisons to treatments of interest. Network meta-analysis (NMA) is a statistical method that allows for the simultaneous evaluation of all treatments within a therapeutic area and allows for indirect comparisons between treatments where head-to-head evidence may not be available. Specifically, NMA can be used to combine direct and indirect evidence regarding any interventions that form a network of RCTs where each trial has at least one intervention (active or placebo) in common with another trial and all RCTs

are sufficiently similar.[16 17] To minimize risk of bias, RCTs should be identified through a comprehensive systematic literature review (SLR) using pre-defined criteria.[18]

This study conducts a SLR and NMA to assess the comparative efficacy and safety of crizanlizumab against relevant competing interventions for older adolescent and adult (≥16 years old) patients with SCD.

METHODS

Systematic literature reviews

The SLR protocol was finalised on 25 June 2018 and the SLR was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] A PRISMA NMA checklist can be found in Appendix D. The SLR approach updated and expended an earlier published SLR by Sins et al.[20] by including non-controlled studies and included additional interventions. Inclusion and exclusion criteria for studies are summarised in Table 1 below. Relevant studies were identified by searching the following databases: Cochrane Central Register of Controlled Trials (CENTRAL); Medical Literature Analysis and Retrieval System Online (MEDLINE); and Excerpta Medica database (Embase). We also searched a trial registry, *ClinicalTrials.gov.* The search strategies were derived from Sins et al.[20] and can be found in Appendix B along with the complete search protocols in Appendices E and F**.** As blood transfusion was not included by Sins et al.,[20] we conducted a separate search for blood transfusion from inception of databases to 30th August 2018. For non-transfusion studies, the search date was from 1st January 2017 to 21st June 2018 to bridge the findings of Sins et al. [20]

Table 1: Study selection criteria to identify trials for the systematic literature review

Criteria	Description
Population	Studies included adult patients with sickle cell disease
Interventions	• Crizanlizumab • L-glutamine • Voxelotor (GBT440) • Red blood cell transfusions • Other types of transfusions • Any pharmacological interventions for preventing crisis, pain and/or vaso-occlusive crisis (VOC)
Comparators	• Placebo or best supportive care • Any of the listed interventions of interest • Any treatment that facilitates an anchored indirect comparison
Outcomes	Primary outcomes: • Pain, crisis and VOC (frequency, intensity and duration in one event) Secondary outcome: • Hospital admission, including emergency department (ED) and nurse visits • SCD complications, including acute chest syndromes (ACS) • Analgesic use • Adverse events*

Study design	• Randomized controlled trials (RCTs) • Single-arm trials when RCTs are not available for the interventions of interest
Language	English

**In addition to efficacy outcomes, adverse events are of interest for the review, but will not be used as study selection criteria.*

Results of searches were managed using Endnote and a Microsoft Excel spreadsheet. Two reviewers screened and selected records independently against inclusion and exclusion criteria using titles and abstracts. Full-texts of potential eligible records were retrieved and screened to assess the eligibility for data extraction. Disagreements were resolved by discussion and consensus. Following reconciliation between the two investigators, a third investigator was included to reach consensus for any remaining discrepancies. The Cochrane Collaboration's Risk of Bias tool was used to assess risk of bias in included RCTs. [21] The Newcastle-Ottawa Scale was used to assess the quality of non-controlled studies.[22]

The primary outcome of this review was sickle cell pain crisis (SCPC), also known as a vaso-occlusive crisis (VOC) leading to a healthcare visit. A variety of definitions for VOC was observed in the included studies. We consulted several medical experts and chose the definition of crisis used in the pivotal Phase II RCT of crizanlizumab.[15] In this trial, a VOC was defined as an acute episode of pain, with no medically determined cause other than a vaso-occlusive event that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral nonsteroidal anti-inflammatory drug. In addition to outcomes specifically named as pain crisis, the outcomes of vaso-occlusive crisis (VOC) and Sickle Cell Disease Crisis (SCDC) were extracted and included with the VOC set if found to use a comparable definition.

Other outcomes identified as of interest and/or extracted included pain-related outcomes, acute chest syndrome (ACS), all-cause hospitalizations, transfusions, analgesic use, death, adverse events, and serious adverse events. In addition to study and intervention characteristics, the patient characteristics were extracted to qualitatively assess comparability of different study populations.

Network meta-analysis

Quantitative synthesis through NMA was planned for reported or derived time-to-event outcomes of VOC, all-cause hospitalization days, adverse events, and serious adverse events, in line with those reported by the Phase II RCT on crizanlizumab.[15] International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Society for Medical Decision (MDM), and UK National Institute for Health and Care Excellence (NICE) guidelines were followed in design of the NMA model.[23-26] As the pivotal study on crizanlizumab was conducted within an older adolescent and adult (≥16 years old) population, the NMA was conducted only on studies that included patients ≥16 years old with SCD. Whilst the pivotal study for L-glutamine (Niihara 2018) included patients aged <16 years old, a decision was made to include the study to enable a comparison with crizanlizumab. The primary comparison examines the outcomes in the whole population. A sensitivity analysis, was subsequently run using the results with Endari in a subgroup of patients aged >18 years old (reported in Niihara 2018).. Evidence networks were generated with nodes corresponding to treatments and edges connecting nodes if at least one RCT comparing corresponding treatments was identified.[27] An extended network including RCTs with a mixture of child, adolescent and adult populations was investigated for additional direct or indirect evidence on any comparison with crizanlizumab 5.0 mg/kg.

Following NICE guidelines, we employed a shared parameter model for hazard ratios to synthesise studies summarising outcomes in different formats and accounting for differences in trial duration.[26] Summaries that could be included were total number of events, percentage of patients with events, mean numbers of events, mean or median rates, numbers of patients with at least one event, and risk or hazard ratio of event. Likelihood and link function for each summary followed MDM and NICE guidelines.[25 26]. Total number of events are modelled with a Poisson likelihood and log link, numbers of patients with at least one event are modelled using a Binomial likelihood and complementary log log link, while risk and hazard ratios are modelled on a log scale with a Normal likelihood and identify link. A Bayesian perspective with vague priors was adopted. Sensitivity to priors was explored. Fixed and random effect were considered with choice being made on basis of model fit; meta-regressions were also explored to assess heterogeneity due to trial duration, proportion female, mean age, proportion homozygous hemoglobin S (HbSS) genotype, proportion hydroxyurea use, and proportion black or African-American.[28] Different doses of the same drug were analysed independently. If a connected evidence network could be formed using only RCTs, single-arm study evidence was discarded. The reference treatment in all analyses was placebo. If feasible, inconsistency between direct and indirect evidence was planned to be tested by node-splitting and an independent means inconsistency model.[16] All analyses were conducted using the Markov Chain Monte Carlo (MCMC) software of OpenBUGS version 3.2.3.[29] Two MCMC chains with 400,000 iterations for burn-in and 30,000 iterations for posterior sampling were used. Convergence was assessed by visual inspection and the Gelman-Rubin statistic.[29] Further details of the modelling methods are provided in Appendix C.

We generated hazard ratios with 95% credible intervals (CrI) of high-dose crizanlizumab 5.0 mg/kg relative to each comparator. We estimated the Bayesian probability that crizanlizumab was superior (lower hazard of event) or inferior (higher hazard of event). These probabilities are the Bayesian equivalent of one-sided p-values. In line with the recommendations of the American Statistical Association, we did not adopt a strict threshold for interpreting these Bayesian probabilities,[30] but instead reported the probability itself. Probabilities are interpreted to suggest evidence in favour of a hypothesis if it lay lower than 5% or above 95%, and weak evidence if the probability was between 5-10% or 90-95%.[31]

RESULTS

Systematic literature review results

We retrieved 3388 records from electronic databases, *ClinicalTrials.gov* and Sins 2017. After removing duplicates and irrelevant records, we screened 250 full-text articles. Fifty one studies (67 references) were included to perform evidence evaluation for the NMA (Figure 1). Full details and references for the 51 studies are included in Appendix B. We also identified fourteen additional ongoing clinical RCTs or completed RCTs without publication, which investigated effects of non-hydroxyurea treatments on SCD patients.[32-45]

Of 51 studies, duration of follow-up was reported in 41 studies and, among RCTs in the ≥16 years old population, duration ranged from 30 days in Wun 2013[46] to 52 weeks in Ataga 2017.[15] This range represents substantial variation in follow-up, but the methods used for NMA model trial follow-up compare annualized hazards in order to adjust for this difference.

The proportion of female patients varied across RCTs, ranging from 0.44 in Glassberg 2017[47] to 0.60 in Sins 2017,[48] so qualitatively similar proportions. Across all 51 studies, the proportion of females varied from 0.23 in Gupta 1995[49] to 1.00 in de Abood 1997,[50] representing a more substantial

difference. In the ≥16 years old population RCTs, age ranged from 20.5 years in Pace 2003[51] to 35.5 years in Ataga 2008.[52] Across all 51 studies, the mean age ranged from 4.8 years in Adegoke 2013[53] to 48.8 years in Bridges 2017.[54] The proportion with HbSS genotype ranged from 0.60 in Wun 2013[46] to 1.00 in several studies that restricted enrolment to patients with HbSS disease alone, including Ataga 2008[52] in the ≥16 years old population. Although HbSS is indicative of absolute outcomes (prognostic factor), there is no known evidence that it is an effect modifier, so the NMA remains feasible.[28] Proportion of patients reported as black or African American ranged from 0.53 in NCT02482298[55] to 1.00 in Styles 2010.[56] Several studies excluded patients with history of hydroxyurea usage, including Bao 2008[57] in the ≥16 years old population. In the ≥16 years old population, this otherwise varied from 0.42 in Sins 2017[48] to 0.67 in Niihara 2018,[12] making it somewhat comparable.

Construction of evidence networks

Of the 51 studies identified, there were 17 non-controlled studies that were excluded from the NMA due to lack of common comparators and potential bias. Of the 34 remaining RCTs , only 8 were conducted solely in older adolescent and adult (≥16 years old) patients.[15 46-48 51 52 55 56]. As the only RCT identified on L-glutamine, Niihara 2018[12] was included in the network. This gave 9 RCTs in the ≥16 years old population evidence networks. Five of these studies used a VOC definition comparable to that in Ataga 2017[12 15 51 52 56] (details in Appendix C). The only study that examined transfusions was a conference abstract by Vichinsky. As the authors did not specify the definition of VOC or a placebo control, this study was excluded from the NMA[58] Appendix A shows the characteristics of included studies in the NMA. Analysed evidence networks are provided in Figure 2.

In addition to crizanlizumab 5.0 mg/kg and 2.5 mg/kg, multiple doses of other drugs were included in the networks. Ticagrelor was studied as both twice daily 45mg (high-dose) and 10mg (low-dose);[55] N-acetylcysteine (NAC) as 600mg (low-dose), 1200mg (mid-dose), and 2400mg (high-dose);[51] Senicapoc with a loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance,[56] and as a low-dose and high-dose formulation corresponding to single loading doses of 100mg and 150mg, respectively, and maintenance 6mg and 10mg daily, respectively.[52]

Cochrane risk of bias assessment for the 9 RCTs included in NMA is reported in full in Appendix C. Risk of bias was low in all categories for three of these studies (two studying senicapoc and one mometasome), and was low in all except incomplete outcome data in Ataga 2017.[15] Three studies were at unclear risk of bias due to random sequence generation and allocation concealment (studying ticagrelor, L-glutamine, and NAC doses).[12 51 55] Sins 2017 (studying NAC) was at low risk of bias for all categories except incomplete outcome data, on which it was at high risk of bias.[48]. Wun 2013 (studying prasugrel) was at unclear risk of bias on random sequence generation, allocation concealment, and blinding but low risk of bias on remaining categories.[46]

Network meta-analysis results

A fixed effects NMA approach was used for the primary analyses. The NMA models converged well and fit, assessed by comparing residual deviance to total number of data points, was good for all fixed effects analyses. Random effects analyses did not converge as only one RCT was available on each treatment contrast. Meta-regression to explore covariate effects did not reveal evidence of effect medication but convergence was poor for these models. Fit statistics and model assessment details are provided in Appendix C. Inconsistency could not be tested as there were no treatment contrasts on which both direct and indirect evidence were available.[16]

We discuss in turn the results of the NMA on VOC, all-cause hospitalization days, adverse events, and serious adverse events. Forest plots of hazard ratios with 95% CI of crizanlizumab vs all comparators are provided in Figure 3. Bayesian probabilities that crizanlizumab 5.0 mg/kg is superior or inferior are also provided in this figure. Pairwise results for all treatment comparisons are provided in Appendix C.

We found evidence that crizanlizumab 5.0 mg/kg had a lower hazard of crisis than L-glutamine (hazard ratio 0.67, 95% CrI (0.51, 0.88); Bayesian probability crizanlizumab 5.0 mg/kg superior 0.9982), placebo (0.55 (0.43, 0.69); >0.9999), and senicapoc (0.46 (0.32, 0.67); >0.9999). We found only weak evidence that hazard of crisis was lower on crizanlizumab 5.0 mg/kg than crizanlizumab 2.5 mg/kg (0.81 (0.63, 1.05); 0.9452) or low-dose NAC (0.48 (0.18, 1.21); 0.9396). We found no evidence of a difference between crizanlizumab 5.0 mg/kg and low-dose senicapoc (0.53 (0.14, 1.95); 0.8334), high-dose NAC (1.91 (0.57, 7.58); 0.1507), mid-dose NAC (0.81 (0.29, 2.18); 0.6619), or high-dose senicapoc (0.57 (0.15, 2.17); 0.8010). Results are summarized in Table 2 below.

Table 2. Bayesian probabilities that crizanlizumab is superior on each outcome analyzed*

	Crisis	All-cause hospitalization	Adverse events	Serious adverse events
Placebo	>0.9999	>0.9999	0.6558	0.5857
L-glutamine	0.9982	0.0731	0.2480	0.2854
Crizanlizumab 2.5mg/kg	0.9452	>0.9999	0.5743	0.8134
Mometasome	-	0.7496	0.9399	-
Low-Dose NAC	0.9396	0.0166	0.6996	0.9744
Mid-Dose NAC	0.6619	-	-	-
High-Dose NAC	0.1507	-	-	-
Prasugrel	-	-	-	0.5242
Senicapoc	>0.9999	-	0.7176	-
High-Dose Senicapoc	0.8010	-	-	-
Low-Dose Senicapoc	0.8334	-	-	-
High-dose Ticagrelor	-	-	-	0.4247
Low-dose Ticagrelor	-	-	-	0.6181

*Proportion of MCMC samples for which crizanlizumab vs comparator hazard ratio is above (inferior) or below (superior) 1. Entry '-' indicates comparator not included in outcome specific evidence network.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelor=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

In a sensitivity analysis using a reported rate ratio of 0.64 with 95% confidence interval (0.45, 0.89) in a subgroup of patients aged >18 years old from Niihara 2018, we found no evidence that crizanlizumab had a lower hazard of crisis than L-glutamine (0.86 (0.57, 1.29); 0.7707). Full results of this analysis are provided in Appendix C.

We found evidence that crizanlizumab 5.0 mg/kg had a lower hazard of all-cause hospitalization days than placebo (0.58 (0.50, 0.68); >0.9999), and crizanlizumab 2.5 mg/kg (0.58 (0.50, 0.68); >0.9999), but found evidence that hazard was higher than on low-dose NAC (2.08 (1.06, 4.66); 0.0166). We found weak evidence that hazard of all-cause hospitalization days was higher on crizanlizumab 5.0

mg/kg than on L-glutamine (1.73 (0.82, 3.76); 0.0731) and no evidence of a difference with mometasome (0.89 (0.63, 1.26); 0.7496). Note that all-cause hospitalization includes admission for crisis but also for adverse events and non-SCD related causes.

The hazard of adverse events—both serious and overall—for crizanlizumab was generally similar or weakly better than other treatments. The exception is that there was weak evidence that crizanlizumab 5.0 mg/kg had a lower hazard than mometasome (0.51 (0.21, 1.19); 0.9399). We found no evidence of a difference in hazard of adverse events between crizanlizumab 5.0 mg/kg and placebo (0.91 (0.59, 1.43); 0.6658), L-glutamine (1.31 (0.62, 3.08); 0.2680), crizanlizumab 2.5 mg/kg (0.96 (0.61, 1.48); 0.5743), low-dose NAC (0.84 (0.45, 1.60); 0.6996), or senicapoc (0.86 (0.52, 1.44); 0.7176). Similarly, the hazard of serious adverse events on crizanlizumab 5.0 mg/kg were lower than on low-dose NAC (0.20 (0.02, 1.00); 0.9744). There was no evidence of a difference on adverse event rates between crizanlizumab 5.0 mg/kg and placebo (0.93 (0.47, 1.87); 0.5857), L-glutamine (1.24 (0.58, 2.70); 0.2854), crizanlizumab 2.5 mg/kg (0.75 (0.39, 1.43); 0.8134), high-dose ticagrelor (1.14 (0.27, 4.81); 0.4247), or low-dose ticagrelor (0.81 (0.21, 3.17); 0.6181).

DISCUSSION

Previous SLRs and meta-analyses of treatments for SCD have demonstrated hydroxyurea to be effective in reducing VOC rates.[59 60] However, patients receiving hydroxyurea therapy can continue to have crises, end-organ damage, and a decreased life expectancy.[61] Crizanlizumab and L-glutamine are promising treatment options for SCD patients not well managed on hydroxyurea, but no direct comparison across these treatments has been conducted.[14 15 62] Our SLR and NMA is the first looking at the comparative efficacy of new treatments for older adolescent and adult (≥16 years old) SCD patients not well managed on hydroxyurea and is therefore of vital importance to this patient population.

Our baseline analysis found that crizanlizumab 5.0 mg/kg reduced crisis compared to L-glutamine, placebo, and senicapoc, and weak evidence of reduction compared to crizanlizumab 2.5 mg/kg and low-dose NAC. These results, however, were sensitive to whether the L-glutamine efficacy was measured for all patients or only those aged >18 years.

We found that crizanlizumab 5.0 mg/kg reduced all-cause hospitalization days compared to placebo and crizanlizumab 2.5 mg/kg. Conversely, we found evidence that low-dose NAC reduced hospitalization compared to crizanlizumab 5.0 mg/kg, and weak evidence that L-glutamine reduced hospitalization compared to crizanlizumab 5.0 mg/kg.

Our analysis found high-dose crizanlizumab 5.0 mg/kg had a lower hazard of adverse events compared to mometasome and of serious adverse events compared to low-dose NAC. There was no evidence of a difference between 5 mg/kg crizanlizumab on safety with other treatments.

Strengths

This SLR was comprehensive in terms of outcomes and interventions and was focused on the target population of crizanlizumab, that of older adolescent and adult (≥16 years old) SCD patients not well managed, or having failed previous treatment, with hydroxyurea. Our review followed the PRISMA guidelines and checklist.[19] Risk of bias was assessed using the best practice Cochrane collaboration tool.[21] To be comprehensive, we searched for both RCT and single-arm evidence but used only RCT evidence in the NMA. Our analysis followed published and international guidelines on indirect comparisons and network meta-analysis.[23-26] On the outcome of VOC, we ensured only studies with a definition compatible with that of the principal crizanlizumab study were analysed. [15] To include a

diverse range of outcome summaries, such as total number of events and numbers of patients with at least one event, a shared parameter Bayesian NMA was employed, as recommended by NICE.[26]

Limitations

There were several limitations to this SLR and NMA. There was at most only one RCT on each of the treatment contrasts. A similar definition of VOC was used across RCTs but the shared parameter NMA combined RCTs without adjusting for differences in statistical analyses, such as methods for managing drop-outs, used. Differences in RCT follow-up (e.g. 30 days in Wun 2013[46] and 52 weeks in Ataga 2017)[15] limit comparability of annualized hazard rates across treatments. The strength of evidence for comparisons on hospitalization, adverse events, and serious adverse events was weak. Furthermore, we could not include transfusions in the NMA as the only available RCT in an adult population —Vichinsky 2010[58]— used an unspecified standard of care rather than a placebo control, did not describe the definition of VOC that was used, and was published only as an abstract.

Due to a lack of evidence, the NMA was not able to estimate the relative impact of crizanlizumab treatment on the rate of complicated crisis or organ damage, both of which are important health outcomes for patients and physicians. Inconsistency in the network could not be assessed as there were no loops in the evidence networks; it was necessary to assume consistency to enable comparisons with crizanlizumab.

A previous SLR in non-hydroxyurea SCD treatments did not conduct quantitative synthesis due to concerns regarding heterogeneity.[20] Although we considered meta-regression on trial duration, proportion female, mean age, proportion HbSS genotype, proportion hydroxyurea use, and proportion black or African-American there was insufficient evidence as there was only one RCT on each treatment contrast. We were also lacking information on the amount of VOCs in the year preceding randomization/treatment start for several of the treatments included in the analysis, a factor known to be prognostic. We therefore had to assume differences in characteristics would not modify treatment effects, even in parameters expected to influence the frequency of VOCs. Although we conducted a sensitivity analysis using results among >18 year olds from Niihara 2018, that study itself concluded that there was “no significant interaction between trial group assignment and age”.[63] On the other hand, if age is an effect modifier, the baseline results should be interpreted cautiously. Future real-world evidence studies may be useful to explore effect modifiers and identify patient types that benefit most from crizanlizumab and other treatments.

Further, caution should be taken when interpreting these results in relation to switching patients from hydroxyurea to crizanlizumab or L-glutamine. Our analysis does not purport to compare crizanlizumab, or indeed L-glutamine or blood transfusions, with hydroxyurea but is instead focused solely on patients who are not well managed on hydroxyurea. Before more evidence is available, physicians should consider treatment with hydroxyurea before consideration of second line treatments.[64]

Conclusion

Our baseline analysis showed from an SLR and NMA that crizanlizumab reduced crises and hospital days compared with placebo and other treatments with an acceptable adverse event profile in older adolescent and adult (≥16 years old) SCD patients when compared to other non-hydroxyurea treatments. The VOC results, however, were sensitive to assumptions regarding whether patient age is an effect modifier.

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DATA SHARING STATEMENT

All necessary data, coda, and initial values for our OpenBUGS models are provided in the network meta-analysis.

AUTHORSHIP CONTRIBUTIONS

HT drafted the manuscript and conducted and designed and conducted the network meta-analysis. NS ensured medical relevance for the review and analysis and provided context for the results. JJ advised on statistical aspects of the analysis. GJ and JS provided oversight to the whole project. LZ provided project management and administrative support. MB provided subject-matter expertise on the review and analysis. HYC led the systematic review. SG validated the network meta-analysis. All authors reviewed and edited the manuscript.

DISCLOSURES OF CONFLICTS OF INTEREST

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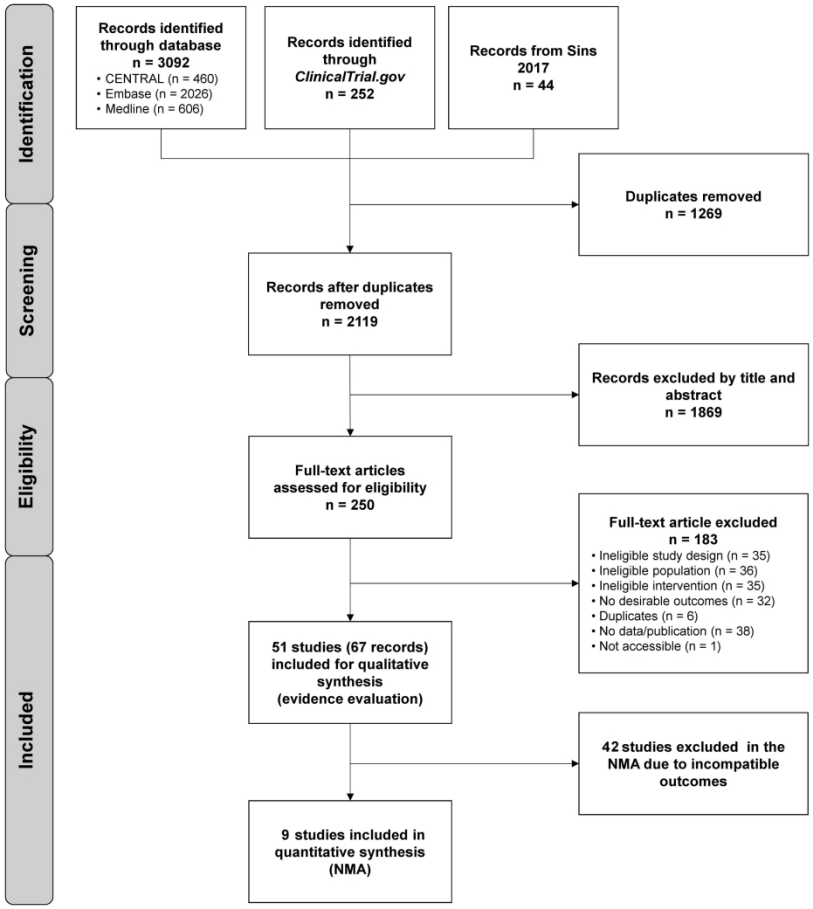


Figure 1. SCD Prisma Flow Chart

209x297mm (300 x 300 DPI)

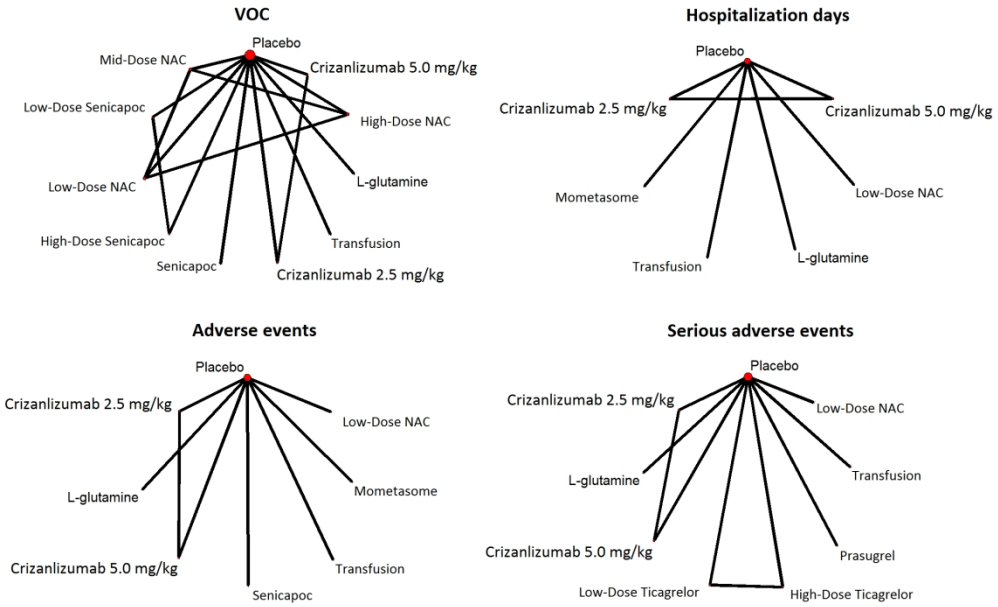


Figure 2. Evidence networks

* Each node represent a treatment and nodes are connected by an edge if at least trial has compared the relevant treatments. Any two treatments can be compared if their corresponding nodes can be connected by a path of one or more edges.

High-dose Crizanlizumab=5mg/kg 14 times over 52 weeks. Low-Dose Crizanlizumab=2.5mg/kg 14 times over 52 weeks. High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelor=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

5 RCTs on crisis = Ataga 2017 (crizanlizumab vs placebo), Niihara 2018 (L-glutamine vs placebo), Ataga 2011 (senicapoc vs. placebo), Ataga 2008 (senicapoc low-dose, senicapoc high-dose vs. placebo), and Pace 2003 (NAC low, mid, and high dose vs. placebo). 4 RCTs on all-cause hospitalization days = Ataga 2017 (crizanlizumab vs placebo), Niihara 2018 (L-glutamine vs placebo), Glassberg 2017 (mometasome vs. placebo), and Sins 2017 (NAC vs. placebo). 5 RCTs on adverse events = Glassberg 2017 (mometasome vs placebo), Ataga 2017 (crizanlizumab vs placebo), Ataga 2011 (senicapoc vs placebo), Sins 2017 (NAC vs placebo), and Niihara 2018 (L-glutamine vs placebo). 5 RCTs on serious adverse events = Ataga 2017 (crizanlizumab vs placebo), Sins 2017 (NAC vs placebo), Wun 2013 (prasugrel vs placebo), NCT02482298 (TICAGRELOR vs placebo), and Niihara 2018 (L-glutamine vs placebo).

291x185mm (192 x 192 DPI)

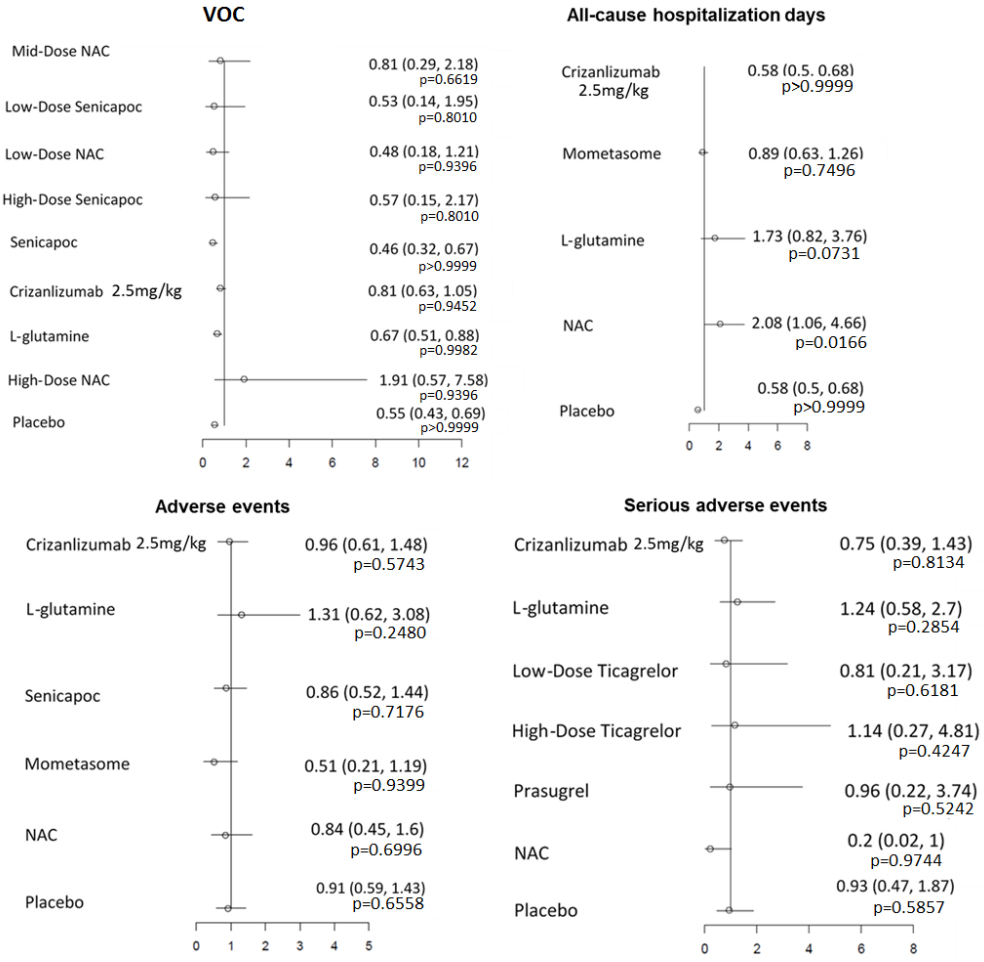


Figure 3. Forest plot

*Hazard ratio less than 1 suggests lower hazard of event on the crizanlizumab. Bayesian probabilities of superiority are proportion of MCMC samples for which crizanlizumab vs comparator hazard ratio is above (inferior) or below (superior) 1.

High-dose Crizanlizumab=5mg/kg 14 times over 52 weeks. Low-Dose Crizanlizumab=2.5mg/kg 14 times over 52 weeks. High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelor=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Appendix A: Characteristics and outcomes of studies included in the network meta-analysis*

Author/Year/Country Ref/Enrolment/NCT registry	Design Total N of PT (N of female); N of arm Follow-ups	Interventions	Crisis	All-cause Hospitalization days	Adverse events (AE)	Serious adverse events (SAE)
Glassberg 2017[47] USA Feb 2014 to Oct 2016 NCT02061202	RCT, triple-blind Adults and adolescents Single centre 54 (23); 2 16 weeks	1. Mometasone furoate 220mcg OD inhale (n=35) In addition to standard SCD care		Rate hospitalization days: 2.67	Total number of AE: 32	
		2. Placebo (n=17) In addition to standard SCD care		Rate of hospitalization days: 4.09	Total number of AE: 9	
Ataga 2017[15] Brazil, Jamaica, USA Aug 2013 to Jan 2015 NCT01895361	RCT, double-blind Adults and adolescents Multicentre 198 (109); 3 52 weeks	1. Crizanlizumab 5 mg/kg IV (n=67) Two doses 2 weeks apart (loading dose) and then every 4 weeks. A total of 14 doses for 50 weeks	Median annual rate of crisis 1.63	Annual rate of days hospitalized 4.00	Number of patients with ≥1 AE: 57	Number of patients with ≥1 SAE: 17
		2. Crizanlizumab 2.5 mg/kg IV (n=66) Two doses 2 weeks apart (loading dose) and then every 4 weeks. A total of 14 doses for 50 weeks	Median annual rate of crisis 2.01	Annual rate of days hospitalized 6.87	Number of patients with ≥1 AE: 56	Number of patients with ≥1 SAE: 21
		3. Placebo (n=65)	Median annual rate of crisis 2.98	Annual rate of days hospitalized 6.87	Number of patients with ≥1 AE: 55	Number of patients with ≥1 SAE: 17
Sins 2017[48] Netherlands, Belgium, UK Apr 2013 to Nov 2015 NCT01849016	RCT, double-blind Adults Multicentre 96 (40); 2 6 months	1. NAC 600mg BID oral (n=27)		Total hospital admission days: 9	Total number of AE: 39	Total number of SAE: 8
		2. Placebo (n=40)		Total hospital admission days: 53	Total number of AE: 36	Total number of SAE: 2
Niihara 2018[12] US	RCT, double-blind (phase 3)	1. L-glutamine 0.3 g/kg BID oral (n=152) Maximum dose: 30mg	Mean number pain crises: 3.2	Total hospitalization days: 12.1	Percentage with ≥1 AE: 0.98	Percentage with ≥1 SAE: 0.782

Jun 2010 to Dec 2013 NCT01179217	Adults and children Multicentre 230 (124); 2 48 weeks	2. placebo (n=78)	Mean number pain crises: 3.9	Total hospitalization days: 18.1	Percentage with ≥1 AE: 1.00	Percentage with ≥1 SAE: 0.871
Ataga 2011[56] United States, Jamaica, Brazil, France, Trinidad and the United Kingdom. Feb 2005 to Apr 2007 NCT00102791	RCT, double-blind (phase 3, terminated early) Adults and adolescents Multicentre 297 (160); 2 52 weeks	1. Senicapoc 20mg/d BID (loading) and then 10mg/dOD oral (n=145)		Total number of crises: 89		Total number of AE: 127
		2. Placebo (n=144)		Total number of crises: 106		Total number of AE: 119
Ataga 2008[52] US Feb 2002 and Jan 2004 NCT00040677	RCT, double-blind (phase 2) Adults Multicentre 90 (45); 3 12 weeks	1. Senicapoc (high-dose): 150 mg (loading dose); 10 mg/d (maintenance) oral OD (n=31)		Total number of crises: 5		
		2. Senicapoc (low-dose): 100 mg (loading dose); 6 mg/d(maintenance) oral OD (n=29)		Total number of crises: 5		
		3. Placebo (n=30)		Total number of crises: 5		
Pace 2003[51] USA	RCT, double-blind Adults and Adolescents Single centre 21 (10); 4 7 months	1. NAC (high-dose) 2400mg/day (n=6) All doses were divided by 3 to be taken		Total number of crises: 5		
		2. NAC (mid-dose) 1200mg/day (n=5) All doses were divided by 3 to be taken		Total number of crises: 5		
		3. NAC (low-dose) 600 mg/day (n=5) All doses were divided by 3 to be taken		Total number of crises: 4		
		4. Placebo (n=5)		Total number of crises: 3		
NCT02482298[55] USA, Egypt, France, Italy, Kenya, Lebanon, UK, Turkey	RCT, double-blind Adults	1. Ticagrelor 45mg BID oral (n=30)				Total number of SAE: 5
		2. Ticagrelor 10MG BID oral (n=27)				Total number of SAE: 6

Jul 2015 to Nov 2016	Multicentre 87 (47); 3 12 weeks	1. Placebo (n =30)	Total number of SAE: 6
Wun 2013[46] United States and Canada 26 Aug 2010 to 13 Jun 2011 NCT01167023	RCT, double-blind (phase 2) Adults Multicentre 62 (30); 2	1. Prasugrel 5 mg/day oral (n=41)	Total number of SAE: 8
		2. placebo (n=19)	Total number of SAE: 4

*ACS: Acute chest syndrome; ALT: Alanine transaminase; CA: Conference abstract; Cr: creatinine; CSRPM: Center for Scientific Research into Plant Medicine; CT: clinical trial registry; DDCF: Doris Duke Charitable Foundation; ED: emergency department; HbSS: Homozygous sickle haemoglobin (HbS); HbSC: sickle haemoglobin S and haemoglobin C; HbSβ: sickle beta thalassemia, type '0' or '+'; HU: hydroxyurea; JA: Journal article; MTX: Methotrexate; NAD: N-acetylcysteine ;NCATS: National Center for Advancing Translational Sciences; NCRR: National Center for Research Resources; NHLBI: National Heart Lung and Blood Institute; NSAID: Nonsteroidal anti-inflammatory drugs; NR: Not reported; OOPD: FDA's Office of Orphan Products Development; PT: patient; SCD: sickle cell disease; TCD: transcranial Doppler; ZonMw: The Netherlands Organisation for Health Research and Development

** Entry is blank if no data provided for crisis, all-cause hospitalization days, adverse events, or serious adverse events. See appendix for relevant link function to connect different outcome summaries to network meta-analysis.

Appendix B: Additional details of Systematic literature review

A.1 Literature search strategies for non-transfusions SLR

Table 1: Search strategy for non-transfusions search of MEDLINE

#	Searches	Concept
1	exp pain/	Outcomes
2	(pain or painfull).tw.	
3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	
4	exp length of stay/	
5	(hospital adj3 (admission or stay)).tw.	
6	(patient adj3 (admission or stay)).tw.	
7	or/1-6	
8	anemia, sickle cell/	Population
9	hemoglobin, sickle/	
10	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	
11	or/8-10	
12	exp antisickling agents/	Interventions
13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or L-glutamine or voxelotor or GBT440).mp.	
14	(8 or 9 or 10) and prevent vaso-occlusiv*.tw.	
15	or/12-14	
16	7 and 11 and 15	
17	meta analysis.pt.	Systematic review and meta-analysis studies
18	((meta adj analys*) or metaanalys or meta-analys*).ti,ab,sh.	
19	(systematic adj5 (review or overview*)).ti,ab,sh.	
20	or/17-19	
21	16 and 20	
22	clinical trial/	RCTs
23	(clinic adj5 trial*).ti,ab,sh.	

#	Searches	Concept
24	single blind method/	
25	double blind method/	
26	random allocation/	
27	placebos/	
28	(placebo or random*).ti,ab,sh.	
29	randomized controlled trial/	
30	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	
31	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	
32	randomi?ed control trial*.tw.	
33	or/22-32	
34	16 and 33	
35	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	Single arm trials
36	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	
37	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	
38	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	
39	Clinical Trial, Phase I.pt.	
40	Clinical Trial, Phase II.pt.	
41	Clinical Trial, Phase III.pt.	
42	(registry or registries).ti,ab,kf,hw.	
43	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	
44	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	
45	(nonrandom* or non-random*).ti,ab,kf.	
46	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	
47	(all adj3 received).ab.	
48	or/35-47	
49	16 and 48	

#	Searches	Concept
50	limit 21 to ed=20170130-20180620	Date limit on rSLR and meta-analysis studies
51	limit 34 to ed=20170130-20180620	Date limit on RCTs
52	limit 49 to ed=20170130-20180620	Date limit on single arm trials

Table 2: Search strategy for non-transfusions search of EMBASE

#	Searches	
1	exp pain/	Outcomes
2	(pain or painfull).tw.	
3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	
4	exp "length of stay"/	
5	(hospital adj3 (admission or stay)).tw.	
6	(patient adj3 (admission or stay)).tw.	
7	or/1-6	
8	sickle cell anemia/	Population
9	hemoglobin S/	
10	(sickle cell or sickle h$emoglobin or drepanocyt* or drepanotic or drepanocytemia or h$emoglobin-s or Hb-S or sickle an$emia or meniscocytosis).mp.	
11	or/8-10	
12	antisickling agent/	Intervention
13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or L-glutamine or voxelotor or GBT440).mp.	
14	(8 or 9 or 10) and prevent vaso-occlusiv*.tw.	
15	or/12-14	
16	7 and 11 and 15	
17	randomized controlled trial/	RCTs
18	(RCT or randomi#ed or randomi#ation).ab,ti,kw,hw.	

#	Searches	
19	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or subsitut* or treat*)).ab,kw.	
20	trial.ti.	
21	crossover procedure/	
22	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dumm*)).ti,ab,kw,hw.	
23	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	
24	or/17-23	
25	16 and 24	
26	prospective study/ or retrospective study/ or longitudinal study/ or cohort analysis/ or cross-sectional study/ or case control study/ or population based case control study/	Single-arm trials
27	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 study).ti,ab,kw.	
28	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	
29	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab,kw.	
30	(registry or registries).ti,ab,kw,hw.	
31	(nonrandom* or non-random*).ti,ab,kw.	
32	((control* adj2 before adj2 after) or CBA study).ti,ab,kw.	
33	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kw.	
34	(all adj3 received).ab.	
35	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 1 clinical trial/	
36	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kw.	
37	or/26-36	
38	16 and 37	
39	limit 25 to em=201705-201825	Date limit on RCTs
49	limit 38 to em=201705-201825	Date limit on single arm trials

Table 3: Search strategy for non-transfusions search of Cochrane Register of Controlled Trials

#	Searches	
#1	MeSH descriptor: [Pain] explode all trees	Outcomes
#2	(pain or painfull):ti,ab,kw	
#3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises):ti,ab,kw	
#4	MeSH descriptor: [Length of Stay] explode all trees	
#5	(hospital near/3 (admission or stay)):ti,ab,kw	
#6	(patient near/3 (admission or stay)):ti,ab,kw	
#7	#1 or #2 or #3 or #4 or #5 or #6	
#8	MeSH descriptor: [Anemia, Sickle Cell] this term only	Population
#9	MeSH descriptor: [Hemoglobin, Sickle] this term only	
#10	(sickle cell or sickle h*emoglobin or drepanocyt* or drepanotic or drepanocytemia or h*emoglobin-s or Hb-S or sickle an*emia or meniscocytosis):ti,ab,kw	
#11	#8 or #9 or #10	
#12	MeSH descriptor: [Antisickling Agents] explode all trees	Interventions
#13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or L-glutamine or voxelotor or GBT440):ti,ab,kw	
#14	(#8 or #9 or #10) and prevent vaso-occlusiv*	
#15	#11 or #12 or #13	
#16	#7 and #11 and #14	

Table 6: Search strategy for non-transfusions search of ClinicalTrials.gov*

#	Searches	Search column
#1	Anemia, Sickle Cell OR Sickle Beta Thalassemia OR Sickle Cell Anemia OR Sickle Cell trait	Condition or disease
#2	SCD OR SCA OR Sickle	Other terms
#3	Drug OR Placebo OR Crizanlizumab OR Hydroxyurea OR L-glutamine OR Voxelotor OR GBT440 OR hydroxycarbamide	Intervention/treatment
#4	pain OR hospitalisation OR hospitalization OR (hospital AND (admission OR stay)) OR crisis OR VOC OR ((vaso OR vein OR vena OR venous) AND (occlusive OR occlusive OR interruption OR obstruction)) OR survival OR quality of life	Outcome Measures
	#1 or #2 or #3 or #4	

*Advanced Search option without any restrictions except search strings listed.

A.2 Literature search strategies for transfusions SLR

Table 4: Search strategy for transfusions search on CENTRAL database

#	Searches	Results
#1	MeSH descriptor: [Anemia, Sickle Cell] this term only	583
#2	MeSH descriptor: [Hemoglobin, Sickle] this term only	19
#3	(sickle cell or sickle h*emoglobin or drepanocyt* or drepanotic or drepanocytemia or h*emoglobin-s or Hb-S or sickle an*emia or meniscocytosis):ti,ab,kw	4790
#4	#1 or #2 or #3	4790
#5	MeSH descriptor: [Blood Transfusion] this term only	1766
#6	MeSH descriptor: [Erythrocyte Transfusion] explode all trees	564
#7	((blood or erythrocyte* or "red cell*" or "red blood cell*" or RBC*) near/5 (transfus* or infus* or unit*))	14775
#8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) near/5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program* or therapy)):ab	30189
#9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)):ti	3612
#10	("allogeneic blood" or (unit* near/2 blood) or "allogenic blood" or (blood near/2 exposure) or "donor blood" or "blood product*" or "blood component*" or "blood support")	3365
#11	hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*	107
#12	(red cell* or erythrocyte* or blood or RBC*) and transfus*:ti	2434
#13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	41927
#14	MeSH descriptor: [Blood Component Transfusion] this term only	115
#15	MeSH descriptor: [Erythrocytes] this term only	1478
#16	(red cell* or red blood cell* or erythrocyte* or RBC*)	12756
#17	#14 and (#15 or #16)	39
#18	#13 or #17	41927
#19	MeSH descriptor: [Pain] explode all trees	42323
#20	(pain or painfull):ti,ab,kw	124349

#	Searches	Results
#21	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises):ti,ab,kw	4404
#22	MeSH descriptor: [Length of Stay] explode all trees	6488
#23	(hospital near/3 (admission or stay)):ti,ab,kw	20854
#24	(patient near/3 (admission or stay)):ti,ab,kw	1779
#25	#19 or #20 or #21 or #22 or #23 or #24	153780
#26	#4 and #18 and #25	332

Table 5: Search strategy for transfusions search on MEDLINE database

#	Searches	Results
1	anemia, sickle cell/	19329
2	hemoglobin, sickle/	3011
3	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	27120
4	1 or 2 or 3	27602
5	Blood Transfusion/	48056
6	Erythrocyte Transfusion/	8033
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	90906
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	47785
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	35184
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	26829
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1217
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	24060
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	183648
14	Blood Component Transfusion/	3477
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	16726

#	Searches	Results
16	14 not 15	3229
17	ERYTHROCYTES/	128578
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	216650
19	17 or 18	258199
20	16 and 19	834
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	13177
22	(((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	3326
23	13 or 20 or 21 or 22	188025
24	exp pain/	362648
25	(pain or painfull).tw.	547392
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	66169
27	exp length of stay/	77857
28	(hospital adj3 (admission or stay)).tw.	104873
29	(patient adj3 (admission or stay)).tw.	6507
30	or/24-29	901074
31	4 and 23 and 30	848
32	clinical trial/	512148
33	(clinic adj5 trial*).ti,ab,sh.	1010
34	single blind method/	25632
35	double blind method/	147368
36	random allocation/	95709
37	placebos/	34063
38	(placebo or random*).ti,ab,sh.	1263924
39	randomized controlled trial/	467730
40	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	786522
41	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	145215
42	randomi?ed control trial*.tw.	6481
43	or/32-42	1565168

#	Searches	Results
44	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	2187051
45	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	1071161
46	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	615678
47	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	340559
48	Clinical Trial, Phase I.pt.	18409
49	Clinical Trial, Phase II.pt.	29604
50	Clinical Trial, Phase III.pt.	14110
51	(registry or registries).ti,ab,kf,hw.	139501
52	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	53439
53	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	114108
54	(nonrandom* or non-random*).ti,ab,kf.	34084
55	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	2644
56	(all adj3 received).ab.	41192
57	or/44-56	3114626
58	31 and 43	120
59	31 and 57	278

Table 6: Search strategy for transfusions search on EMBASE database

#	Searches	Results
1	exp Anemia, Sickle Cell/	32009
2	(h?emoglobin s or h?emoglobin sc or h?emoglobin se or h?emoglobin ss or h?emoglobin c or h?emoglobin d or Hb s or Hb sc or Hb se or Hb ss or Hb c or Hb d or sc disease*).tw.	5794
3	(sickle cell or sicklemia or sickled or sickling or meniscocyt* or drepanocyt*).tw.	29569
4	1 or 2 or 3	38361
5	Blood Transfusion/	108332
6	Erythrocyte Transfusion/	23021
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	135137
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	77239
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	38387
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	43111
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1555
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	28985
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	273982
14	Blood Component Transfusion/	2629
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	19765
16	14 not 15	2279
17	ERYTHROCYTES/	112741
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	256379
19	17 or 18	278120
20	16 and 19	523
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	22304
22	(((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	4095
23	13 or 20 or 21 or 22	279695

#	Searches	Results
24	exp pain/	1146280
25	(pain or painfull).tw.	789805
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	82887
27	exp length of stay/	150699
28	(hospital adj3 (admission or stay)).tw.	169748
29	(patient adj3 (admission or stay)).tw.	12514
30	or/24-29	1690290
31	4 and 23 and 30	2325
32	randomized controlled trial/	508600
33	(RCT or randomi#ed or randomi#ation).ab,ti,kw,hw.	1062285
34	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or subsitut* or treat*)).ab,kw.	560662
35	trial.ti.	248694
36	crossover procedure/	56042
37	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dumm*)).ti,ab,kw,hw.	276112
38	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	99658
39	or/32-38	1386841
40	prospective study/ or retrospective study/ or longitudinal study/ or cohort analysis/ or cross-sectional study/ or case control study/ or population based case control study/	1771952
41	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 study).ti,ab,kw.	1282224
42	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	790240
43	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab,kw.	500633
44	(registry or registries).ti,ab,kw,hw.	183687
45	(nonrandom* or non-random*).ti,ab,kw.	42777
46	((control* adj2 before adj2 after) or CBA study).ti,ab,kw.	3333
47	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kw.	80316
48	(all adj3 received).ab.	75969

#	Searches	Results
49	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 1 clinical trial/	126474
50	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kw.	205403
51	or/40-50	3180246
52	31 and 39	245
53	31 and 51	599

Table 7: Search strategy for transfusions search on clinicaltrials.gov database

#	Searches	Search column
#1	Anemia, Sickle Cell OR Sickle Beta Thalassemia OR Sickle Cell Anemia OR Sickle Cell trait	Condition or disease
#2	SCD OR SCA OR Sickle	Other terms
#3	Transfusion OR blood OR RBC OR hematocrit OR erythrocyte	Intervention/treatment
#4	pain OR hospitalisation OR hospitalization OR (hospital AND (admission OR stay)) OR crisis OR VOC OR ((vaso OR vein OR vena OR venous) AND (occlusive OR occlusive OR interruption OR obstruction)) OR survival OR quality of life	Outcome Measures
	#1 or #2 or #3 or #4	

*Advanced Search option without any restrictions except search strings listed.

A.3 Additional results from systematic literature review

Table 8: Cochrane risk of bias assessment of randomized controlled trials included in the feasibility assessment

Trial ID	Random sequence generation	Allocation concealment	Blinding (personnal)	Blinding (outcome assessor)	Incomplete outcome data	Selective reporting	Other bias
Arruda 2013	Low	Low	Unclear	Unclear	Low	Unclear	None
Ataga 2008	Low	Low	Low	Low	Low	Low	Industry funded; Any conflict of interest of authors
Ataga 2011	Low	Low	Low	Low	Low	Low	Industry funded; Any conflict of

Trial ID	Random sequence generation	Allocation concealment	Blinding (personnal)	Blinding (outcome assessor)	Incomplete outcome data	Selective reporting	Other bias
							interest of authors
Ataga 2017	Low	Low	Low	Low	Unclear	Low	Industry funded; Any conflict of interest of authors
Bao 2008	Unclear	Unclear	Low	Low	Low	Low	None
Cabannes 1984	Low	Low	Low	Low	Unclear	Low	Baseline imbalances or not assessed
Deceulaer 1982	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Baseline imbalances or not assessed; Industry funded
Diop 2011	Low	Low	Low	Low	Low	Low	None
Glassberg 2017	Low	Low	Low	Low	Low	Low	None
NCT02482298	Unclear	Unclear	Low	Low	Low	Low	Industry funded
Niihara 2018	Unclear	Unclear	Low	Low	High	Low	Industry funded
Pace 2003	Unclear	Unclear	Low	Low	High	Low	Industry funded
Schlaeger 2017	Low	Low	Low	Low	Low	Low	None
Sins 2017	Low	Low	Low	Low	High	Low	None
Tomer 2001	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Baseline imbalances
Wun 2013	Unclear	Unclear	Unclear	Low	Low	Low	Industry funded
Adegoke 2013	Low	Unclear	High	High	High	Unclear	No placebo used in control group
Alvim 2005	Unclear	Unclear	Unclear	Unclear	Low	Unclear	None
Charnigo 2017	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Subset of a RCT database
Daak 2013	Low	Low	Low	Low	Low	Low	Industry funded
Daak 2018	Unclear	Unclear	Low	Low	Low	Unclear	Baseline imbalances or not assessed
de Abood 1997	High	High	High	High	Unclear	Unclear	Baseline imbalances or not assessed; No placebo used in control group
Eke 2003	Low	Low	High	High	Low	Low	Baseline imbalances or not assessed

Trial ID	Random sequence generation	Allocation concealment	Blinding (personnal)	Blinding (outcome assessor)	Incomplete outcome data	Selective reporting	Other bias
Gail 1982	Low	Low	Low	Low	Low	Unclear	None
Gupta 1995	Low	Unclear	Low	Low	Unclear	Unclear	None
Heeney 2016	Low	Low	Low	Low	Low	Low	Industry funded; Any conflict of interest of authors
Isaacs 1972	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Baseline imbalances or not assessed; Industry funded
Mann 1974	Unclear	Unclear	High	High	Low	Unclear	Risk of carry-over effect in crossover study; No placebo used in control group
Manrique 1987	Unclear	Unclear	Unclear	Unclear	Low	High	None
Oski 1968	Unclear	Unclear	Low	Low	Low	Unclear	Industry funded; Risk of carry-over effect in crossover study
Reid 2014	Unclear	Low	Low	Low	High	Low	Industry funded; Any conflict of interest of authors
Vinchinsky 2010	Unclear	Unclear	High	High	Unclear	Unclear	Industry funded
Wambebe 2001	Low	Low	Low	Unclear	Unclear	Unclear	Risk of carry-over effect in crossover study
Zago 1984	Unclear	Unclear	Unclear	Unclear	High	Unclear	Risk of carry-over effect in crossover study

** Note: Trial bolded were base case studies; Trials shaded in grey were not included in the final network meta-analyses.*

Table 9: Newcastle-Ottawa quality assessment of non-randomized controlled trials included in the feasibility assessment

Trial ID	Selection				Comparability		Outcomes			Total
	Representativeness of the exposed	Selection of the nonexposed	Ascertainment of exposure	Outcome of interest not present at start	Comparability: basic characteristics	Comparability: additional factors	Assessment of Outcome	Follow-Up Long Enough	Adequacy of follow-up	
Al Hashmi 2017	---	★	★	---	★	---	---	---	★	4
Brandalise 2017	---	★	★	---	★	★	★	---	★	6
Bridges 2017	---	★	★	---	---	---	---	---	★	3
Bumma 2017	---	★	★	---	★	---	---	---	---	3
Colombatti 2018	★	★	★	---	★	---	---	★	★	6
Di Maggio 2018	★	★	★	---	★	★	---	★	★	7
Hoppe 2017	★	★	---	---	★		---	---	---	3
Keikhaei 2015	★	★	★	---		---	---	---	★	4
Kwiatkowski 2017	★	★	---	---	---	---	---	★	★	4
LeBlanc 2016	---	★	★	★	---	---	---	★	★	5
Lemonne 2017	---	★	★	---	---	---	★	★	★	5
NCT01476696	---	★	---	---	---	---	---	---	★	2
Quarmyne 2017	★	★	★	---	★	---	---	★	---	5
Rigano 2018	★	★	★	---	★	★	---	★	★	7
Sethy 2018	★	★	★	---	---		---	★	★	5
Styles 2010	---	★	★	★	---	---	---	---	---	3
Youssry 2017	★	★	★	---	★	★	---	★	★	7

Figure 1: Cochrane assessment of randomized controlled trials included in the feasibility assessment

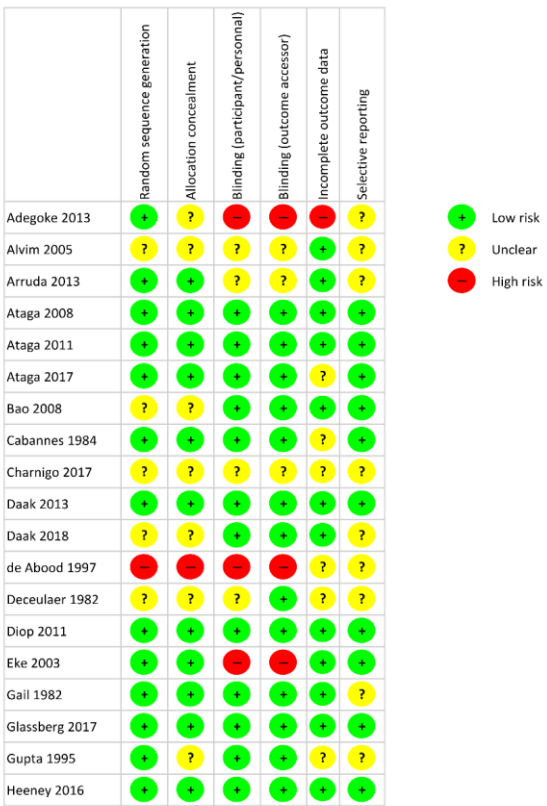


Table 10: Study characteristics of trials included in the feasibility assessment

Trial	Registry number	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Blinding	Design	Follow-up	Country
Adegoke 2013	---	Lime juice + Routine oral drugs	Control (Routine oral drugs)	---	---	Open	RCT	6 months	Nigeria
Alvim 2005	---	Piracetam	Placebo	---	---	Double-blind	RCT, crossover	1 year (6 months, then crossover with 2 weeks washout period)	Saudi Arabia
Arruda 2013	---	Placebo	Vitamins C and E	---	---	Double-blind	RCT	180 days	Brazil
Ataga 2008	NCT00040677	Senicapoc (high-dose)	Senicapoc (low-dose)	Placebo	---	Double-blind	RCT	12 week	US
Ataga 2011	NCT00102791	Senicapoc	Placebo	---	---	Double-blind	RCT	52 weeks	United States, Jamaica, Brazil, France, Trinidad and the United Kingdom.
Ataga 2017	NCT01895361	Crizanlizumab (high-dose)	Crizanlizumab (low-dose)	Placebo	---	Double-blind	RCT (Phase 2)	52 weeks	Brazil, Jamaica, USA
Bao 2008	---	Zinc	Placebo	---	---	Double-blind	RCT	3 months	US
Cabannes 1984	---	Ticlopidine	Placebo	---	---	Double-blind	RCT	6 months	Africa
Charnigo 2017	---	PF-04447943	Placebo	---	---	---	RCT (Phase 1b)	29 days	---
Daak 2013	ISRCTN80844630	Omega-3	Placebo	---	---	Double-blind	RCT	1 year	Sudan
Daak 2018	---	AltemiaTM	Placebo	---	---	Double-blind	RCT (Phase 2)	2 months	USA

Trial	Registry number	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Blinding	Design	Follow-up	Country
de Abood 1997	---	DMPA	Levonorgestrel + ethinyl estradiol	Surgical sterilized (injectable)	---	Double-blind	RCT	12 months	Spain
Deceulaer 1982	---	Medroxyprogesterone acetate	Placebo	---	---	Double-blind	RCT, crossover	2 years (9 months, then crossover after 6 months washout)	Jamaica
Diop 2011	---	Sulfadoxine-pyrimethamine	Placebo	---	---	Open	RCT	3 months	Senegal
Eke 2003	---	Placebo (Vitamin c)	Proguanil	---	---	Open	RCT (Phase 2)	9 months	Nigeria
Gail 1982	---	Urea	Control	---	---	Double-blind	RCT (Phase 2)	Average: 13.7 months	Ghana
Glassberg 2017	NCT02061202	Mometasone furoate	Placebo	---	---	Triple-blind	RCT	16 weeks	US
Gupta 1995	---	Zinc	Placebo	---	---	Double-blind	RCT (Phase 2)	1.5 years	India
Heeney 2016	NCT01794000	Prasugrel	Placebo	---	---	Double-blind	RCT (Phase 3)	A minimum of 9 months and a maximum of 24 months	Americas, Europe, Asia and Africa
Isaacs 1972	---	Steroid (Testoserone/ Progesterone)	Saline	---	---	---	RCT, crossover (preliminary report before crossover)	4-6 months	Nigeria
Mann 1974	---	Folic acid	Folic acid + Sodium bicarbonate	---	---	---	RCT, crossover	2 years (crossover after 1 year, no washout)	UK
Manrique 1987	---	Pentoxifylline	Placebo	---	---	---	RCT (Phase 2)	6 weeks	Brazil
NCT02482298	NCT02482298	Ticagrelor 45 mg	Ticagrelor 10 mg	Placebo	---	Double-blind	RCT	12 weeks	USA, Egypt, France, Italy

Trial	Registry number	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Blinding	Design	Follow-up	Country
									Kenya, Lebanon, Turkey
Niihara 2018	NCT01179217	L-glutamine	Placebo	---	---	Double-blind	RCT (Phase 3)	48 weeks	USA
Oski 1968	---	Promazine hydrochloride	Placebo	---	---	Double-blind	RCT, crossover	3 months	USA
Pace 2003	---	NAC (high-dose)	NAC (mid-dose)	NAC (low-dose)	Placebo	Double-blind	RCT	7 months	USA
Reid 2014	NCT01601340	HQK-1001	Placebo	---	---	Double-blind	RCT	48 weeks	United States, Lebanon, Egypt, Jamaica and Canada
Schlaeger 2017	---	Pregabalin	Placebo	---	---	Double-blind	RCT	3 months	USA
Sins 2017	NCT01849016	NAC	Placebo	---	---	Double-blind	RCT	6 months	Netherlands, Belgium, US
Styles 2010	---	GMI-1070	---	---	---	---	Single-arm	1 month	USA
Tomer 2001	---	mehaden fish oil	Placebo (olive oil)	---	---	Double-blind	RCT	12 months	US
Vichinsky 2010	---	Transfusion	Standard of care	---	---	---	RCT	---	USA
Wambebe 2001	---	Niprisan	Placebo	---	---	Phase 2	RCT, crossover (Phase 2)	13 months (6 months per treatment, 1-month washout in-between)	Nigeria
Wun 2013	NCT01167023	Prasugrel	Placebo	---	---	Double-blind	RCT (Phase 2)	30 days	United States and Canada
Zago 1984	---	Aspirin	Placebo	---	---	---	RCT, crossover (Phase 2)	10 months (5 months per treatment)	Brazil

Trial	Registry number	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Blinding	Design	Follow-up	Country
Al Hashmi 2017	---	Hydroxyurea	---	---	---	---	Single-arm	6 months	Oman
Brandalise 2017	---	Methotrexate	---	---	---	---	Single-arm	12 weeks	Brazil
Bridges 2017	---	GBT440	---	---	---	---	Single-arm	10 weeks	Unclear
Bumma 2017	---	Scheduled outpatient red cell exchange programme	---	---	---	---	Single-arm	1 year	---
Colombatti 2018	NCT02709681	Hydroxyurea	---	---	---	---	Single-arm	1 years	Italy
Di Maggio 2018	---	Hydroxyurea	---	---	---	---	Single-arm	Mean: 6.6 years	Italy
Hoppe 2017	NCT00508027	Simvastatin	---	---	---	---	Single-arm	3 months	USA
Keikhaei 2015	---	Hydroxyurea	---	---	---	---	Single-arm	1 year	Iran
Kwiatkowski 2017	---	Deferiprone	---	---	---	---	Single-arm	1 year	USA
LeBlanc 2016	NCT02709681	Methadone	---	---	---	---	Single-arm	Mean: 2.1 years	USA
Lemonne 2017	---	Hydroxyurea	---	---	---	---	Single-arm	2 years	Guadeloupe
NCT01476696	NCT01476696	Prasugrel	---	---	---	---	Single-arm (Phase 2 part B)	28 days	USA
Quarmyne 2017	---	Hydroxyurea	---	---	---	---	Single-arm	3 months	USA
Rigano 2018	---	Hydroxyurea	---	---	---	---	Single-arm	Median: 7 years	Italy
Sethy 2018	---	Hydroxyurea	---	---	---	---	Single-arm	12 months	India
Youssry 2017	---	Hydroxyurea	---	---	---	---	Single-arm	up to 120 months	Egypt

Note: Trial bolded were base case studies; Trials shaded in grey were not included in the final network meta-analyses.

Table 11: Eligibility criteria of RCTs included in the feasibility assessment

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Adegoke 2013	Lime juice + Routine oral drugs (folic acid, vitamin B complex and proguanil) vs Control (Routine oral drugs (folic acid, vitamin B complex and proguanil))	---	---	Steady state (no painful episode, anemic crisis, or infection on the day of recruitment)	No hydroxyurea treatment	---	Not on any other alternative medicine commonly used by some patients with SCA in Nigeria such as Aloe vera gel, Moringa oleifera, Solamine syrup, and Ciklavit (Cajanus cajal) suspension as well as Discriovite suspension and or Nicosan (Niprisan) capsule
Alvim 2005	Piracetam vs Placebo	5-20 years	---	---	No hydroxyurea treatment	Regular blood transfusion programmes	---
Arruda 2013	Placebo vs Vitamins C and E	≥ 18 years	HbSS or HbSβ^0	---	---	---	Other investigational drugs in the last 12 months

Commented [HT1]: Vincent, is this the best table to use for patient characteristics? Note that I've added Vichinsky 2010 and Styles 2010 which weren't in the report.

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Ataga 2008	Senicapoc (high-dose) vs Senicapoc (low-dose) vs Placebo	18-60 years	HbSS	≥ 1 nacute sickle-related painful episode that had required hospitalization, but none in the 4 weeks prior to screening	Stable dose for a minimum of 3 months at study enrollment.	Received a transfusion within 30 days of enrollment or undergone an exchange transfusion within 60 days of enrollment	One or more nonallowed medications within 30 days of enrollment (eg, amiodarone, chlorperazine, disopyramide, dofedilide, haloperidol, procainamide, quinidine, risperidone, sotalol, thioridazine, trifluoperazine, warfarin sodium, and erythropoietin)
Ataga 2011	Senicapoc vs Placebo	16-65 years	HbSS, HbSC, HbSβ^0, HbSβ$^+$	≥ 2 acute sickle-related painful crises in the previous 12 months	Received hydroxyurea for the preceding 12 months and their dose was stabilized for at least 3 months prior to the study	Participated in a chronic transfusion programme	Received previous treatment with senicapoc
Ataga 2017	Crizanlizumab (high-dose) vs Crizanlizumab (low-dose) vs Placebo	16-65 years	HbSS, HbSC, HbSβ^0, HbSβ$^+$	2-10 SCD-related pain crises in the 12 months before enrollment	---	Undergoing long-term red-cell transfusion therapy	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Bao 2008	Zinc vs Placebo	---	HbSS	---	No hydroxyurea treatment	receiving > 6 transfusions per year	---
Cabannes 1984	Ticlopidine vs Placebo	---	---	---	---	---	Received no antisickling treatment for 2 months before admission
Charnigo 2017	PF-04447943 vs Placebo	---	SCD	---	---	---	---
Daak 2013	Omega-3 vs Placebo	---	---	Steady state, defined as no evidence of fever, infection, or crisis for .4 wk before the start of the study	No hydroxyurea treatment	Prescence of blood transfusion	---
Daak 2018	AltemiaTM vs Placebo	5–17 years	---	2-10 documented sickle cell crises during the 12 months prior to screening	Either not received, or were on a stable regimen of hydroxyurea	---	---
de Abood 1997	DMPA vs Levonorgestrel + ethinyl estradiol vs Surgical sterilized (injectable)	---	---	---	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Deceulaer 1982	Medroxyprogesterone acetate vs Placebo	---	---	---	---	---	---
Diop 2011	Sulfadoxine-pyrimethamine vs Placebo	---	---	---	---	---	---
Eke 2003	Placebo (Vitamin c) vs Proguanil	1-16 years	HbSS	---	---	---	---
Gail 1982	Urea vs Control	---	HbSS	---	---	---	---
Glassberg 2017	Mometasone furoate vs Placebo	≥ 15 years	HbSS or HbSβ^0	< 15 ED visits for SCD pain over the prior 12 months	---	---	---
Gupta 1995	Zinc vs Placebo	> 5 years	HbSS	---	---	---	Patients on drug therapy for some other disease
Heeney 2016	Prasugrel vs Placebo	2-18 years	HbSS, HbSβ^0	≥2 VOC in the year prior to screening	---	History of chronic RBC transfusion for prevention of stroke or current chronic treatment with RBC for any reason.	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Isaacs 1972	Steroid (Testoserone/Progesterone) vs Saline	---	HbSS	Moderately severe pain at least once in 3 months (with little or no fever or exacerbations of jaundice)	---	---	---
Mann 1974	Folic acid vs Folic acid + Sodium bicarbonate	5-17 years	HbSS, HbSC, HbSβ	Previously suffered painful crises	---	---	---
Manrique 1987	Pentoxifylline vs Placebo	---	HbSS	---	---	---	---
NCT02482298 2017	Ticagrelor 45 mg vs Ticagrelor 10 mg vs Placebo	18-30 years	HbSS, HbSβ^0	---	Dose must have been stable for 3 months	Treatment with chronic red blood cell transfusion therapy.	Chronic treatment with anticoagulants or antiplatelet drugs
Niihara 2018	L-glutamine vs Placebo	> 5 years	HbSS, HbSβ^0	≥ 2 pain crises (no upper limit) documented during the previous year	Stable dose within 3 months and continue during the trial	Received any blood products within 3 weeks before screening	Received treatment with l-glutamine within 30 days before the screening
Oski 1968	Promazine hydrochloride vs Placebo	---	---	≥2 painful episodes during	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
				the 2 year period prior to study.			
Pace 2003	NAC (high-dose) vs NAC (mid-dose) vs NAC (low-dose) vs Placebo	> 15 years	HbSS, HbSβ^0	With dense cells greater than 6% and 2 or more VOC episodes per year for the 2 years prior to enrollment	---	Chronic transfusions	Investigational drug therapy
Reid 2014	HQK-1001 vs Placebo	12-60 years	HbSS, HbSβ	≥ 1 acute SCD-related complication or leg ulcers in 12 months	No current (i.e., within 3 months prior to enrolment) hydroxyurea treatment	Regular transfusion program or transfusion in the preceding 3 months unless Hb A had decreased to less than 20%	---
Schlaeger 2017	Pregabalin vs Placebo	18-82 years	---	Pain now score ≥ 4 on a 0-10 scale at registration	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Sins 2017	NAC vs Placebo	≥ 12 years	HbSS, HbSC, HbSβ^0, HbSβ$^+$	≥ 1 VOC per year in the past 3 years	Stable dose for 6 months piror to study	Chronic blood transfusion or transfusion in the preceding 3 months	Use of pain medication for sickle-cell related pains on more than 15 days per month in the past 6 months
Styles 2010	GMI-1070	18-50 years	HbSS and HBSB0thal	---	---	---	---
Tomer 2001	mehaden fish oil vs Placebo (olive oil)	≥ 18 years	---	Frequent pain episodes (≥3 events/year)	Not on hydroxyurea	---	---
Vichinsky 2010	Transfusions vs standard of care	21-55 years	---	---	30% on hydroxyurea on transfusion, 50% on hydroxyurea on standard of care	---	---
Wambebe 2001	Niprisan vs Placebo	2-45 years	HbSS	≥ 3 painful or vaso-occlusive crises in the previous year	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Wun 2013	Prasugrel vs Placebo	18 to 55 years	HbSS, HbSC, HbSβ^0, HbSβ$^+$	Did not have a diagnosis of acute VOC within 30 days of the study screening visit	Stable dose 30 days prior to randomization	---	---
Zago 1984	Aspirin vs Placebo	---	---	---	---	---	---
Al Hashmi 2017	Hydroxyurea	≥ 18 years	---	> 3 admissions with VOC/year, history of acute chest syndrome, history of priapism, history of splenic sequestration crises	On hydroxyurea 5-10mg/kg/day	Blood transfusion during the study	---
Brandalise 2017	Methotrexate	---	---	> 3 severe VOC episodes/year, that were refractory to opioids for periods longer than 3 weeks duration.	Under chronic hydroxyurea treatment	---	---
Bridges 2017	GBT440	---	SCD and severe anemia, i.e.	---	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
			HB < 6.5 g/dL				
Bumma 2017	Scheduled outpatient red cell exchange programme	---	---	---	---	---	---
Colombatti 2018	Hydroxyurea	---	---	2-3 vaso-occlusive crisis and/or hospitalizations in the last year	---	---	---
Di Maggio 2018	Hydroxyurea	---	---	>3 painful VOC per year and/or >2 Acute Chest Syndrome	New to hydroxyurea treatment	---	---
Hoppe 2017	Simvastatin	>10 years	HbSS or HbSβ^0	≥ 3 vaso-occlusive pain episodes in the preceding year	At a stable dose for ≥ 3 months	Red cell transfusion within the 30 days prior to enrolment	Current treatment with statins, amiodarone or other drugs with known metabolic interactions with statins (e.g. cytochrome P450 3A4 metabolism)
Keikhaei 2015	Hydroxyurea	6-18 years	SCD	---	---	---	Treatment other than hydroxyurea

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Kwiatkowski 2017	Deferiprone	---	---	---	---	---	---
LeBlanc 2016	Methadone	---	---	> 5 pain events per year	---	---	---
Lemonne 2017	Hydroxyurea	---	---	Absence of acute episodes (infection, VOC, ACS, stroke, priapisrn) at least one month before inclusion into the study.	---	No blood transftisions in the previous three months	---
NCT01476696	Prasugrel	≥2 to <18 years of age and ≥ 12 kg body weigh t	HbSS, HbSβ^0	---	A stable dose for the 60 days prior to enrolment	Treatment with packed RBC or whole blood transfusion therapy within 30 days prior to dosing	Any nonsteroidal anti-inflammatory drug (NSAID) use within 5 days prior to screening or Any aspirin, warfarin, thienopyridine, or other antiplatelet medication use within 10 days prior to dosing or Anticipated use of aspirin, warfarin, thienopyridine, or other antiplatelet medication during the study period

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Quarmyne 2017	Hydroxyurea	---	HbSS, HbSβ^0	---	---	Concurrent chronic transfusion	---
Rigano 2018	Hydroxyurea	---	---	2–3 VOC and/or acute chest syndrome in the year prior	Received hydroxyurea therapy	---	---
Sethy 2018	Hydroxyurea	≥ 18 years	HbSS	> 2 attacks of VOC per year and/or rate of transfusion 1–2 units/month	---	---	---
Youssry 2017	Hydroxyurea	---	---	---	On hydroxyurea ≥3 consecutive months	Chronic blood transfusion protocol	---

** - VOC: vaso-occlusive crisis; SCD: sickle cell disease; ED: emergency department; Note: Trial bolded were base case studies; Trials shaded in grey were not included in the final network meta-analyses.*

A.4 Outcome definitions

Table 12: Definitions of crisis used in 5 RCTs included in adult network

Study	Treatments	Crisis
Ataga 2017	Placebo, High-dose Crizanlizumab, Low-dose Crizanlizumab	Sickle cell–related pain crises were defined as acute episodes of pain, with no medically determined 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 nonsteroidal anti-inflammatory drug. The acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism were also considered to be crisis events.
Ataga 2011	Placebo, senicapoc	A painful crisis was defined as an episode of acute pain with no cause other than a vaso-occlusive event that required a medical facility visit and treatment with oral or parenteral narcotics, or parenteral non-steroidal anti-inflammatory drugs. Included in the definition of painful crisis were acute chest syndrome, hepatic sequestration, splenic sequestration, priapism, stroke and death (with the exception of homicide, suicide, or accidental death). To ensure consistency across sites, all protocol-defined sickle-related painful crises identified by the Investigators that resulted in a visit to a medical facility were adjudicated by an independent, blinded, Crisis Review Committee (CRC).
Ataga 2008	Placebo, senicapoc (low-dose), senicapoc (high-dose)	An independent, blinded crisis review committee adjudicated all sickle cell painful crises and related adverse event data (Document S1). A painful crisis was defined as a period of severe pain (with no explanation other than SCD) lasting 4 or more hours in duration, requiring a visit to a health care facility, and requiring parenteral opiate or other narcotic for relief
Pace 2003	Placebo, NAC (low-dose) 600 mg/day, NAC (mid-dose) 1200mg/day, NAC (high-dose) 2400mg/day	Defined as a visit to a medical facility that lasted more than 4 hr for acute pain related to vaso-occlusion requiring parenteral narcotics. The occurrence of acute chest syndrome, priapism, splenic, or hepatic sequestration was also counted as a VOC episode. Acute chest syndrome included those subjects with chest wall pain and a new infiltrate on chest X ray.
Niihara 2018	Placebo, L-glutamine	A pain crisis was defined as pain leading to treatment with a parenterally administered narcotic or ketorolac in an emergency department (ED) (or outpatient treatment center) or during hospitalization.

A.5 Additional risk of bias results

Overall, the RCTs were considered to have low risk of bias based on assessment using the Cochrane Collaboration's tool. Almost 50% were at unclear risk of bias due to allocation concealment, selective reporting, and random sequence generation. Also, 10-15% were at high risk of bias due to incomplete outcome data, blinding of outcome assessor, and blinding of personnel. Full results are in the appendix.

Overall, the single-arm studies were at high risk of bias due on several domains of the Newcastle-Ottawa scaleFigure 4): 93.7% at high risk of bias due to outcome of interest not being present at start, 87.5% at high risk of bias due to assessment of outcome, and 75% at high risk of bias due to comparability on additional factors. Also, almost 50% were at high risk of bias due to representativeness of exposed cohort, comparability on basic factors, or the follow-up not being long enough. This high risk of bias further discourages use of the single-arm studies for analysis.

Figure 2: Cochrane risk of bias assessment of 9 randomized controlled studies included in network meta-analysis

Figure 3: Cochrane risk of bias assessment across all studies included in review presented as percentages across studies.

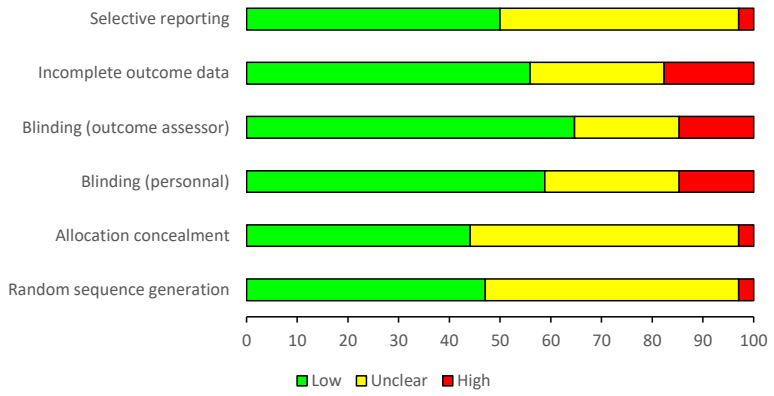
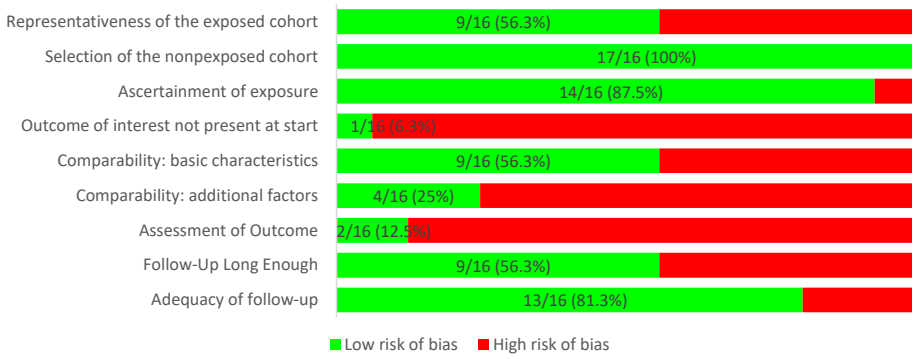


Figure 4: Newcastle-Ottawa quality assessment of non-randomized trials presented as percentages across studies.



A.6 Table of characteristics and references for of all studies identified by SLR

Author/Year/Country Ref/Enrolment /NCT registry	Design Total N of PT (N of female); N of arm	Main in/exclusion criteria	Participants					Interventions			Sponsor	Pub type
			Age (years)† Race (n, %)†	Total N of SCD types (n, %)	Total N of HU use (n, %)	Baseline pain/crisis/VOC (n or %) †	Other baseline characteristics (n or %) †	Group	Duration	Other concomitant therapy		
Schlaeger 2017 USA [1]	RCT, double-blind Single centre 22 (16); 2	1. 18-82 years 2. history of SCD pain that was not well controlled (pain now score ≥ 4 on a 0-10 scale at registration) Exclusion: renal impairment	Adults Mean (SD): 33.1 (9.9) African american: 11 (100%)	HbSS: 15 (68%) HbSC: 6 (27%) HbSβ: 1 (5%)	NR	NR	NR	1. Pregabalin 75mg BID oral (n=11) 2. Placebo (n=11)	3 months	NR	NR	JA
Hoppe 2017 USA [2] NCT00508027	Single-arm Single centre 24 (13); 1	1. >10 years 2. history of ≥ 3 vaso-occlusive pain episodes requiring treatment with a prescribed oral or parenteral analgesic in the preceding year 3. Patients receiving treatment with HU at a stable dose for ≥3 months were eligible	Adults and children Overall mean: 18.5 (range 10-34)	HbSS: 17 (89%) HbSβ⁰: 2 (11%)	10 (53%)	NR	NR	Simvastatin (n=19*) OD oral Dose adjusted by weight: 40 mg (weight >60 kg); 30 mg (weight 45–60 kg); 25 mg (weight 35–44 kg)	3 months	NR	DDCF, NHLBI and NCRR	JA
Glassberg 2017 USA [3] Feb 2014 to Oct 2016 NCT02061202	RCT, triple-blind Single centre 54 (23); 2	1. HbSS or HbSβ⁰ 2. ≥15 years 3. self-report of cough or wheeze over the preceding two months Exclusion: Diagnosis of asthma, incareration, pregnancy, ≥15 ED visits for SCD pain over the prior 12 months and discharge from the hospital within the previous 7 days	Adults and adolescents Mean (SD): 30(8.56)	HbSS: 50 (96%) HbSβ⁰: 2 (4%)	34 (65%)	NR	Prior ED Utilization (past 12 months) 0-5 visits: 71% 6-10 visits: 24% 11-15 visits: 6%	1. Mometasone furoate 220mcg OD inhale (n=35*) 2. Placebo (n=17*) In addition to standard SCD care	16 weeks	NR	NHLBI	JA

Ataga 2017 Brazil, Jamaica, USA [4-8] Aug 2013 to Jan 2015 NCT01895361	RCT, double-blind Multicentre 198 (109); 3	1. HbSS, HbSC, HbSβ^0, HbSβ$^+$ 2. 16-65 years 3. two to ten SCD-related pain crises in the 12 months before the enrolment Exclusion: long-term red-cell transfusion	Adults and adolescents Median: 26 (range 16-56) Black, or African American: 60 (90%) White: 4 (6%) Other: 3 (4%)	HbSS: 141 (71%) HbSC: 32 (16%) HbSβ^0: 12 (6%) HbSβ$^+$: 10 5%) Other: 3 (2%)	123 (62%)	N of SCD-related pain crises during previous 12 months 2-4: 63% 5-10: 37%	NR	1. High-dose Crizanlizumab 5 mg/kg IV (n=67) 2. Low-dose Crizanlizumab 2.5 mg/kg IV (n=66) 3. Placebo (n=65) Two doses 2 weeks apart (loading dose) and then every 4 weeks. A total of 14 doses for 50 weeks	52 weeks	NR	Selexys Pharmaceuticals, NHLBI and OOPD	JA, JA supp
Lemonne 2017 Guadeloupe [9]	Single-arm Single centre 28 (13); 1	1. at the beginning of the HU therapy 2. patients were at steady state, i.e., no blood transfusions in the previous three months and absence of acute episodes (infection, VOC, ACS, stroke, priapism) at least one month before inclusion into the study. Exclusion: renal insufficiency, hepatic insufficiency or human immunodeficiency virus infection	Adults Overall mean: 37.0(SD 11.6)	All SCA (50% with α-thalassemia)	N/A	Frequent hospitalized VOC: 14 (50%) N of ACS ≥ 1: 10 (36%)	NR	HU Therapy (n=28)	2 years	NR	Region of Guadeloupe.	JA
Quarmyne 2017 USA [10] 2009-2011	Single-arm Retrospective 134 (74); 1	1. HbSS, HbSβ^0 2. started HU in 2009-2011 Exclusion: concurrent chronic transfusion and hydroxyurea therapy, underwent bone marrow transplant, no follow-up data	Adults and Children Overall Median: 7.5 ≤5 years: 39% 6-10 years: 33% 11-15 years: 20% >15 years: 8%	NR	None	NR	NR	HU oral (n=78*) Dose: 20 mg/kg/day (initially), followed by dose escalation every 2 months to 25–30 mg/kg/day or maximum tolerated dose if lower	~3 months	NR	NCATS, NIH and the Abraham J. & Phyllis Katz Foundation.	JA
Daak 2018 USA [11]	RCT, double-blind Multicentre 67(NR); 2	1. 5–17 years 2. two and ten (inclusive) documented SCC during the 12 months prior to screening 3. either not received, or were on a stable regimen of hydroxyurea (HU)	Children and Adolescents NR	NR	51 (76%)	NR	NR	1. AltemiaTM (n=50) 2. Placebo (n=17)	2 months	NR	NR	CA
Bridges 2017 Unclear	Single-arm	Patients with SCD and severe anaemia, i.e. Hb < 6.5 g/dL	Adults	HbSS:6 (86%) HbSβ: 1 (14%)	NR	Baseline VOC admission (total n): 15	Baseline transfusions (total n): 24	GBT440 900mg OD (n=7)	10 weeks	NR	NR	CA

[12]	Single centre 7(4); 1		Overall mean: 48.6(SD 15.8)									
Charnigo 2017 Unclear **[13]**	RCT (phase 1b) Retrospective 29 (NR); 2	Stable SCD patients	NR	NR	NR	NR	NR	1. PF-04447943 25mg or 5mg BID oral (n=22) 2. Placebo (n=7)	29 days	NR	Pfizer	CA
Sins 2017 Netherlands, Belgium, UK [14, 15] Apr 2013 to Nov 2015 NCT01849016	RCT, double-blind Multicentre 96 (40); 2	1. HbSS, HbSC, HbSβ^0, HbSβ$^+$ 2. ≥ 12 years 3. History of at least 1.0 VOC per year in the past 3 years Exclusion: Chronic blood transfusion or transfusion in the preceding 3 months, VOC in the last 4 weeks, pregnancy, active gastric/duodenal ulcers, HU treatment with unstable dose in the last 3 months or started on HU shorter than 6 months prior to study, use of pain medication for SCD-related pains on more than 15 days per month in the past 6 months, poor compliance	Adults Mean (SD): 28.4(8.9) Latin-America/Caribbean: 17 (43%) Africa :23 (57%)	HbSS/HbSβ^0: 46 (69%) HbSC/HbSβ$^+$:21 (31%)	28 ((42%)	N of VOC over past three years Median: 11 (IQR 6-20)	Number of hospital admission over past three years Median: 3 (IQR 1-6)	1. Placebo (n=40*) 2. NAC 600mg BID oral (n=27*)	6 months	NR	ZonMw, the Academic Medical Centre, JANIVO Stichting, Egbers Stichting,	JA
Niihara 2018 US [16-20] Jun 2010 to Dec 2013 NCT01179217	RCT, double-blind (phase 3) Multicentre 230 (124); 2	1. > 5 years 2. had had at least two pain crises (no upper limit) documented during the previous year 3. HU at stable dose within 3 months and continue during the trial	Adults and children Mean (SD): 21.4(12.42) Black: 144 (95%) Hispanic: 4 (3%) Other: 4 (3%)	SCA: 207 (90%) HbSβ^0: 21 (9%) HbSβ^{+}: 2 (1%)	153 (66.5%)	N of SCD pain crises in the year before trial 0-1: 0.7% 2-5: 84.2% 6-9: 9.9% ≥ 10: 5.3%	NR	1. L-glutamine 0.3 g/kg BID oral (n=152) 2. placebo (n=78) Maximum dose: 30mg	48 weeks	NR	Emmaus Medical	JA
Sethy 2018 India **[21]** 2013 to 2016	Single-arm Single site 142 (46); 1	1. HbSS 2. ≥ 18 years 3. > 2 attacks of VOC per year and/or rate of transfusion 1–2 units/month were included in the study Exclusion: pregnancy, human immunodeficiency virus infection or medications that could potentially enhance HU toxicity, abnormal serum Cr/ALT levels	Adults	All HbSS	N/A	64% presented with repeated VOC, 13% with transfusion dependency and 23% with both the above features	NR	HU 10 mg/kg/day oral (n=128*)	12 months	All the patients were advised to take folic acid (5 mg/day) and ensure adequate fluid intake	NR	JA

Di Maggio 2018 Italy [22] January 2000 to April 2014	Single-arm Retrospective 140 (71); 1	1. start HU treatment 2. >3 painful vaso-occlusive crises per year and/or >2 Acute Chest Syndrome	Adults and children Median(range): 35 (0.4-61)	HbSS: 25 (18%) HbSβ⁰: 54 (39%) HbSβ⁺ : 56 (40%) HbSα-β: 4 (3%) HbSLepore: 1 (0.7%)	90 (64%)	NR	NR	HU oral (n=140) Starting dose: 10 mg/kg daily Titration: increased at a rate of 5 mg/kg/week	Mean follow-up: 6.6 years	NR	NR	JA, JA supp
Youssry 2017 Egypt [23]	Single-arm Retrospective 60 (37); 1	Patients who were on HU therapy for at least 3 consecutive months Exclusion: Chronic blood transfusion, chronic disabling hepatic/renal disease	Adults and children Mean: 12.8 (SD 5.5) (range 4 to 24)	HbSS: 27 (45%) HbSβ: 33 (55%)	N/A	NR	NR	HU 15-30mg/kg/day oral (n=60)	Up to 120 months	NR	NR	JA
Bumma 2017 USA [24] 1/1/2000 to 1/15/2016	Single-arm Retrospective 104 (60); 1	NR	Adults and Adolescents Median (range): 24(15-62)	HbSS: 89 (86%)	13%	NR	NR	Scheduled outpatient red cell exchange (n=104)	1 year	NR	NR	CA
Kwiatkowski 2017 USA [25]	Single-arm Registry data 291 (166); 0	Inclusion on a patient registry has been maintained for all US patients who receive deferiprone	Adults and children Mean: 29.5 (SD15.7) ≤ 18years: 79	NR	NR	NR	NR	Deferiprone oral (n=291)	Mean: 1.3 years (range 0-4.1)	NR	NR	CA
Rigano 2018 Italy [26]	Single-arm Retrospective cohort 652 (302); 1	1. On HU therapy 2. The indication for HU initiation was 2–3 vaso-occlusive crisis and/or acute chest syndrome in the year prior	Adults and children Mean: 24.5 (SD 15) Median: 24 (range 1-67) Caucasian: 400/621 Africa: 221/621	HbSS: 277 (47%) HbSβ⁰: 167 (28%) HbSβ⁺: 131 (20%) Other: 19 (3%) Total N: 594	N/A	NR	NR	HU oral (n=628*) 10 mg/kg/day, and adjusted or escalated according to tolerance	Median duration: 7 years (range <1-29)	Folic acid was concomitantly used in 71.3% of patients (n/N = 388/448).	NR	JA

Al Hashmi 2017 Oman [27]	Single-arm Single centre 18 (6); 1	1. Aged ≥ 18 years 2. on HU 5-10mg/kg/day 3. history of more than three admissions with vaso-occlusive crises /year, history of acute chest syndrome, history of priapism, history of splenic sequestration crises Exclusion: pregnancy, blood transfusion during the study, follow-up of < 6 months	Adults	NR	N/A	NR	NR	HU 5-10mg/kg/day oral (n=18)	At least 6 months	NR	NR	CA
Colombatti 2018 Italy [28]	Single arm Multicentre 204 (20); 1	1. On HU therapy	Children and adolescents Overall mean: 7.68 (range 11-221 months) Nigeria: 65 (32%) Ghana: 32 (16%) Senegal: 12 (6%) Italy and Albania: 37 (18%) Central America and India: 10 (5%) Unknown: 10 (5%)	HbSS:172 (84%) HbSβ⁰: 22 (11%) HbSC: 8 (4%) HbSβ⁺: 3 (1.5%) Other: 1 (0.5%)	N/A	NR	NR	HU therapy (varied by centre) (n=204)	1 year	NR	NR	JA
Brandalise 2017 Brazil [29] RBR-2s9xvn	Single arm Single centre 14 (5); 1	1. Under chronic hydroxyurea treatment 2. >3 severe VOC episodes/year, that were refractory to opioids for periods longer than 3 weeks duration Exclusion: pregnancy, concomitant infection	Adults Overall median: 23.5 (range 18-32)	HbSS:11(79%) HbSC:3 (11%)	14 (100%)	Previous VOC/month: 3.3 (95% CI 2.0-5.0) (excluding one PT with 19.3 VOC/month)	Avascular necrosis: 7	MTX 10mg weekly IM (n=14)	12 weeks	NR	Boldrini Children's Center and UNIEMP Institute.	JA
Keikhaei 2015 Iran Cohort [30] 2013 to 2014	Single-arm Single centre 48 (24); 1	1. admitted to Shafa Hospital, Ahvaz, Iran, from 2013 to 2014 2. aged 6-18	Children and adolescents Overall mean 13.7 (range 6 to 18)	NR	NR	NR	NR	HU 10 mg/kg/day oral (n=48)	1 year	NR	Ahvaz Jundishapur University of Medical Sciences	JA

LeBlanc 2016 USA **[31]** NCT02709681	Single-arm Retrospective cohort study 16 (6); 1	More than 5 pain events per year	Adults and adolescents Mean: 15.5 (SD 2.8)	HbSS: 14 (88%) HbSβ⁰: 1 (6%) HbSC: 1 (6%)	NR	NR	ED visit/month: Mean 0.31 (SD 0.27) Hospitalization/month: 0.19 Chronic transfusions: 10	Methadone oral (n=16) Flexible dose	Mean: 2.1 years	NR	NR	CA
Heeney 2016 Americas, Europe, Asia and Africa **[32, 33]** May 2013 to Jun 2015 NCT01794000	RCT, double-blind (phase 3) Multicentre 341 (173); 2	1. HbSS, HbSβ⁰ 2. At least 2 VOC in the year prior to screening 3. TCD within the last year for patients ≤16 years of age 4. Children aged 2 to <18 years 5. Body weight ≥12 kg Exclusion: abnormal/conditional TCD, chronic transfusion, hepatic/renal dysfunction, history of transient ischemic attach or haemorrha, severe head traumatic stroke, chronic treatment with NSAID, use of anticoagulants or other antiplatelet drugs	Children and adolescents Mean:10.6 (SD 4.3) White: 58/169 Black: 109/169 Multiple: 2/169	NR	153 (45%)	N of VOCs in previous year: Mean 4.0 (SD 7.9)	NR	1. Placebo (n=170) 2. Prasugrel oral (n=171) Individual dose-adjustment strategy: Initial dose: 0.08 mg/kg; maintenance: 0.04-0.12 mg/kg (maximum 10mg) by a targeted level of platelet reactivity	9 to 24 months	No anticoagulants or antiplatelet drugs during the study No NSAID drugs	Daiichi Sankyo and Eli Lilly	JA
Reid 2014 United States, Lebanon, Egypt, Jamaica and Canada **[34]** Aug 2012 to May 2013 NCT01601340	RCT, double-blind (phase 2, terminated early) Multicentre 76 (49); 2	1. HbSS or HbSβ 2. Aged 12-60 years 3. at least one acute SCD-related complication or leg ulcers in 12 months prior to enrolment 4. no current (i.e., within 3 months prior to enrolment) HU treatment Exclusion: regular transfusion, an acute vaso-occlusive event within 3 weeks, pulmonary hypertension requiring oxygen therapy, symptomatic untreated peptic ulcer or gastroesophageal reflux disease, history of pancreatitis, abnormal ALT/AST levels, HIV infection	Adults and children Mean: 27.8 (range 12-55) Black or African-American: 24 (63%) White :14 (37%)	HbSS: 60 (79%) HbSβ⁰: 16 (21%)	N/A	N of pain crises in the 12 months before enrolment 0-1: 13 >2: 25	NR	1. HQK-1001 15 mg/kg BID oral (n=38) 2. placebo (n=38)	48 weeks	Folic acid daily	HemaQuest Pharmaceuticals	JA

Adegoke 2013 Nigeria **[35]** Jul to Dec 2011	RCT, open Multicentre 113 (56); 2	Steady state (no painful episode, anemic crisis, or infection on the day of recruitment) Exclusion: alternative medicine (Aloe vera gel, Moringa oleifera, Solamine syrup, and Ciklavit (Cajanus cajal) suspension), hydroxyurea, Discriovite suspension, Niprisan	Children and adolescents Mean: 4.55 (SD 3.57)	NR	NR	N of previous significant painful episodes Mean: 3.27 (SD 3.93)	N of previous Transfusion Mean: 1.29 (SD 0.77) N of Previous hospitalization Mean: 2.12 (SD 2.67)	1. Lime juice + Routine oral drugs (folic acid, vitamin B complex and proguanil) BID oral (n=58) 2. Control (Routine oral drugs (folic acid, vitamin B complex and proguanil)) BID (n=55) Adjusted by body weight: ≤10kg: 5 ml; 11-20 kg: 10 ml; ≥20 kg: 15 mg	6 months	NR	NR	JA
Arruda 2013 Brazil **[36]** Sep to Dec 2010	RCT, double-blind Single centre 83 (53); 2	1. HbSS or HbSβ^0 Exclusion: hospitalized patients, pregancy, untreated iron overload, other investigational drugs in the last 12 months or contraindications to Vitamin C/E	Adults Overall median: 27 (range 18-68)	HbSS: 73 (88%)	NR	NR	Chronic use of NSAIDs: 52 Chronic use of opioids: 16 Transfused patients (past 12 months): 18	1. Placebo (n=39) 2. Vitamins C 1400 mg/day and E 800 mg/day oral (n=44)	6 months	NR	FAPESP and CNPq	JA
Wun 2013 United States and Canada **[37-39]** 26 Aug 2010 to 13 Jun 2011 NCT01167023	RCT, double-blind (phase 2) Multicentre 62 (30); 2	1. HbSS, HbSC, HbSβ^0, HbSβ$^+$ 2. aged 18 to 55 years 3. did not have a diagnosis of acute VOC within 30 days of the study screening visit 4. NSAIDs for treatment of pain were not permitted in the 5 days prior to randomization or for ≥5 consecutive days during the study period. 5. HU was permitted in patients already on a stable dose 30 days prior to randomization Exclusion: hepatic/renal dysfunction, HCt < 18%, risk of excessive bleeding, history of bleeding disorders, haemorrhagic or ischemic stroke, retinal haemorrhage, TIA or intracranial haemorrhage	Adults Mean:31.5	HbSS: 37 (61%) HbSC: 15 (25%) HbSβ^0: 3 (5%) HbSβ þ+: 6 (8%)	NR	Vaso-occlusive crisis: 61% Pain intensity: Mean: 1.8 vs 2.4	Acute chest syndrome: 22.0% (prasugrel) vs 9.5% (placebo) Pulmonary hypertension: 17.1% (prasugrel) vs 9.5% (placebo)	1. Prasugrel 5 mg/day oral (n=41) 2. placebo (n=19*)	30 days	NR	Daiichi Sankyo Co., Ltd. and Eli Lilly and Company.	JA
Daak 2013 Sudan **[40]** Apr 2009 to May 2010	RCT, double-blind Single centre 140 (61); 2	Steady state, defined as no evidence of fever, infection, or crisis for >4 week before the start of the study Exclusion: other chronic diseases, transfusion within 4 months,	Children and adolescents Mean (SD): 7.8(5.5)	All HbSS	NR	NR	Crisis-induced hospitalization (N/year) No. admission: 9.8%	1. Placebo (n=61*) 2. Omega-3 (n=67*)	1 year	All of the patients were receiving regular folate supplementatio n, and those ,5	Marie Curie Transfer of Knowledge Programme, Efamol, and the Kitchner	JA

ISRCTN80844630		hydroxyurea treatment, history of overt stroke, pregnancy					1-2: 43.7% 3-5: 24.1% > 5: 22.4%			y of age were receiving standard oral prophylactic penicillin.	Memorial Trust Fund and University of Khartoum	
Ataga 2011 [41] United States, Jamaica, Brazil, France, Trinidad and the United Kingdom. Feb 2005 to Apr 2007 NCT00102791	RCT, double-blind (phase 3, terminated early) Multicentre 297 (160); 2	1. HbSS, HbSC, HbSβ^0, HbSβ$^+$ 2. aged 16-65 years 3. at least two acute sickle-related painful crises in the previous 12 months 4. Patients were permitted to receive concomitant therapy with HU if they had received HU for the preceding 12 months and their dose was stabilized for at least 3 months prior to the study Exclusion: unstable cardiovascular, neurological, endocrine, hepatic, or renal disorders, Hb < 40 or > 110 g/L, chronic transfusion, cancer diagnosis within 5 years, or hepatitis B/C or HIV infection	Adults and adolescents Mean: 28.5(SD 9.9) Black: 134 (92%) Multiracial: 6 (4%) Caucasian: 3 (2%) Other: 2 (2%)	HbSS: 245 (85%) HbSC: 16 (6%) HbSβ^0: 21(7%) HbSβ$^+$: 4 (1%) Other: 3 (1%)	163 (56%)	SCD crises history in past 12 months (%) 2-4: 59% >5: 41%	NR	1. Senicapoc 20mg/d BID (loading) and then 10mg/dOD oral (n=145*) 2. placebo (n=144*)	52 weeks	NR	Icagen (Research Triangle Park)	JA
Diop 2011 Senegal **[42, 43]** Sep 2007 to Feb 2008	RCT, open Single centre 60 (31); 2	1. Follow-up at least 2 years before in the clinic with records of standardized clinical and laboratory Exclusion: allergic to sulfonamide	Adults and adolescents Mean: 23.2 (SD 6.9)	All SCA	NR	N of VOC/year: Mean 0.8 (SD 1.25)	N of SCD with chronic complications: 8	1. Sulfadoxine-pyrimethamine (S: 25 mg/kg/P: 1.25 mg/kg) OD oral (n=30) 2. Placebo (n=30) The treatment was given once during the following months: September, October, and November	3 months	1. Folic acid, paracetamol during pains 2. Artemisinin-based combination therapy or injectable quinine for malaria attacks	NR	JA

Alvim 2005 Saudi Arabia **[44, 45]** Sep 1998 to Dec 1999	RCT, crossover, double-blind 73 (40); 2	Exclusion: renal, hepatic, cardiac or coagulation disorders secondary or not to SCD, regular transfusion, hydroxyurea use, age > 20 or < 5 years, cognitive dysfunction	Adults and children Median: 12.1 (range 5 to 20)	HbSS: 42 (58%) HbSC: 26 (36%) HbSβ⁰: 5 (7%)	NR	NR	History of transfusion: once: 13; 2-5 times: 19; More than 5: 18 Splenectomy: 5 Cholecystectomy: 5 Osteomyelitis: 11 Acute splenic sequestration: 12 Aplastic crisis: 1 Avascular necrosis of femoral head: 4	1. Piracetam 4.8 g/m^2/day QID (n=73*) 2. Placebo (n=73*)	6 months, then crossover with 2 weeks washout period	NR	FAPEMIG, CNPq	JA
Bao 2008 US **[46]**	RCT, double-blind Single centre 36 (14); 2	Exclusion: non-ambulatory, receiving more than 6 transfusions per year or taking hydroxyurea, history of substance abuse, neurological or psychiatric deficits that could affect compliance, use of immunosuppressive drugs, HIV and hepatitis B	Adults Overall mean: 32.9 (SD 9.7) (range 18-47) All black	HbSS: 32 (89%) HbSC: 3 (8%) HbSβ: 1 (3%)	None	N of sickle pain episode 3-month prior to the study: 5 (placebo); 3 (zinc)	NR	1. Placebo (n=18) 2. Zinc 25mg TID (n=18)	3 months	NR	NR	JA
Ataga 2008 **US** **[47]** **Feb 2002 and Jan 2004** **NCT00040677**	RCT, double-blind (phase 2) Multicentre 90 (45); 3	1. HbSS 2. Aged 18-60 years 3. at least one prior acute sickle-related painful episode (commonly referred to as painful crisis) that had required hospitalization, but none in the 4 weeks prior to screening Exclusion: Hb< 40 g/L or > 100 g/L, received a transfusion within 30 days or underwent an exchange transfusion within 60 days, hepatitis B, HIV, cancer diagnosis within 5 years, mediations (eg, amiodarone, chlorperazine, disopyramide, dofedilide, haloperidol, procainamide, quinidine, risperidone, sotalol, thioridazine, trifluoperazine, warfarin sodium, and erythropoietin)	Adults Mean: 33.6(range 19-55)	All HbSS	24 (27%)	Hospitalizations due to painful episodes in previous 12 months: None: 12 (39%) 1: 6 (19%) 2-3: 6 (19%) ≥3: 7 (23%)	NR	1. Placebo (n=30) 2. Senicapoc (low-dose): 100 mg (loading dose); 6 mg/d (maintenance) oral OD (n=29) 3. Senicapoc (high-dose): 150 mg (loading dose); 10 mg/d (maintenance) oral OD (n=31)	12 weeks	NR	Icagen (Research Triangle Park, NC)	JA

Eke 2003 Nigeria **[48]**	RCT, open (phase 2) Single centre 101 (48); 3	1. HbSS 2. Aged 1-16 years 3. Stable condition Exclusion: loss to 2 consecutive follow-up, pregnancy	Children and Adolescents Mean: 8.1 (SD 4.3) (Range 2-16)	HbSS: 101 (100%)	NR	NR	Total N of malarial parasites: 20 (equally distributed)	1. Pyrimethamine 0.5 mg/kg once weekly oral (n=36*) 2. Proguanil 1.5 mg/kg OD oral (n=32*) 3. Placebo (Vitamin c 7 mg/kg) OD oral (n=29*)	9 months	NR	Combating Childhood Communicable Diseases (Atlanta, Georgia)	JA
Pace 2003 **US** **[49]**	RCT, double-blind Single centre 21 (10); 4	1. HbSS or HbSβ^0 2. Aged above 15 years 3. With dense cells greater than 6% and 2 or more VOC episodes per year for the 2 years prior to enrollment. Exclusion: pregnancy, narcotic addition, chronic transfusions, history of stroke, HIV, investigational drug	Adults and Adolescents Mean:17.9 (SD1.2)	NR	NR	N of VOC episodes Mean: 5 (SD 2)	NR	1. Placebo (n=5) 2. NAC (low-dose) 600 mg/day (n=5) 3. NAC (mid-dose) 1200mg/day (n=5) 4. NAC (high-dose) 2400mg/day (n=6) All doses were divided by 3 to be taken	7 months	NR	Zambon Corp.	JA
Wambebe 2001 Nigeria **[50, 65]**	RCT, cross-over, double-blind (Phase 2) 82 (46); 2	1. HbSS 2. Aged 2-45 years 3. at least 3 painful or vaso-occlusive crises in the previous year Exclusion: HIV, hepatitis, pregnancy	Adults and children Overall (years) < 9: 1 (1%) 10-19: 67 (82%) 20-29: 11 (13%) 30-39: 3 (4%)	All HbSS	NR	Mild to Moderate Pains (Mean): 18.38 Severe Pains: 12.67	NR	1. Niprisan 12 mg/kg OD (n= 70*) 2. Placebo (n=70*)	6 months, then crossover without washout	NR	NR	JA
Tomer 2001 US **[51, 52]**	RCT, double-blind Single centre 13 (NR); 2	1. Frequent pain episodes (≥3 events/year) 2. Not on HU	Adults NR	NR	None	Frequency of pain episodes in 12 months: 7.8	NR	1. Mehaden fish oil: 0.25 g/kg/day OD oral daily (n=5*) 2. Placebo (n=5*)	12 months	NR	NR	JA
de Abood 1997 Spain **[53]**	RCT, double-blind Single centre 43 (43); 3	1. HbSS 2. history of at least one painful crisis per month were included	Adults Overall range: 17-39	All HbSS	NR	NR	NR	1. DMPA 150mg per month for first three months, then usual dose of 150mg every 3 months oral (n=13) 2. levonorgestrel/ethinyl estradiol (0.15/0.03 mg) OD oral (n=14) 3. Surgically sterilized (n=16) [not eligible]	12 months	NR	Special Programme of Human Reproduction of WHO	JA

Gupta 1995 India [54]	RCT, double-blind Phase 2 145 (34); 0	1. > 5 years 2. HbSS Exclusion: chronic persistent infection or exposed to extremes of temperature variation frequently, on drug therapy for some other disease, evidence of organ failure	Adults and children Mean: 16.4 (range12-27)	All HbSS	NR	NR	NR	1. Zinc: 220 mg TID oral (n=65*) 2. Placebo (n=65*)	1.5 years	NR	NR	JA
Manrique 1987 Brazil [55]	RCT Phase 2 60 (23); 2	HbSS Exclusion: acute infections	Adults and children Range: 7-34	All HbSS	NR	Overall pain events (n) None: 11 < 5 times: 7 < 10 times: 15 > 10 times: 11 Persistent: 14 Not clear: 2 Overall pain duration (days) None: 11 < 5 days: 12 < 10 days: 17 > 10 days: 4 Persistent: 14 Not clear: 2 All in 6 months observation period		1. Placebo (n=29*) 2. Pentoxifylline :(Adults: 1200mg; children: 400-600 mg, depending on body weight) oral (n=28*)	6 weeks	NR	NR	JA
Zago 1984 Brazil [56]	RCT, crossover 42 (NR); 2	NR	Adults and children Median: 12 (range 4 - 31)	HbSS: 25 (86%) HbSβ⁰: 4 (14%)	NR	NR	NR	1. Aspirin 17-45 mg/kg OD (n=29*) 2. Placebo (n=29*)	5 months, then crossover without washout	NR	NR	JA
Cabannes 1984 Africa [57]	RCT, double-blind Multicentre 140 (NR); 2	No antisickling treatment for two months before admission to the study Exclusion: other than HbSS; uncontrolled parasitic disease; malnutrition; a history of drug abuse; glaucoma, prostatis hypertrophy, urinary retention, hypersensitivity to ticlopidine or anticholingeric drugs, acute cerebro-vascular accidents, severe intercurrent infection, pulmonary oedema or renal failure	Adults and adolescents Overall range 15-45	All HbSS	NR	N of crises in 6 months before study: 223	NR	1. Ticlopidine 250mg BID if body weight <45kg; 250mg TID if body weight >45kg oral (n=70) 2. Placebo (n=70)	6 months	Acute crises treatment varied depends on regions but including transfusions, analgesic, antibiotics and anticoagulants	NR	JA

Gail 1982 Ghana [58] Sep 1976 to Sep 1978	RCT, double-blind Phase 2 79 (39); 2	HbSS Exclusion: other major illnesses	Adults and children Overall: < 5 years: 21 5-14 years: 28 > 14 years: 30	All HbSS	NR	Number of crises in the previous year 0-2: 18 > 2: 21	NR	1. Control (n=39) 2. Urea: 0.266 g/kg Low-dose: twice a week; High-dose: daily (n=40)	Average: 13.7 months	1. Folic acid (1 mg) and multivitamins daily 2.Chloroquine was given with urea or sucrose placebo	International Sickle Cell Anemia Research Institute and CSRPM	JA
Deceulaer 1982 Jamaica [59]	RCT, crossover, double-blind Single centre 25 (25); 2	HbSS	Adults Overall age range: 20-41	All HbSS	NR	NR	NR	1. placebo (n=10*) 2. medroxyprogesterone acetate 150mg every 3-month IM (n=13*)	2 years (9 months, then crossover after 6 months washout)	NR	NR	JA
Mann 1974 UK [60]	RCT, crossover Single centre 18 (12); 2	1. HbSS, HbSC, HbSβ 2. 5-17 years 3. Previously suffered painful crises	Children and adolescents Overall mean 8.4 (SD 3.2)	HbSS: 15 (83%) HbSC: 2 (11%) HbSβ: 1 (6%)	NR	NR	NR	1. Folic acid 5 mg daily oral (n=25) 2. Folic acid 5mg + Sodium bicarbonate 0.06-0.2 gm/kg/day initially, then 0.1-0.4 mg/kg/day oral (n=25)	2 years (1 year than crossover without washout	NR	United Birmingham Hospitals and Endowment Research Fund	JA
Isaacs 1972 Nigeria [61]	RCT, crossover (preliminary report before crossover) 44 (28); 2	1. HbSS 2. Moderately severe pain at least once in three months (with little or no fever or exacerbations of jaundice)	Adults and children Overall range 2-35	All HbSS	NR	NR	NR	1. Saline IM (n=44*) 2. Steroid (Testoserone/Progesterone) Male: testosterone 10 mg; Female: progesterone 10 mg every week IM (n=44*)	4-6 months	All patients were on regular folates and had high or normal serum-iron values	Glaxo Allenburys of Nigeria	Journ al article
Oski 1968 USA [62]	RCT, crossover, double-blind 14 (5); 2	At least 2 painful episodes during the 2 year period prior to study	Adults and children NR	HbSS: 10 (71%) HbSC: 4 (29%)	NR	NR	NR	1. Promazine hydrochloride oral (n=14*) Based on weight: 2 tablets a day: 40-80 pounds; 3 tablets a day: 80-120 pounds; 4 tablets a day: > 120 pounds 2. Placebo (n=14*)	3 months	NR	NR	JA

NCT02482298 USA, Egypt, France, Italy, Kenya, Lebanon, UK, Turkey [63] Jul 2015 to Nov 2016	RCT, double-blind Multicentre 87 (47); 3	1. HbSS, HbSβ⁰ 2. Aged 18-30 3. If treated with hydroxyurea, the dose must have been stable for 3 months	Adults Mean: 21.6 (SD 3.42) Black Or African American: 17 (57%) White: 13 (43%)	NR	NR	NR	NR	1. Placebo (n =30) 2. Ticagrelor 10MG BID oral (n=27) 3. Ticagrelor 45mg BID oral (n=30)	12 weeks	NR	AstraZeneca	CT
NCT01476696 USA [64] Feb 2014 to Oct 2016 NCT01476696	Single-arm Phase 2 (Part B) 18 (NR); 1	1. HbSS, HbSβ 2. ≥2 to <18 years of age and ≥ 12 kg body weight 3. Participants on hydroxyurea must be on a stable dose for the 60 days prior to enrolment without signs of hematologic toxicity at screening	Children and adolescents NR (only reported overall, part A+B)	NR	NR	NR	NR	Prasugrel 0.06-0.12 mg/kg depending on their steady-state PD response oral (n=18)	14 ± 4 days	NR	Eli Lilly and Company	CT
Vichinsky 2010 [66]	RCT 36 (NR)	1. HbSS 2. Normal neurological exam, WAIS III PIQ score ≤ 90, hemoglobin ≤ 9 g/dL 3. Aged 21-55	Adults Mean: 29	All HbSS	HU: 14 (39%)	NR	Transfusion group had average of 5.6 transfusions (which differ from standard care group) ACS: 35%	1. Chronic transfusion (n = 20) maintaining a hemoglobin of 2 g/dL rise over baseline with matched red cells for D, C/c, E/e, and Kell antigens 2. Standard care (n = 16)	4 weeks	NR	NR	CT
Styles USA [67]	Single-arm Open-label ½ study Three centers 15 (0); 1	NR	Adults Mean: 32 (range 18-50) All African-American	HbSS: 13 HbSβ⁰: 2	HU: 4 (26.7%)	VOC: 6 (past year)	ACS: 2 (past year) Transfusion: 2 (past year) Priapism: 1 (past year)	GMI-1070 20mg/kg (first dose) and 10 mg/kg after 10 hours	28 days	NR	NR	CT

†If not stated, only one arm data were shown as representative

*final number used for analysis or crossover design

ACS: Acute chest syndrome; ALT: Alanine transaminase; CA: Conference abstract; Cr: creatinine; CSRPM: Center for Scientific Research into Plant Medicine; CT: Clinical trial registry; DDCF: Doris Duke Charitable Foundation; ED: emergency department; HbSS: Homozygous sickle haemoglobin (HbS); HbSC: sickle haemoglobin S and haemoglobin C; HbSβ: sickle beta thalassemia, type '0' or '+'; HU: hydroxyurea; JA: Journal article; MTX: Methotrexate; NAD: N-acetylcysteine ;NCATS: National Center for Advancing Translational Sciences; NCRR: National Center for Research Resources; NHLBI: National Heart Lung and Blood Institute; NSAID: Non-steroidal anti-inflammatory drugs; NR: Not reported; OOPD: FDA's Office of Orphan Products Development; PT: patient; SCD: sickle cell disease; TCD: transcranial Doppler; ZonMw: The Netherlands Organisation for Health Research and Development

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Appendix C. Additional details of the network meta-analysis

B.1 Methods of the network meta-analysis

We first define the Bayesian network meta-analysis (NMA) statistical models used to synthesize transformed outcomes, on the log hazard scale, from each randomized controlled trial (RCT). The link functions to connect these models to the different data summaries are then presented. The same statistical models are used for crisis, hospitalization days, adverse events, and serious adverse events but the link functions vary depending on what data is reported by each RCT (see main text for outcomes analyzed). The NMA models are in line with the recommendations of the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) technical support documents (TSD), in particular NICE DSU TSD 2. OpenBUGS code is provided for each outcome in appendix **B.4.**

For all random parameters (i.e. $\mu_{..}$ and $d_{..}$) vague $Normal(0, 0.001)$ priors were used.

Fixed-effects network meta-analysis model

When the available evidence consists of a network of multiple pairwise comparisons (i.e. AB-trials, AC-trials, BC-trials, etc.) the standard fixed effects model for NMA can be specified as follows:

$$\theta_{jk} = \begin{cases} \mu_{jb} & \text{if } k = b \\ \mu_{jb} + d_{bk} = \mu_{jb} + d_{Ak} - d_{Ab} & \text{if } k \succ b \end{cases} \qquad (3)$$
$$d_{AA} = 0$$

There are *k* treatments labelled as A, B, C, etc., and treatment A is taken to be the reference treatment for the analysis. μ_{jb} is the (transformed) outcome in study *j* on 'baseline' treatment *b* which will vary across studies. d_{bk} is the fixed effect of treatment *k* relative to 'baseline treatment' *b.* d_{bk} are identified by expressing 0them in terms of the reference treatment A: $d_{bk} = d_{Ak} - d_{Ab}$ with $d_{AA} = 0$.

Random-effects network meta-analysis model

$$\theta_{jk} = \begin{cases} \mu_{jb} & \text{if } k = b \\ \mu_{jb} + \delta_{jbk} & \text{if } k \succ b \end{cases} \qquad (4)$$

$$\delta_{jbk} \sim Normal(d_{bk}, \sigma^2) = Normal(d_{Ak} - d_{Ab}, \sigma^2)$$
$$d_{AA} = 0$$

δ_{jbk} is the trial-specific treatment effect of *k* relative to treatment *b*. These trial-specific effects are drawn from a random-effects distribution: $\delta_{jbk} \sim N(d_{bk}, \sigma^2)$ Again, the pooled effects, d_{bk}, are identified by expressing them in terms of the reference treatment A. The heterogeneity σ^2 is assumed constant for all treatment comparisons. (A fixed effect model is obtained if σ^2 equals zero.)

This random-effects model treats multiple-arm trials (>2 treatments) without taking account of the correlations between the trial-specific δs that they estimate. Bayesian random-effects models with a heterogeneity parameter for d_{Ak} can be easily extended to fit trials with 3 or more treatment arms by decomposing a multivariate normal distribution as a series of conditional univariate distributions.[1]

$$\begin{pmatrix} \delta_{jbk_1} \\ \vdots \\ \delta_{jbk_p} \end{pmatrix} \sim Normal\left(\begin{pmatrix} d_{bk_1} \\ \vdots \\ d_{bk_p} \end{pmatrix}, \begin{pmatrix} \sigma^2 & \cdots & \frac{\sigma^2}{2} \\ \vdots & \ddots & \vdots \\ \frac{\sigma^2}{2} & \cdots & \sigma^2 \end{pmatrix} \right) \quad (5)$$

Then the conditional univariate distributions for arm *i* given the previous *1,….(i-1)* arms are:

$$\delta_{jbk_i} \left| \begin{pmatrix} \delta_{jbk_1} \\ \vdots \\ \delta_{jbk_{i-1}} \end{pmatrix} \sim Normal\left(d_{bk_i} + \frac{1}{i}\sum_{j=1}^{i-1} \left(\delta_{jbk_j} - d_{bk_j} \right), \frac{(i-1)}{2i}\,\sigma^2 \right) \right. \quad (6)$$

Random-effects network meta-analysis model with constant covariate interaction term

$$\theta_{jk} = \begin{cases} \mu_{jb} & \text{if } k = b \\ \mu_{jb} + \delta_{jbk} & \text{if } k \succ b \end{cases}$$

$$\delta_{jbk} = \begin{cases} Normal\left(d_{Ak} - d_{Ab} + \beta X_j, \sigma^2\right) & \text{if } b = A \\ Normal\left(d_{Ak} - d_{Ab}, \sigma^2\right) & \text{if } b \neq A \end{cases}$$

$$d_{AA} = 0$$

X_j is the trial-specific covariate value. β is the corresponding treatment-by-covariate interaction term, which is the same for all interventions.

Link functions for shared parameter models

As described above, the available data is connected to the model via the likelihood and the link function $\theta_{jk} = g(\gamma_{jk})$. If different data summaries are used by different studies, it is necessary to use a shared parameter model, where different link functions and likelihoods are used for each study[2]. Our underlying model will be on the log hazard ratios $d_{..}$, which can be fixed or random and include meta-regression effects as discussed. In SCD it will be necessary to connect the following data summaries.

1) Estimated annualized event log rate $\log(\lambda_{jk})$ (mean or median) with standard error se_{jk} are modelled with identity link and Normal likelihood

$$\log(\lambda_{jk}) \sim Normal(\theta_{jk}, se_{jk}^2)$$

2) Total number of events r_{jk} over exposure E_{jk} are modelled with log link and Poisson likelihood

$$r_{jk} \sim Pois(\lambda_{jk} E_{jk})$$

$$\theta_{jk} = \log(\lambda_{jk})$$

3) Mean number of events per patient $\bar{r}_{jk}$ over n_{jk} patients is transformed to total number of events r_{jk} and modelled as type 2 data.

4) Number of patients w_{ij} with ≥1 event over mean follow-up time t_{ij} are modelled with a binomial likelihood and complementary log log (cloglog) link with log time as offset

$$r_{jk} \sim Binomial(P_{jk}, n_{jk})$$

$$cloglog(P_{jk}) = \log(-\log(P_{jk})) = \log(t_{jk}) + \theta_{jk}$$

5) Log hazard ratio or log rate ratio $\log(hr_{jk})$ with standard error se_{jk} between active arm k and control arm b. This is slightly different as we no longer have data on both arms, only on the contrasts.

$$\log(hr_{jk}) \sim Normal(\theta_{jk}, se_{jk}^2), \text{ for } k \succ b$$

and

$$\theta_{jk} = d_{bk} \text{ if fixed effects}$$

$$\theta_{jk} = \delta_{jbk}, \text{ if random effects or meta-regressions}$$

An adjusted standard error is needed for log hazard ratios if trials have more than 2 arms, as there is induced correlation between arms due to the common control.

Table 1 Summary of analyses planned for different outcome measures on each of the outcomes

Outcome	Outcome measure	Analysis planned	Why this analysis
Crisis	Total pain crises	Poisson likelihood, log link (Type 2 data)	Multiple events per patient so modelling underlying log hazard with a Poison likelihood.

	Mean or rate pain crises	Scale to total pain crises	Mean per patient gives total when scaled by patient number.
	Patients with ≥1 pain crisis	Binomial likelihood with cloglog link (type 4 data)	At most one such 'event' per patient, giving a binomial. Convert to log hazard scale modelled via Poisson using a cloglog function and a log follow-up time offset.
	Risk ratio/hazard ratio of crisis	Normal likelihood with identity link (type 5 data)	Direct observation of difference in log rates/hazards.
Hospitalization	Total hospitalization days	Poisson likelihood, log link (Type 2)	Multiple events per patient so modelling underlying log hazard with a Poison likelihood.
	Mean, median, or rate hospitalization days	Scale to total hospitalization days	Mean per patient gives total when scaled by patient number.
Adverse events or serious adverse events	Total events	Poisson likelihood, log link (Type 2)	Multiple events per patient so modelling underlying log hazard with a Poison likelihood.
	No. of patients with ≥ 1 event	Binomial likelihood with cloglog link (type 4 data)	At most one such 'event' per patient, giving a binomial. Convert to log hazard scale modelled via Poisson using a cloglog function and a log follow-up time offset.
	% patients with ≥ 1 event	Scale to number of patients with ≥ 1 event	Percentage gives total when multiplied by patient numbers

B.2 Outcome definitions used in the analyzed trials

Table 2: Definitions of crisis used in 5 RCTs included in base case crisis network

Study	Treatments	Crisis
Ataga 2017	Placebo, High-dose Crizanlizumab, Low-dose Crizanlizumab	Sickle cell–related pain crises were defined as acute episodes of pain, with no medically determined 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 nonsteroidal anti-inflammatory drug. The acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism were also considered to be crisis events.
Ataga 2011	Placebo, senicapoc	A painful crisis was defined as an episode of acute pain with no cause other than a vaso-occlusive event that required a medical facility visit and treatment with oral or parenteral narcotics, or parenteral non-steroidal anti-inflammatory drugs. Included in the definition of painful crisis were acute chest syndrome, hepatic sequestration, splenic sequestration, priapism, stroke and death (with the exception of homicide, suicide, or accidental death). To ensure consistency across sites, all protocol-defined sickle-related painful crises identified by the Investigators that resulted in a visit to a medical facility were adjudicated by an independent, blinded, Crisis Review Committee (CRC).
Ataga 2008	Placebo, senicapoc (low-dose), senicapoc (high-dose)	An independent, blinded crisis review committee adjudicated all sickle cell painful crises and related adverse event data (Document S1). A painful crisis was defined as a period of severe pain (with no explanation other than SCD) lasting 4 or more hours in duration, requiring a visit to a health care facility, and requiring parenteral opiate or other narcotic for relief
Pace 2003	Placebo, NAC (low-dose) 600 mg/day, NAC (mid-dose) 1200mg/day, NAC (high-dose) 2400mg/day	Defined as a visit to a medical facility that lasted more than 4 hr for acute pain related to vaso-occlusion requiring parenteral narcotics. The occurrence of acute chest syndrome, priapism, splenic, or hepatic sequestration was also counted as a VOC episode. Acute chest syndrome included those subjects with chest wall pain and a new infiltrate on chest X ray.
Niihara 2018	Placebo, L-glutamine	A pain crisis was defined as pain leading to treatment with a parenterally administered narcotic or ketorolac in an emergency department (ED) (or outpatient treatment center) or during hospitalization.

Table 3: Adverse events reported in the 8 RCTs in the base case adverse events network

Study	Treatments	Outcome name	Adverse events included
Ataga 2017	Placebo, High-dose Crizanlizumab,	Adverse events	"Headache, Back pain, Nausea, Arthralgia, Pain in extremity, Urinary tract infection, Upper respiratory tract infection, Pyrexia, Diarrhea,

	Low-dose Crizanlizumab		Musculoskeletal pain, Pruritus, Vomiting, Chest pain
		Serious adverse events	Pyrexia, Influenza, Pneumonia
Ataga 2011	Placebo, senicapoc	Adverse events	Nausea, Urinary tract Infection, Headache, Arthralgia, Upper respiratory tract Infection, Vomiting, Pyrexia, Pneumonia, Back pain, Pain in extremity, Nasopharyngitis, Cough, Constipation, Fatigue, Hypokalaaemia, Haematuria, Diarrhoea, Abdominal pain, Pharyngolaryngeal pain, Pruritus, Drug hypersensitivity
Ataga 2008	Placebo, senicapoc (low-dose), senicapoc (high-dose)	Adverse events	Diarrhea, Nausea, Constipation, Gastroenteritis, Upper respiratory tract infection, Chest pain, Increased SGOT, Arthralgia, Back pain
Niihara 2018	Placebo, L-glutamine	Adverse events	Tachycardia, Constipation, Nausea, Vomiting, Abdominal pain upper, Diarrhea, Chest pain (noncardiac), Fatigue, Urinary tract infection, Pain in extremity, Back pain, Headache, Dizziness, Nasal congestion
		Serious adverse events	A serious adverse event was defined as any adverse event, occurring while the patient was receiving the trial medication or placebo at any dose, that resulted in death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or clinically significant disability or incapacity, or a congenital anomaly or birth defect. Notable medical events that might not have resulted in death, been life-threatening, or required hospitalization could be considered serious adverse events if it was determined, on the basis of appropriate medical judgment, that they could place the patient's health in jeopardy and might require medical or surgical intervention to prevent one of the outcomes listed in the definition of serious adverse events.

Glassberg 2017	mometasome placebo		Hoarseness of voice, thrush, sore throat
Sins 2017	NAC placebo	Adverse events	Gastro-intestinal complaints, Pruritus / Rash, plus Discontinuation of study drug or placebo because of adverse event and serious adverse events
		Serious adverse events	Acute Chest Syndrome, Liver/spleen sequestration, Pyelonefritis with admission, Cholelithiasis with admission, Gastrointestinal perforation, Pulmonary embolism, Pneumonia with admission
Wun 2013	Prasugrel, placebo	Any serious adverse event	No detail given but they were non-hemorrhagic events
NCT02482298	Placebo TICAGRELOR 10MG, TICAGRELOR 45MG	Adverse events	Sickle cell anaemia with crisis, Abdominal pain, nausea, toothache, vomiting, fatigue, non-cardiac chest pain, pain, pneumonia, Upper respiratory tract infection, Urinary tract infection, Arthralgia, Back pain, Musculoskeletal chest pain, Musculoskeletal pain, pain in extremity, Headache, Dysmenorrhoea, Cough, Epistaxis, Oropharyngeal pain
		Serious adverse events	Reticulocytopenia, Sickle cell anemia with crisis, Local swelling, Hepatic ischemia, Cellulitis, Gastroenteritis, Lower respiratory tract infection, Face injury, Arthralgia, Back pain, Musculoskeletal chest pain, headache, Acute chest syndrome, Vascular occlusion
Glassberg 2017	mometasome placebo		Hoarseness of voice, thrush, sore thr`oat

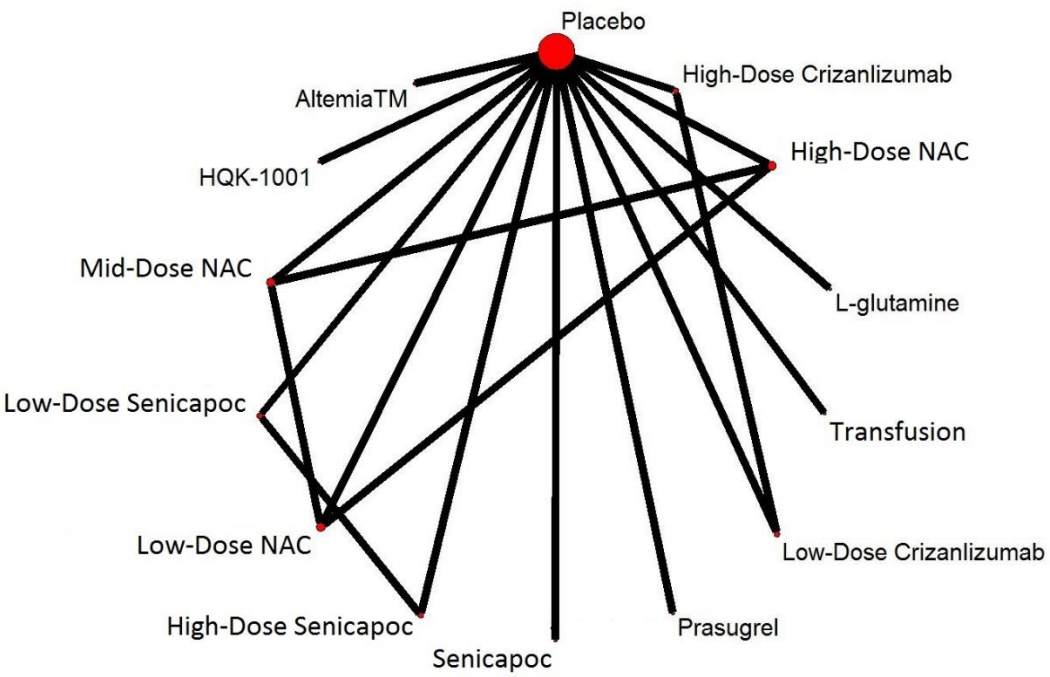
B.3 Additional results of the network meta-analysis

Extended network for potential indirect evidence

We wished to assess whether additional direct or indirect evidence would be provided on comparators studied in the 9 RCTs of the adult only NMA by including the 25 excluded non-adult RCTs as well as Vichinsky 2010 on transfusions under the assumption that their standard of care was a placebo. To do this we plotted the evidence networks including non-adult RCTs reporting on crisis, hospitalization days, adverse events, and serious adverse events and connected to high-dose crizanlizumab. However, there were only additional RCTs connected to high-dose crizanlizumab reporting on the crisis outcome. No additional RCTs connected to high-dose crizanlizumab reported on hospitalization days, adverse events, and serious adverse events.

The extended evidence network for crisis is presented in Figure 1. This network consists of 9 RCTs, including 4 RCTs not in the adult only network: Daak 2018 (AltemiaTM vs placebo)[3], Heeney 2016 (prasugrel vs placebo)[4], Reid 2014 (HQK-1001 vs placebo)[5], Vichinsky 2010 (transfusions vs standard of care)[6]. The extended network included 3 treatments not in the base case (AltemiaTM, HQK-1001, and Prasugrel). However, these additional RCTs did not provide direct or indirect evidence on any comparisons in the base case network.

Figure 1. Network of evidence for crisis in the extended population. Consists of 9 RCTs and 14 treatments.*

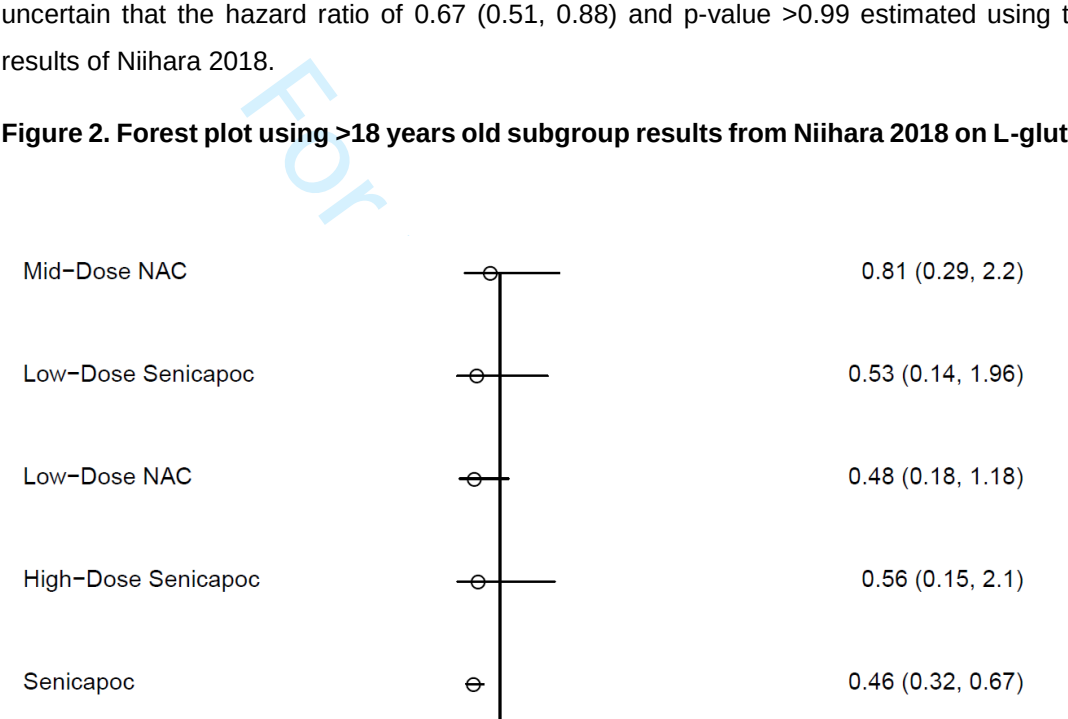


* Network included adult (base case) and non-adult studies. Adult studies: Ataga 2017 (crizanlizumab vs placebo), Ataga 2011 (senicapoc vs placebo), Ataga 2008 (senicapoc low-dose, senicapoc high-dose vs placebo), Pace 2003 (NAC vs placebo), Niihara 2017 (L-glutamine vs placebo), Vichinsky 2010 (transfusion vs placebo). Non-adult studies: Daak 2018 (AltemiaTM vs placebo), Heeney 2016 (prasugrel vs placebo), Reid 2014 (HQK-1001 vs placebo)

Sensitivity analysis using >18 years old subgroup results from Niihara 2018 on L-glutamine

As our target population was patients ≥16 years old the Niihara 2018 study with 51 patients aged 5-12, 67 aged 13-18, and 112 aged >18 potentially differed in important effect modifiers. We used the reported rate ratio of 0.64 with 95% confidence interval (0.45, 0.89) in a subgroup of patients aged >18 years old to repeat our NMA. The results are presented as forest plots in Figure 2 with p-value table in Table 4 and pairwise results in Table 13. Notably, the hazard ratio for crises on crizanlizumab vs L-glutamine is 0.86 (0.57, 1.29) with p-value 0.77; this is higher and more uncertain that the hazard ratio of 0.67 (0.51, 0.88) and p-value >0.99 estimated using the full results of Niihara 2018.

Figure 2. Forest plot using >18 years old subgroup results from Niihara 2018 on L-glutamine



Sd

Table 4. Bayesian probabilities that crizanlizumab is superior or inferior on each outcome analyzed using >18 year old subgroup results from Niihara 2018.

Treatment	Probability superior
Placebo	>0.9999
NAC (high-dose 2400mg)	0.1495
L-glutamine	0.7707
Low-Dose Crizanlizumab	0.9454
Senicapoc	>0.9999
High-Dose Senicapoc	0.8066
Low-Dose NAC	0.9429
Low-Dose Senicapoc	0.8354
Mid-Dose NAC	0.6649

Model assessment of the crisis network meta-analysis

Model fit and meta-regressions were explored. The base case fixed effects model fit well (total residual deviance close to number of data points[7]) but the meta-regressions did not converge (Gelman-Rubin Rhat statistic far from 1.000, very wide credible intervals for the regression coefficient). This was because there was only one RCT on each treatment contrast. Deviance and DIC do not in any case suggest evidence of effect modification as they are similar to the fixed effects analysis.

Table 5. Crisis among the adult population: Model comparison

Model	Number data points	Total residual deviance	DIC	Regression coefficient	Gelman-Rubin Rhat for regression
Base FE	14	15.44 (6.11, 25.85)	102.8	NA	NA
Proportion female FE	14	15.59 (6.14, 26.23)	102.9	45.66 (-83.88, 188.64)	1.681

Mean age FE	14	16.07 (6.23, 27.08)	103.8	-3.89 (-4.95, -2.85)	9.652
Proportion HbSS FE	14	15.4 (6.15, 25.73)	102.7	44.14 (8.16, 72.78)	2.018
Proportion HU use FE	14	15.29 (6.18, 25.44)	102.5	76.07 (47.4, 106.76)	7.392
Trial duration FE	14	15.18 (6, 25.34)	102.5	-7.35 (-50.24, 37.51)	7.528
Proportion black FE	14	15.77 (6.37, 26.29)	103.3	-2.93 (-78.26, 72.71)	21.211

Model assessment of the hospitalization days network meta-analysis

Model assessment and exploration of meta-regressions are presented in Table 6. The base case fixed effects model fits well (total residual deviance close to number of data points). Meta-regressions did not converge (Rhat statistic far from 1.000 and very wide credible intervals on the regression coefficient) as there was only one study on each treatment contrast. The deviance and DIC do not in any case suggest evidence of effect modification.

Table 6. Hospitalization days among the adult population: Model comparison

Model	Number data points	Total residual deviance	DIC	Regression coefficient	Gelman-Rubin Rhat for regression
Base FE	9	10.32 (3.02, 18.67)	72.69	NA	NA
Proportion female FE	9	10.46 (2.93, 19.2)	72.6	37.75 (-98.37, 172.76)	24.655
Mean age FE	9	10.52 (3.09, 19.2)	72.57	-5.85 (-7.09, -4.67)	6.029
Proportion HbSS FE	9	10.28 (2.91, 18.68)	72.71	39.4 (-33.02, 108.38)	21.868

Proprotion HU use FE	9	10.22 (2.99, 18.53)	72.44	78.51 (15.98, 139.67)	7.582
Trial duration FE	9	10.03 (2.9, 18.16)	72.33	16.54 (-3.57, 36.27)	34.345
Proportion black FE	9	9.99 (3.05, 17.91)	72.25	29.18 (-26.53, 86)	27.376

Model assessment for the adverse events network meta-anlaysis

Model assessment and exploration of meta-regressions are presented in Table 7. The base case fixed effects model fits well (total residual deviance close to number of data points). Meta-regressions did not converge (Rhat statistic far from 1.000 and very wide credible intervals on the regression coefficient) as there was only one study on each treatment contrast. The deviance and DIC do not in any case suggest evidence of effect modification.

Table 7. Adverse events among the adult population: Model comparison

Model	Number data points	Total residual deviance	DIC	Regression coefficient	Gelman-Rubin Rhat for regression
Base FE	11	12.38 (4.25, 21.55)	71.72	NA	NA
Proportion female FE	11	12.51 (4.27, 21.81)	71.96	57.94 (2, 114.04)	1.838
Mean age FE	11	12.35 (4.11, 21.73)	71.46	0.27 (-4.32, 4.95)	38.731
Proportion HbSS FE	11	12.65 (4.22, 22.29)	71.84	-45.33 (-137.28, 42.08)	10.813
Proprotion HU use FE	11	12.15 (4.25, 21.02)	71.4	-25.25 (-81.24, 28)	5.985

Trial duration FE	11	12.02 (4.18, 20.87)	71.11	21.33 (-1.45, 43.98)	20.575
Proportion black FE	11	12.31 (4.33, 21.3)	71.61	-20.3 (-48.26, 3.68)	4.349

Model assessment for the serious adverse events network meta-anlaysis

Model assessment and exploration of meta-regressions are presented in Table 8. The base case fixed effects model fits well (total residual deviance close to number of data points). Meta-regressions did not converge (Rhat statistic far from 1.000 and very wide credible intervals on the regression coefficient) as there was only one study on each treatment contrast. The deviance and DIC do not in any case suggest evidence of effect modification.

Table 8. Serious adverse events among the adult population: model comparison

Model	Number data points	Total residual deviance	DIC	Regression coefficient	Gelman-Rubin Rhat for regression
Base FE	12	13.49 (4.86, 23.2)	70.89	NA	NA
Proportion female FE	12	13.87 (4.96, 23.98)	71.27	-57.35 (-183.99, 65.33)	1.204
Mean age FE	12	13.98 (5.08, 24.06)	71.49	-2.06 (-4.45, 0.36)	40.773
Proportion HbSS FE	12	14.08 (5.04, 24.24)	71.96	51.6 (35.74, 65.75)	1.652
Proportion HU use FE	12	13.49 (4.92, 23.1)	70.99	-140.71 (-210.66, -68.54)	13.326
Trial duration FE	12	13.62 (4.92, 23.54)	70.87	-19.04 (-34.58, -3.28)	15.267

Proportion black FE	12	13.37 (4.75, 23.13)	70.66	-5.77 (-118.35, 104.8)	36.318

B.3 OpenBUGS code for the network meta-analysis

The code for the four shared parameter models used to analyze crisis, hospitalization days, adverse events, and serious adverse events are presented below. This code was run in OpenBUGS version 3.2.3 [8] with two MCMC chains of 400,000 iterations for burn-in and 30,000 iterations for posterior sampling.

Fixed effects model used for analyzing crisis.

```
model{
        # Data type 2; r2 events in exposure E2
        # Poisson likelihood, log link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns2){                    # LOOP THROUGH STUDIES
                mu2[i] ~ dnorm(0,.0001)             # vague priors for all trial baselines
                for (k in 1:na2[i]) {           # LOOP THROUGH ARMS
                        r2[i,k] ~ dpois(theta2[i,k])   # Poisson likelihood
                        theta2[i,k] <- lambda[i,k]*E2[i,k] # failure rate * exposure
                        # model for linear predictor
                        log(lambda[i,k]) <- mu2[i] + d[t2[i,k]] - d[t2[i,1]]
                        #Deviance contribution
                        dev2[i,k] <- 2*((theta2[i,k]-r2[i,k]) + r2[i,k]*log(r2[i,k]/theta2[i,k]))
                        }
                        #  summed residual deviance contribution for this trial
                        resdev2[i] <- sum(dev2[i,1:na2[i]])
                }
        totresdev2 <- sum(resdev2[])          #Total Residual Deviance
totresdev<-totresdev2+0
        # Treatment effect model is shared between the three likelihoods
        d[1]<-0       # treatment effect is zero for control arm
        # vague priors for treatment effects
        for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
        for(k in 1:nt)
        {
                # Bayesian one-sided p-values
                # Probability that treatment j has higher hazard than treatment k
                # step(x) is 1 if x>=0
                for (j in 1:nt){ pval[j,k] <- step(d[j]-d[k]) }
        }
}

# Data in BUGS format (some data is redundant)
list(E2= structure(.Data= c(6.50000E+01, 6.70000E+01, 6.60000E+01, NA, 1.44000E+02,
1.45000E+02, NA, NA, 6.92308E+00, 7.15385E+00, 6.69231E+00, NA, 1.75000E+00,
2.91667E+00, 2.33333E+00, 2.91667E+00, 7.20000E+01, 1.40308E+02, NA, NA), .Dim=c(5, 4)),
t2= structure(.Data= c(1.00000E+00, 2.00000E+00, 5.00000E+00, NA, 1.00000E+00, 6.00000E+00,
NA, NA, 1.00000E+00, 7.00000E+00, 9.00000E+00, NA, 1.00000E+00, 3.00000E+00,
8.00000E+00, 1.00000E+01, 1.00000E+00, 4.00000E+00, NA, NA), .Dim=c(5, 4)), r2=
structure(.Data= c(1.93700E+02, 1.09210E+02, 1.32660E+02, NA, 8.90000E+01, 1.06000E+02,
```

NA, NA, 5.00000E+00, 5.00000E+00, 5.00000E+00, NA, 8.00000E+00, 4.00000E+00, 1.20000E+01, 9.00000E+00, 3.04200E+02, 4.86400E+02, NA, NA), .Dim=c(5, 4)), n4= structure(.Data= c(3.80000E+01, 3.80000E+01), .Dim=c(1, 2)), ns1=0.00000E+00, ns2=5.00000E+00, ns4=0.00000E+00, ns5=0.00000E+00, na1=0.00000E+00, na2=c(3.00000E+00, 2.00000E+00, 3.00000E+00, 4.00000E+00, 2.00000E+00), na4=c(0.00000E+00, 0.00000E+00), na5=c(0.00000E+00, 0.00000E+00), nt=1.00000E+01, x= structure(.Data= c(NA, NA, NA, NA, NA, NA, 5.50505E-01, 2.80152E+01, 7.12121E-01, 6.21212E-01, 1.00000E+00, 9.19192E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 5.53633E-01, 2.89983E+01, 8.47751E-01, 5.64014E-01, 1.00000E+00, 9.51557E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 5.00000E-01, 3.54833E+01, 1.00000E+00, 5.37603E-01, 2.30769E-01, 8.14103E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 4.76190E-01, 2.05286E+01, 8.49869E-01, 5.37603E-01, 5.83333E-01, 8.14103E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 5.39130E-01, 2.20609E+01, 9.00000E-01, 6.65217E-01, 9.23077E-01, 9.43478E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA), .Dim=c(5, 4, 6)), mx=c(5.38790E-01, 2.52754E+01, 8.49869E-01, 5.37603E-01, 9.51465E-01, 8.14103E-01), r2.base=c(1.93700E+02, 1.22000E+02, 8.90000E+01, 5.00000E+00, 8.00000E+00, 3.04200E+02), E2.base=c(6.50000E+01, 1.27500E+02, 1.44000E+02, 6.92308E+00, 1.75000E+00, 7.20000E+01), r4.base=1.90000E+01, *time4.base=4.61538E-01, n4.base=3.80000E+01, ns2.base=6.00000E+00, ns4.base=1.00000E+00)*

```
# Initial values (includes initial values for meta-regressions, which are redundant)
# Inits 1
list(B=5.00000E-01, d=c( NA, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00), sd=1.00000E+00, mu.base=1.00000E+00, mu2=c(1.40000E+00, 1.40000E+00, 1.40000E+00, 1.40000E+00, 1.40000E+00))

# Inits 2
list(B=1.00000E-01, d=c( NA, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01), sd=5.00000E-01, mu.base=5.00000E-01, mu2=c(7.00000E-01, 7.00000E-01, 7.00000E-01, 7.00000E-01, 7.00000E-01))
```

Fixed effects model used for analyzing hospitalization days.

```
model{
        # Data type 2; r2 events in exposure E2
        # Poisson likelihood, log link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns2){                    # LOOP THROUGH STUDIES
                mu2[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
                for (k in 1:na2[i]) {            # LOOP THROUGH ARMS
                        r2[i,k] ~ dpois(theta2[i,k])   # Poisson likelihood
                        theta2[i,k] <- lambda[i,k]*E2[i,k] # failure rate * exposure
                        # model for linear predictor
                        log(lambda[i,k]) <- mu2[i] + d[t2[i,k]] - d[t2[i,1]]
                        #Deviance contribution
                        dev2[i,k] <- 2*((theta2[i,k]-r2[i,k]) + r2[i,k]*log(r2[i,k]/theta2[i,k]))
                        }
                        #  summed residual deviance contribution for this trial
                        resdev2[i] <- sum(dev2[i,1:na2[i]])
                }
        totresdev2 <- sum(resdev2[])           #Total Residual Deviance
totresdev<-totresdev2+0
        # Treatment effect model is shared between the three likelihoods
        d[1]<-0       # treatment effect is zero for control arm
        # vague priors for treatment effects
        for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
        for(k in 1:nt)
        {
```

```
                # Bayesian one-sided p-values
                # Probability that treatment j has higher hazard than treatment k
                # step(x) is 1 if x>=0
                for (j in 1:nt){ pval[j,k] <- step(d[j]-d[k]) }
        }
}

# Data in BUGS format (some data is redundant)
list(ns5=0.00000E+00, ns4=0.00000E+00, E2= structure(.Data= c(6.53846E+00, 1.34615E+01,    NA,
6.50000E+01,  6.70000E+01,  6.60000E+01,  8.50000E+00,  5.00000E+00,        NA,  7.20000E+01,
1.40308E+02,       NA), .Dim=c(4, 3)), t2= structure(.Data= c(1.00000E+00, 5.00000E+00,       NA,
1.00000E+00,  2.00000E+00,  6.00000E+00,  1.00000E+00,  3.00000E+00,        NA,  1.00000E+00,
4.00000E+00,       NA), .Dim=c(4, 3)), r2= structure(.Data= c(6.95300E+01, 9.34500E+01,       NA,
4.46550E+02,  2.68000E+02,  4.53420E+02,  5.30000E+01,  9.00000E+00,        NA,  1.81000E+01,
1.21000E+01,       NA), .Dim=c(4, 3)), ns1=0.00000E+00, ns2=4.00000E+00, na1=0.00000E+00,
na2=c(2.00000E+00,  3.00000E+00,  2.00000E+00,  2.00000E+00), nt=6.00000E+00,  x=
structure(.Data= c(  NA,  NA,  NA,  NA,  NA,  NA, 4.42308E-01, 3.19615E+01, 9.61538E-01,
5.23307E-01, 3.07692E-01, 8.09945E-01,    NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,
NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA, 5.50505E-01, 2.80152E+01, 7.12121E-01,
6.21212E-01, 1.00000E+00, 9.19192E-01,    NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,
NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA, 5.97015E-01, 2.88836E+01,
6.86567E-01, 4.17910E-01, 5.00000E-01, 5.67164E-01,    NA,  NA,  NA,  NA,  NA,  NA,  NA,
NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA, 5.39130E-01, 2.20609E+01,
9.00000E-01, 6.65217E-01, 9.23077E-01, 9.43478E-01,    NA,  NA,  NA,  NA,  NA,  NA,  NA,
NA,  NA,  NA,  NA,  NA), .Dim=c(4, 4, 6)), mx=c(5.32240E-01, 2.81176E+01, 8.15057E-01,
5.23307E-01, 6.82692E-01, 8.09945E-01))


# Initial values (includes initial values for meta-regressions, which are redundant)
# Inits 1
list(B=5.00000E-01,  d=c(        NA,  1.00000E+00,  1.00000E+00,  1.00000E+00,  1.00000E+00,
1.00000E+00),  sd=1.00000E+00,  mu.base=1.00000E+00,  mu2=c(1.40000E+00,  1.40000E+00,
1.40000E+00, 1.40000E+00))

# Inits 2
list(B=1.00000E-01, d=c(   NA, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01),
sd=5.00000E-01, mu.base=5.00000E-01, mu2=c(7.00000E-01, 7.00000E-01, 7.00000E-01, 7.00000E-
01))
```

Fixed effects model used for analyzing adverse events.

```
model{
        # Data type 2; r2 events in exposure E2
        # Poisson likelihood, log link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns2){                # LOOP THROUGH STUDIES
                mu2[i] ~ dnorm(0,.0001)         # vague priors for all trial baselines
                for (k in 1:na2[i]) {           # LOOP THROUGH ARMS
                        r2[i,k] ~ dpois(theta2[i,k])   # Poisson likelihood
                        theta2[i,k] <- lambda[i,k]*E2[i,k] # failure rate * exposure
                        # model for linear predictor
                        log(lambda[i,k]) <- mu2[i] + d[t2[i,k]] - d[t2[i,1]]
                        #Deviance contribution
                        dev2[i,k] <- 2*((theta2[i,k]-r2[i,k]) + r2[i,k]*log(r2[i,k]/theta2[i,k]))
                        }
                        #  summed residual deviance contribution for this trial
                        resdev2[i] <- sum(dev2[i,1:na2[i]])
                }
        totresdev2 <- sum(resdev2[])          #Total Residual Deviance
```

```
        # Data type 4; number of patients r4 out of n4 with >=1 event in time4
        # Binomial likelihood, cloglog link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns4){                    # LOOP THROUGH STUDIES
            mu4[i] ~ dnorm(0,.0001)         # vague priors for all trial baselines
            for (k in 1:na4[i]) {           # LOOP THROUGH ARMS
                r4[i,k] ~ dbin(p[i,k],n4[i,k]) # Binomial likelihood
                # model for linear predictor
                cloglog(p[i,k]) <- log(time4[i,k]) + mu4[i] + d[t4[i,k]] - d[t4[i,1]]
                rhat[i,k] <- p[i,k] * n4[i,k]        # expected value of the numerators
                #Deviance contribution
                dev4[i,k] <- 2 * (r4[i,k] * (log(r4[i,k])-log(rhat[i,k]))
            +  (n4[i,k]-r4[i,k]) * (log(n4[i,k]-r4[i,k]) - log(n4[i,k]-rhat[i,k])))        }
                #  summed residual deviance contribution for this trial
                resdev4[i] <- sum(dev4[i,1:na4[i]])
            }
        totresdev4 <- sum(resdev4[])           #Total Residual Deviance
totresdev<-totresdev2+totresdev4+0
        # Treatment effect model is shared between the three likelihoods
        d[1]<-0      # treatment effect is zero for control arm
        # vague priors for treatment effects
        for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
        for(k in 1:nt)
        {
            # Bayesian one-sided p-values
            # Probability that treatment j has higher hazard than treatment k
            # step(x) is 1 if x>=0
            for (j in 1:nt){ pval[j,k] <- step(d[j]-d[k]) }
        }
}

# Data in BUGS format (some data is redundant)
list(ns5=0.00000E+00, ns1=0.00000E+00, E2= structure(.Data= c(3.92308E+00, 8.07692E+00,
2.40000E+01, 2.40000E+01, 1.44000E+02, 1.45000E+02), .Dim=c(3, 2)), t2= structure(.Data=
c(1.00000E+00, 3.00000E+00, 1.00000E+00, 2.00000E+00, 1.00000E+00, 4.00000E+00), .Dim=c(3,
2)), r2= structure(.Data= c(9.00000E+00, 3.20000E+01, 3.60000E+01, 3.90000E+01, 1.19000E+02,
1.27000E+02), .Dim=c(3, 2)), time4= structure(.Data= c(1.00000E+00, 1.00000E+00, 1.00000E+00,
9.23077E-01, 9.23077E-01,    NA), .Dim=c(2, 3)), n4= structure(.Data= c(6.20000E+01, 6.60000E+01,
6.40000E+01, 7.80000E+01, 1.52000E+02,    NA), .Dim=c(2, 3)), t4= structure(.Data= c(1.00000E+00,
5.00000E+00, 7.00000E+00, 1.00000E+00, 6.00000E+00,    NA), .Dim=c(2, 3)), r4= structure(.Data=
c(5.50000E+01, 5.70000E+01, 5.60000E+01, 7.75000E+01, 1.48460E+02,    NA), .Dim=c(2, 3)),
ns2=3.00000E+00,    ns4=2.00000E+00,    na2=c(2.00000E+00,    2.00000E+00,    2.00000E+00),
na4=c(3.00000E+00, 2.00000E+00), nt=7.00000E+00, x= structure(.Data= c(    NA,    NA,    NA,    NA,
NA,    NA, 4.42308E-01, 3.19615E+01, 9.61538E-01, 5.31449E-01, 3.07692E-01, 8.45348E-01,
5.50505E-01, 2.80152E+01, 7.12121E-01, 6.21212E-01, 1.00000E+00, 9.19192E-01,    NA,    NA,
NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA, 5.97015E-01, 2.88836E+01,
6.86567E-01, 4.17910E-01, 5.00000E-01, 5.67164E-01, 5.39130E-01, 2.20609E+01, 9.00000E-01,
6.65217E-01, 9.23077E-01, 9.43478E-01,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,
NA,    NA,    NA, 5.53633E-01, 2.89983E+01, 8.47751E-01, 5.64014E-01, 1.00000E+00, 9.51557E-
01,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA), .Dim=c(3, 4,
6)), mx=c(5.36518E-01, 2.82643E+01, 8.21596E-01, 5.31449E-01, 7.46154E-01, 8.45348E-01),
r2.base=c(9.00000E+00, 3.60000E+01, 1.19000E+02), E2.base=c(3.92308E+00, 2.40000E+01,
1.44000E+02), r4.base=c(5.50000E+01, 7.75000E+01), time4.base=c(1.00000E+00, 9.23077E-01),
n4.base=c(6.20000E+01, 7.80000E+01), ns2.base=3.00000E+00, ns4.base=2.00000E+00)


# Initial values (includes initial values for meta-regressions, which are redundant)
# Inits 1
```

```
list(B=5.00000E-01, d=c( NA, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00,
1.00000E+00, 1.00000E+00), sd=1.00000E+00, mu.base=1.00000E+00, mu2=c(1.40000E+00,
1.40000E+00, 1.40000E+00), mu4=c(5.00000E-01, 5.00000E-01))

# Inits 2
list(B=1.00000E-01, d=c( NA, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01,
5.00000E-01), sd=5.00000E-01, mu.base=5.00000E-01, mu2=c(7.00000E-01, 7.00000E-01,
7.00000E-01), mu4=c(2.50000E-01, 2.50000E-01))
```

Fixed effects model used for analyzing serious adverse events.

```
model{
        # Data type 2; r2 events in exposure E2
        # Poisson likelihood, log link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns2){                # LOOP THROUGH STUDIES
                mu2[i] ~ dnorm(0,.0001)         # vague priors for all trial baselines
                for (k in 1:na2[i]) {           # LOOP THROUGH ARMS
                        r2[i,k] ~ dpois(theta2[i,k])   # Poisson likelihood
                        theta2[i,k] <- lambda[i,k]*E2[i,k] # failure rate * exposure
                        # model for linear predictor
                        log(lambda[i,k]) <- mu2[i] + d[t2[i,k]] - d[t2[i,1]]
                        #Deviance contribution
                        dev2[i,k] <- 2*((theta2[i,k]-r2[i,k]) + r2[i,k]*log(r2[i,k]/theta2[i,k]))
                        }
                        #  summed residual deviance contribution for this trial
                        resdev2[i] <- sum(dev2[i,1:na2[i]])
                }
        totresdev2 <- sum(resdev2[])          #Total Residual Deviance

        # Data type 4; number of patients r4 out of n4 with >=1 event in time4
        # Binomial likelihood, cloglog link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns4){                # LOOP THROUGH STUDIES
                mu4[i] ~ dnorm(0,.0001)         # vague priors for all trial baselines
                for (k in 1:na4[i]) {           # LOOP THROUGH ARMS
                        r4[i,k] ~ dbin(p[i,k],n4[i,k]) # Binomial likelihood
                        # model for linear predictor
                        cloglog(p[i,k]) <- log(time4[i,k]) + mu4[i] + d[t4[i,k]] - d[t4[i,1]]
                        rhat[i,k] <- p[i,k] * n4[i,k]        # expected value of the numerators
                        #Deviance contribution
                        dev4[i,k] <- 2 * (r4[i,k] * (log(r4[i,k])-log(rhat[i,k]))
                +  (n4[i,k]-r4[i,k]) * (log(n4[i,k]-r4[i,k]) - log(n4[i,k]-rhat[i,k])))     }
                        #  summed residual deviance contribution for this trial
                        resdev4[i] <- sum(dev4[i,1:na4[i]])
                }
        totresdev4 <- sum(resdev4[])          #Total Residual Deviance
totresdev<-totresdev2+totresdev4+0
        # Treatment effect model is shared between the three likelihoods
        d[1]<-0      # treatment effect is zero for control arm
        # vague priors for treatment effects
        for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
        for(k in 1:nt)
        {
                # Bayesian one-sided p-values
                # Probability that treatment j has higher hazard than treatment k
                # step(x) is 1 if x>=0
                for (j in 1:nt){ pval[j,k] <- step(d[j]-d[k]) }
        }
}
```

 # Data in BUGS format (some data is redundant)
list(ns5=0.00000E+00, ns1=0.00000E+00, E2= structure(.Data= c(2.40000E+01, 2.40000E+01, NA, 1.56164E+00, 3.36986E+00, NA, 6.92308E+00, 6.92308E+00, 6.00000E+00), .Dim=c(3, 3)), t2= structure(.Data= c(1.00000E+00, 2.00000E+00, NA, 1.00000E+00, 3.00000E+00, NA, 1.00000E+00, 4.00000E+00, 5.00000E+00), .Dim=c(3, 3)), r2= structure(.Data= c(2.00000E+00, 8.00000E+00, NA, 4.00000E+00, 8.00000E+00, NA, 6.00000E+00, 5.00000E+00, 6.00000E+00), .Dim=c(3, 3)), time4= structure(.Data= c(1.00000E+00, 1.00000E+00, 1.00000E+00, 9.23077E-01, 9.23077E-01, NA), .Dim=c(2, 3)), n4= structure(.Data= c(6.20000E+01, 6.60000E+01, 6.40000E+01, 7.80000E+01, 1.52000E+02, NA), .Dim=c(2, 3)), t4= structure(.Data= c(1.00000E+00, 6.00000E+00, 8.00000E+00, 1.00000E+00, 7.00000E+00, NA), .Dim=c(2, 3)), r4= structure(.Data= c(1.70000E+01, 1.70000E+01, 2.10000E+01, 6.79380E+01, 1.18864E+02, NA), .Dim=c(2, 3)), ns2=3.00000E+00, ns4=2.00000E+00, na2=c(2.00000E+00, 2.00000E+00, 3.00000E+00), na4=c(3.00000E+00, 2.00000E+00), nt=8.00000E+00, x= structure(.Data= c(NA, NA, NA, NA, NA, NA, 5.97015E-01, 2.88836E+01, 6.86567E-01, 4.17910E-01, 5.00000E-01, 5.67164E-01, 5.50505E-01, 2.80152E+01, 7.12121E-01, 6.21212E-01, 1.00000E+00, 9.19192E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 4.83871E-01, 3.24258E+01, 5.96774E-01, 5.23307E-01, 6.45161E-02, 7.39642E-01, 5.39130E-01, 2.20609E+01, 9.00000E-01, 6.65217E-01, 9.23077E-01, 9.43478E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 5.40230E-01, 2.22448E+01, 7.23866E-01, 5.23307E-01, 2.30769E-01, 5.28736E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA), .Dim=c(3, 4, 6)), mx=c(5.42150E-01, 2.72162E+01, 7.23866E-01, 5.23307E-01, 5.43672E-01, 7.39642E-01), r2.base=c(2.00000E+00, 4.00000E+00, 6.00000E+00), E2.base=c(2.40000E+01, 1.56164E+00, 6.92308E+00), r4.base=c(1.70000E+01, 6.79380E+01), time4.base=c(1.00000E+00, 9.23077E-01), n4.base=c(6.20000E+01, 7.80000E+01), ns2.base=3.00000E+00, ns4.base=2.00000E+00)

 # Initial values (includes initial values for meta-regressions, which are redundant)
 # Inits 1
list(B=5.00000E-01, d=c(NA, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00), sd=1.00000E+00, mu.base=1.00000E+00, mu2=c(1.40000E+00, 1.40000E+00, 1.40000E+00), mu4=c(5.00000E-01, 5.00000E-01))

 # Inits 2
list(B=1.00000E-01, d=c(NA, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01), sd=5.00000E-01, mu.base=5.00000E-01, mu2=c(7.00000E-01, 7.00000E-01, 7.00000E-01), mu4=c(2.50000E-01, 2.50000E-01))

B.4 Pairwise results of the NMA

Table 9 Hazard ratios comparing all treatments on crisis*

Placebo	1.83 (1.45, 2.31)	3.48 (1.06, 13.60)	1.22 (1.06, 1.40)	1.49 (1.19, 1.85)	0.84 (0.64, 1.12)	1.03 (0.28, 3.88)	0.88 (0.33, 2.15)	0.97 (0.26, 3.49)	1.48 (0.55, 3.90)
0.55 (0.43, 0.69)	High-Dose Crizanlizumab	1.91 (0.57, 7.58)	0.67 (0.51, 0.88)	0.81 (0.63, 1.05)	0.46 (0.32, 0.67)	0.57 (0.15, 2.17)	0.48 (0.18, 1.21)	0.53 (0.14, 1.95)	0.81 (0.29, 2.18)
0.29 (0.07, 0.95)	0.52 (0.13, 1.76)	High-Dose NAC	0.35 (0.09, 1.16)	0.43 (0.11, 1.42)	0.24 (0.06, 0.82)	0.30 (0.04, 1.77)	0.25 (0.07, 0.74)	0.27 (0.04, 1.65)	0.42 (0.11, 1.32)
0.82 (0.71, 0.95)	1.50 (1.14, 1.97)	2.85 (0.86, 11.31)	L-glutamine	1.22 (0.94, 1.59)	0.69 (0.50, 0.95)	0.85 (0.23, 3.22)	0.72 (0.27, 1.79)	0.80 (0.21, 2.90)	1.21 (0.44, 3.22)
0.67 (0.54, 0.84)	1.23 (0.96, 1.59)	2.34 (0.70, 9.28)	0.82 (0.63, 1.07)	Low-Dose Crizanlizumab	0.57 (0.40, 0.81)	0.70 (0.18, 2.65)	0.59 (0.22, 1.48)	0.65 (0.17, 2.39)	1.00 (0.36, 2.65)
1.18 (0.89, 1.57)	2.17 (1.50, 3.13)	4.12 (1.22, 16.55)	1.45 (1.05, 1.99)	1.76 (1.23, 2.53)	senicapoc	1.23 (0.32, 4.75)	1.04 (0.38, 2.63)	1.15 (0.30, 4.29)	1.75 (0.62, 4.75)
0.97 (0.26, 3.63)	1.77 (0.46, 6.74)	3.39 (0.57, 22.44)	1.18 (0.31, 4.43)	1.44 (0.38, 5.47)	0.82 (0.21, 3.15)	High-Dose Senicapoc	0.84 (0.17, 4.19)	0.93 (0.25, 3.47)	1.42 (0.27, 7.25)

1.14 (0.46, 3.00)	2.09 (0.82, 5.65)	3.97 (1.36, 15.03)	1.39 (0.56, 3.68)	1.70 (0.68, 4.58)	0.97 (0.38, 2.62)	1.19 (0.24, 6.02)	Low-Dose NAC	1.11 (0.22, 5.61)	1.70 (0.71, 4.16)
1.03 (0.29, 3.88)	1.89 (0.51, 7.20)	3.65 (0.61, 23.66)	1.26 (0.34, 4.76)	1.54 (0.42, 5.86)	0.87 (0.23, 3.38)	1.08 (0.29, 3.97)	0.90 (0.18, 4.46)	Low-Dose Senicapoc	1.53 (0.30, 7.79)
0.68 (0.26, 1.83)	1.23 (0.46, 3.46)	2.36 (0.76, 8.95)	0.82 (0.31, 2.26)	1.00 (0.38, 2.80)	0.57 (0.21, 1.61)	0.70 (0.14, 3.67)	0.59 (0.24, 1.41)	0.65 (0.13, 3.35)	Mid-Dose NAC

***** Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Table 10 Hazard ratios comparing all treatments on all-cause hospitalization days*

Placebo	1.72 (1.48, 2.00)	3.57 (1.85, 7.95)	2.97 (1.44, 6.35)	1.53 (1.12, 2.09)	1.00 (0.88, 1.14)
0.58 (0.50, 0.68)	High-Dose Crizanlizumab	2.08 (1.06, 4.66)	1.73 (0.82, 3.76)	0.89 (0.63, 1.26)	0.58 (0.50, 0.68)
0.28 (0.13, 0.54)	0.48 (0.21, 0.95)	Low-Dose NAC	0.83 (0.28, 2.28)	0.43 (0.18, 0.89)	0.28 (0.12, 0.55)
0.34 (0.16, 0.70)	0.58 (0.27, 1.22)	1.21 (0.44, 3.52)	L-glutamine	0.51 (0.23, 1.13)	0.34 (0.16, 0.71)

0.66 (0.48, 0.90)	1.13 (0.80, 1.58)	2.35 (1.13, 5.47)	1.95 (0.89, 4.41)	Mometasome	0.66 (0.47, 0.92)
1.00 (0.88, 1.14)	1.72 (1.48, 2.00)	3.57 (1.82, 8.03)	2.97 (1.42, 6.45)	1.52 (1.09, 2.14)	Low-Dose Crizanlizumab

***** Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Table 11 Hazard ratios comparing all treatments on adverse events*

Placebo	0.92 (0.59, 1.46)	0.57 (0.25, 1.13)	0.94 (0.74, 1.21)	1.09 (0.70, 1.70)	1.42 (0.79, 2.97)	1.05 (0.67, 1.64)
1.08 (0.69, 1.71)	Low-Dose NAC	0.61 (0.25, 1.42)	1.02 (0.61, 1.72)	1.19 (0.62, 2.24)	1.56 (0.74, 3.66)	1.14 (0.60, 2.17)
1.77 (0.88, 4.01)	1.64 (0.70, 4.08)	Mometasome	1.67 (0.80, 3.86)	1.95 (0.84, 4.83)	2.55 (1.02, 7.58)	1.86 (0.80, 4.59)
1.06 (0.82, 1.36)	0.98 (0.58, 1.65)	0.60 (0.26, 1.25)	Senicapoc	1.16 (0.69, 1.91)	1.51 (0.80, 3.30)	1.11 (0.67, 1.86)
0.91 (0.59, 1.43)	0.84 (0.45, 1.60)	0.51 (0.21, 1.19)	0.86 (0.52, 1.44)	High-Dose Crizanlizumab	1.31 (0.62, 3.08)	0.96 (0.61, 1.48)
0.70 (0.34, 1.26)	0.64 (0.27, 1.36)	0.39 (0.13, 0.98)	0.66 (0.30, 1.25)	0.76 (0.32, 1.60)	L-glutamine	0.73 (0.31, 1.53)
0.95 (0.61, 1.50)	0.88 (0.46, 1.68)	0.54 (0.22, 1.25)	0.90 (0.54, 1.50)	1.04 (0.67, 1.63)	1.37 (0.65, 3.21)	Low-Dose Crizanlizumab

***** *Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.*

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Table 12 Hazard ratios comparing all treatments on serious adverse events*

Placebo	0.22 (0.03, 0.92)	1.04 (0.27, 3.36)	1.22 (0.35, 4.39)	0.88 (0.27, 2.85)	1.08 (0.54, 2.14)	1.34 (0.95, 1.89)	0.80 (0.42, 1.53)
4.50 (1.08, 37.94)	Low-Dose NAC	4.67 (0.68, 50.13)	5.70 (0.81, 63.02)	4.05 (0.59, 43.70)	4.92 (1.00, 42.52)	6.05 (1.40, 50.86)	3.66 (0.75, 31.45)
0.96 (0.30, 3.64)	0.21 (0.02, 1.48)	Prasugrel	1.19 (0.22, 7.18)	0.85 (0.16, 4.95)	1.04 (0.27, 4.55)	1.30 (0.38, 5.12)	0.78 (0.20, 3.32)
0.82 (0.23, 2.82)	0.18 (0.02, 1.24)	0.84 (0.14, 4.63)	High-Dose Ticagrelor	0.72 (0.20, 2.42)	0.87 (0.21, 3.69)	1.10 (0.29, 3.97)	0.65 (0.16, 2.66)
1.14 (0.35, 3.75)	0.25 (0.02, 1.69)	1.18 (0.20, 6.24)	1.40 (0.41, 5.00)	Low-Dose Ticagrelor	1.23 (0.32, 4.86)	1.53 (0.45, 5.28)	0.92 (0.24, 3.52)
0.93 (0.47, 1.87)	0.20 (0.02, 1.00)	0.96 (0.22, 3.74)	1.14 (0.27, 4.81)	0.81 (0.21, 3.17)	High-Dose Crizanlizumab	1.24 (0.58, 2.70)	0.75 (0.39, 1.43)

0.74 (0.53, 1.05)	0.17 (0.02, 0.71)	0.77 (0.20, 2.64)	0.91 (0.25, 3.41)	0.65 (0.19, 2.22)	0.80 (0.37, 1.72)	L-glutamine	0.60 (0.29, 1.24)
1.24 (0.65, 2.40)	0.27 (0.03, 1.33)	1.29 (0.30, 4.95)	1.54 (0.38, 6.35)	1.09 (0.28, 4.20)	1.34 (0.70, 2.58)	1.67 (0.81, 3.47)	Low-Dose Crizanlizumab

* Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Table 13 Hazard ratios comparing all treatments on crisis using >18 year old subgroup results from Niihara 2018*

Placebo	1.83 (1.44, 2.32)	3.49 (1.09, 13.48)	1.56 (1.11, 2.19)	1.48 (1.19, 1.86)	0.85 (0.64, 1.12)	1.02 (0.28, 3.75)	0.88 (0.34, 2.10)	0.97 (0.26, 3.52)	1.47 (0.55, 3.90)
0.55 (0.43, 0.69)	High-Dose Crizanlizumab	1.91 (0.58, 7.46)	0.86 (0.57, 1.29)	0.81 (0.63, 1.05)	0.46 (0.32, 0.67)	0.56 (0.15, 2.10)	0.48 (0.18, 1.18)	0.53 (0.14, 1.96)	0.81 (0.29, 2.20)
0.29 (0.07, 0.92)	0.52 (0.13, 1.72)	High-Dose NAC	0.45 (0.11, 1.52)	0.43 (0.11, 1.40)	0.24 (0.06, 0.81)	0.29 (0.04, 1.66)	0.25 (0.07, 0.74)	0.27 (0.04, 1.60)	0.42 (0.11, 1.32)
0.64 (0.46, 0.90)	1.17 (0.77, 1.77)	2.24 (0.66, 8.93)	L-glutamine	0.95 (0.63, 1.43)	0.54 (0.35, 0.84)	0.65 (0.17, 2.51)	0.56 (0.20, 1.43)	0.62 (0.16, 2.35)	0.94 (0.33, 2.66)

0.67 (0.54, 0.84)	1.23 (0.96, 1.59)	2.35 (0.71, 9.19)	1.05 (0.70, 1.58)	Low-Dose Crizanlizumab	0.57 (0.40, 0.81)	0.69 (0.18, 2.57)	0.59 (0.22, 1.45)	0.65 (0.17, 2.43)	0.99 (0.37, 2.69)
1.18 (0.89, 1.57)	2.16 (1.50, 3.12)	4.14 (1.23, 16.30)	1.85 (1.19, 2.88)	1.76 (1.23, 2.51)	Senicapoc	1.21 (0.32, 4.58)	1.04 (0.38, 2.60)	1.14 (0.30, 4.29)	1.75 (0.62, 4.79)
0.98 (0.27, 3.61)	1.79 (0.48, 6.83)	3.45 (0.60, 22.24)	1.53 (0.40, 5.91)	1.45 (0.39, 5.48)	0.82 (0.22, 3.14)	High-Dose Senicapoc	0.86 (0.18, 4.13)	0.94 (0.25, 3.47)	1.43 (0.28, 7.35)
1.13 (0.48, 2.94)	2.08 (0.85, 5.48)	3.98 (1.35, 14.62)	1.77 (0.70, 4.89)	1.68 (0.69, 4.45)	0.96 (0.38, 2.61)	1.17 (0.24, 5.71)	Low-Dose NAC	1.10 (0.23, 5.49)	1.68 (0.72, 4.17)
1.04 (0.28, 3.84)	1.89 (0.51, 7.17)	3.66 (0.63, 23.10)	1.63 (0.43, 6.32)	1.54 (0.41, 5.82)	0.88 (0.23, 3.39)	1.07 (0.29, 3.93)	0.91 (0.18, 4.36)	Low-Dose Senicapoc	1.53 (0.30, 7.76)
0.68 (0.26, 1.81)	1.24 (0.46, 3.41)	2.36 (0.76, 9.08)	1.06 (0.38, 3.00)	1.01 (0.37, 2.73)	0.57 (0.21, 1.60)	0.70 (0.14, 3.53)	0.60 (0.24, 1.39)	0.65 (0.13, 3.31)	Mid-Dose NAC

***** Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

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Appendix D. PRISMA Checklist

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**Page 1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**Page 2 (but used 'objectives' rather than 'background' to align with BMJ Open style guide.**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	**Page 3**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**Page 4 (Table 1)**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Appendix D and E.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as	**Page 4 &5(Table 1&2)**

		criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**Page 4**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Page 4 and Appendix A, D, and E**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**Page 4&5**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**Page 4 (Table 1, appendix)**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**Page 4 (Table 1)**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***Page 5***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**Page 4**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**Page 4&5**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	**Page 5 and Appendix B**
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Page 5 and Appendix B

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**Page 4**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	**Page 5, and appendix B**
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 5 (Figure 1)
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Figure 2**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**Page 6**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2, Appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Page 6 and Appendix A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**Table 2**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	**Figure 3 and appendix**

Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	***Page 7 (no independent loops of evidence on which to test for inconsistency)***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Appendix A
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses*, and so forth).	***Page 6, 9, and Appendix B***
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Page 7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	Page 8 and 9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***Page 10***

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Box. Terminology: Reviews With Networks of Multiple Treatments

Different terms have been used to identify systematic reviews that incorporate a network of multiple treatment comparisons. A brief overview of common terms follows.

Indirect treatment comparison: Comparison of 2 interventions for which studies against a common comparator, such as placebo or a standard treatment, are available (i.e., indirect information). The direct treatment effects of each intervention against the common comparator (i.e., treatment effects from a comparison of interventions made within a study) may be used to estimate an indirect treatment comparison between the 2 interventions (**Appendix Figure 1, A**). An indirect treatment comparison (ITC) may also involve multiple links. For example, in **Appendix Figure 1, B**, treatments B and D may be compared indirectly on the basis of studies encompassing comparisons of B versus C, A versus C, and A versus D.

Network meta-analysis or *mixed treatment comparison*: These terms, which are often used interchangeably, refer to situations involving the simultaneous comparison of 3 or more interventions. Any network of treatments consisting of strictly unclosed loops can be thought of as a series of ITCs (**Appendix Figure 1, A and B**). In mixed treatment comparisons, both direct and indirect information is available to inform the effect size estimates for at least some of the comparisons; visually, this is shown by closed loops in a network graph (**Appendix Figure 1, C**). Closed loops are not required to be present for every comparison under study. "Network meta-analysis" is

an inclusive term that incorporates the scenarios of both indirect and mixed treatment comparisons.

Network geometry evaluation: The description of characteristics of the network of interventions, which may include use of numerical summary statistics. This does not involve quantitative synthesis to compare treatments. This evaluation describes the current evidence available for the competing interventions to identify gaps and potential bias. Network geometry is described further in **Appendix Box 4**.

Appendix Box 1. The Assumption of Transitivity for Network Meta-Analysis

Methods for indirect treatment comparisons and network meta-analysis enable learning about the relative treatment effects of, for example, treatments A and B through use of studies where these interventions are compared against a common therapy, C.

When planning a network meta-analysis, it is important to assess patient and study characteristics across the studies that compare pairs of treatments. These characteristics are commonly referred to as *effect modifiers* and include traits such as average patient age, gender distribution, disease severity, and a wide range of other plausible features.

For network meta-analysis to produce valid results, it is important that the distribution of effect modifiers is similar, for example, across studies of A versus B and A versus C. This balance increases the plausibility of reliable findings from an indirect comparison of B versus C through the common comparator A. When this balance is present, the assumption of transitivity can be judged to hold.

Authors of network meta-analyses should present systematic (and even tabulated) information regarding patient and study characteristics whenever available. This information helps readers to empirically evaluate the validity of the assumption of transitivity by reviewing the distribution of potential effect modifiers across trials.

Appendix Box 2. Differences in Approach to Fitting Network Meta-Analyses

Network meta-analysis can be performed within either a frequentist or a Bayesian framework. Frequentist and Bayesian approaches to statistics differ in their definitions of probability. Thus far, the majority of published network meta-analyses have used a Bayesian approach.

Bayesian analyses return the posterior probability distribution of all the model parameters given the data and prior beliefs (e.g., from external information) about the values of the parameters. They fully encapsulate the uncertainty in the parameter of interest and thus can make direct probability statements about these parameters (e.g., the probability that one intervention is superior to another).

Frequentist analyses calculate the probability that the observed data would have occurred under their sampling distribution for hypothesized values of the parameters. This approach to parameter estimation is more indirect than the Bayesian approach.

Bayesian methods have been criticized for their perceived complexity and the potential for subjectivity to be introduced by choice of a prior distribution that may affect study findings. Others argue that explicit use of a prior distribution makes transparent how individuals can interpret the same data differently. Despite these challenges, Bayesian methods offer considerable flexibility for statistical modeling. In-depth introductions to Bayesian methods and discussion of these and other issues can be found elsewhere.

Appendix Box 3. Network Meta-Analysis and Assessment of Consistency

Network meta-analysis often involves the combination of direct and indirect evidence. In the simplest case, we wish to compare treatments A and B and have 2 sources of information: direct evidence via studies comparing A versus B, and indirect evidence via groups of studies comparing A and B with a common intervention, C. Together, this evidence forms a closed loop, ABC.

Direct and indirect evidence for a comparison of interventions should be combined only when their findings are similar in magnitude and interpretation. For example, for a comparison of mortality rates between A and B, an odds ratio determined from studies of A versus B should be similar to the odds ratio comparing A versus B estimated indirectly based on studies of A versus C and B versus C. This assumption of comparability of direct and indirect evidence is referred to as *consistency* of treatment effects.

When a treatment network contains a closed loop of interventions, it is possible to examine statistically whether there is agreement between the direct and indirect estimates of intervention effect.

Different methods to evaluate potential differences in relative treatment effects estimated by direct and indirect comparisons are grouped as *local approaches* and *global approaches.* Local approaches (e.g., the Bucher method or the node-splitting method) assess the presence of inconsistency for a particular pairwise comparison in the network, whereas global approaches (e.g., inconsistency models, I^2 measure for inconsistency) consider the potential for inconsistency in the network as a whole.

Tests for inconsistency can have limited power to detect a true difference between direct and indirect evidence. When multiple loops are being tested for inconsistency, one or a few may show inconsistency simply by chance. Further discussions of consistency and related concepts are available elsewhere.
Inconsistency in a treatment network can indicate lack of transitivity (see **Appendix Box 1**).

Appendix Box 4. Network Geometry and Considerations for Bias

The term *network geometry* is used to refer to the architecture of the treatment comparisons that have been made for the condition under study. This includes what treatments are involved in the comparisons in a network, in what abundance they are present, the respective numbers of patients randomly assigned to each treatment, and whether particular treatments and comparisons may have been preferred or avoided.

Networks may take on different shapes. Poorly connected networks depend extensively on indirect comparisons. Meta-analyses of such networks may be less reliable than those from networks where most treatments have been compared against each other.

Qualitative description of network geometry should be provided and accompanied by a network graph. Quantitative metrics assessing features of network geometry, such as *diversity* (related to the number of treatments assessed and the balance of evidence among them), *co-occurrence* (related to whether comparisons between certain treatments are more or less common), and *homophily* (related to the extent of comparisons between treatments in the same class versus competing classes), can also be mentioned.

Although common, established steps for reviewing network geometry do not yet exist, however examples of in-depth evaluations have been described related to treatments for tropical diseases and basal cell carcinoma and may be of interest to readers. An example based on 75 trials of treatments for pulmonary arterial hypertension (**Appendix Figure 3**) suggests that head-to-head studies of active therapies may prove useful to further strengthen confidence in interpretation of summary estimates of treatment comparisons.

Appendix Box 5. Probabilities and Rankings in Network Meta-Analysis

Systematic reviews incorporating network meta-analyses can provide information about the hierarchy of competing interventions in terms of treatment rankings.

The term *treatment ranking probabilities* refers to the probabilities estimated for each treatment in a network of achieving a particular placement in an ordering of treatment effects from best to worst. A network of 10 treatments provides a total of 100 ranking probabilities—that is, for each intervention, the chance of being ranked first, second, third, fourth, fifth, and so forth).

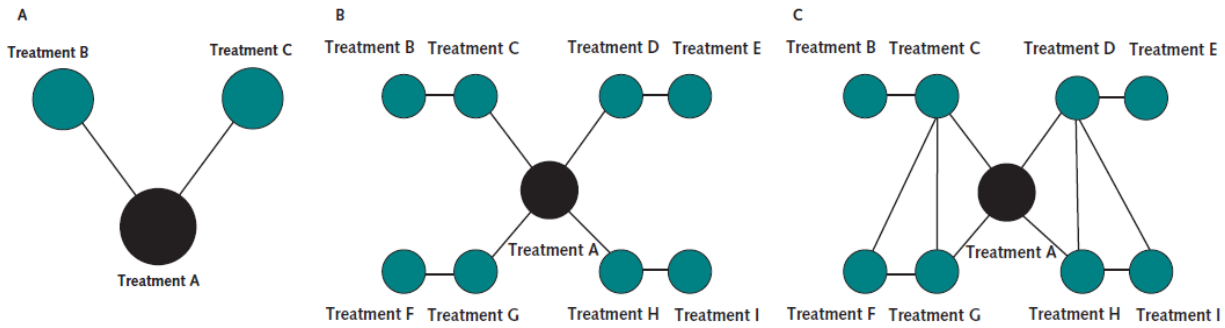
Several techniques are feasible to summarize relative rankings, and include graphical tools as well as different approaches for estimating ranking probabilities. **Appendix Figure 6** shows 2 approaches to presenting such information, on the basis of a comparison of adjuvant interventions for resected pancreatic adenocarcinoma.

Robust reporting of rankings also includes specifying median ranks with uncertainty intervals, cumulative probability curves, and the surface under the cumulative ranking (SUCRA) curve.

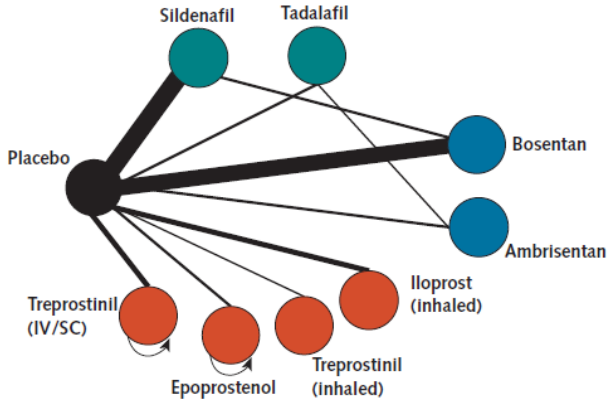
Rankings can be reported along with corresponding estimates of pairwise comparisons between interventions. Rankings should be reported with probability estimates to minimize misinterpretation from focusing too much on the most likely rank.

Rankings may exaggerate small differences in relative effects, especially if they are based on limited information. An objective assessment of the strength of information in the network and the magnitude of absolute benefits should accompany rankings to minimize potential biases.

Appendix Figure 1A-1C



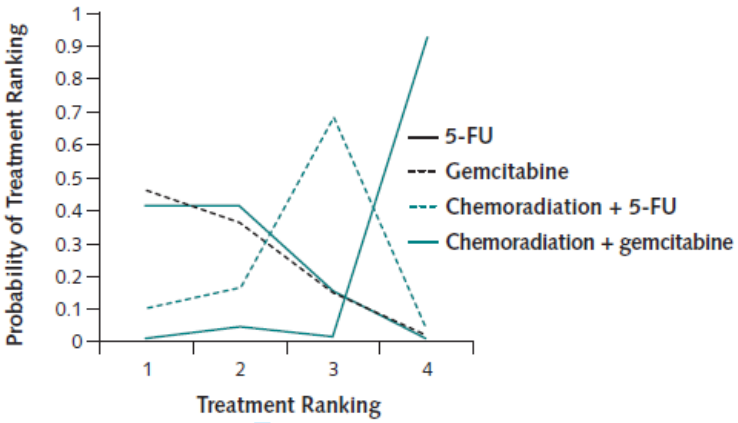
Appendix Figure 3



Appendix Figure 6

Ranking	Treatment and Cooresponding Ranking Probabilities Grade 3 or 4 Hematologic Toxicity			
	5-FU	Gemcitabine	Chemoradiation + 5-FU	Chemoradiation + gemcitabine
1	0.42	0.42	0.15	0.01
2	0.46	0.36	0.15	0.02
3	0.10	0.17	0.68	0.04
4	0.02	0.05	0.02	0.93

B



Appendix E Systematic review protocol main (non-transfusions)

Contents

Tables

Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
EMBASE	Excerpta Medica dataBASE
MEDLINE	Medical Literature Analysis and Retrieval System Online
PICOS	Population, Interventions, Comparisons, Outcomes, and Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RBC	Red blood cells
RCT	Randomized controlled trial
SCD	Sickle cell disease
SLR	Systematic literature review
VOC	Vaso-occlusive crisis

1 Introduction

Sickle cell disease (SCD) is a genetic blood disorder characterized by abnormality in the oxygen-carrying protein hemoglobin found in red blood cells (RBCs), depicted by RBCs having a rigid sickle-like shape.[1] Vaso-occlusive crises (VOCs) are the hallmark of SCD, with the disease being associated with serious complications, multi-organ failure, and an increased risk of death.[2] Quality of life is severely impaired for these patients due to recurrent chronic pain crises, regular use of analgesics, repeated hospitalization due to VOCs, and multiple organ failure.[3] The ability to modify the disease and prevent VOC episodes can decrease the risk of complications, organ damage, and the subsequent risk of death in SCD patients, as well as reduce health-resource utilization episodes.

There are limited treatment options are for SCD patients.[2] Hydroxyurea (HU) is the mainstay of treatment; however, majority of patients do not persist on HU, or will not take or cannot take HU, and among the HU-treated patients, some still continue to experience VOCs, fatal organ damage, and a shortened life span.[2] Novartis has developed crizanlizumab for the prevention of VOCs in SCD patients. In a recent randomized, double-blind, placebo-controlled Phase 2 trial, the safety and efficacy of crizanlizumab with or without hydroxyurea was assessed in SCD patients still experiencing ≥2VOCs/ year at time of enrollment.[2] Treatment with high-dose crizanlizumab resulted in a 45.3% reduction in annual rate of VOCs compared to placebo;[2] in addition, the median times to first and second VOC were 2-3 times as long for patients receiving crizanlizumab compared to those receiving placebo.[2]

2 Objective

The key parameters for the economic model relate to the treatment effects of the interventions used for the treatment of SCD. Treatment effects of the relevant alternative interventions of interest will be based on currently available published clinical trial evidence identified by means of a systematic literature review and synthesized with meta-analysis techniques. The current document defines the scope and process of the systematic literature review (SLR).

3 Methodology

3.1 Eligibility criteria

The SLR will focus on identifying clinical trials evaluating the treatment effects of relevant competing interventions for the treatment of SCD and will be an update of the recent review by Sins et al.[4] The scope will be expanded by incorporating recently published studies and including single arm trials when RCTs are not available for the relevant interventions of interest. Study eligibility criteria are defined in terms of the population, interventions, comparisons, outcomes, and study design (PICOS) outlined in **Table 1**, which will guide the identification and selection of studies considered relevant.

Table 1: Eligibility criteria

Criteria	Description
Population	*Inclusion criteria:* x Adult patients with sickle cell disease
Interventions	x Crizanlizumab x Hydroxyurea x Endari x Voxelotor (GBT440) x Any pharmacological interventions for preventing vaso-occlusive crisis (VOC)*
Comparators	x Placebo or best supportive care x Any of the listed interventions of interest x Any treatment that facilitates an anchored indirect comparison
Outcomes	x Any efficacy related outcome**
Study design	x RCTs x Single-arm trials when RCTs are not available for the interventions of interest
Language	x Only studies published in English

**We exclude interventions such as gene therapy, stem cell therapy and bone marrow transplantation, as these interventions aim to cure sickle cell disease in severe sickle cell disease patients*

***In addition to efficacy outcomes, adverse events are of interest for the review, but will not be used as study selection criteria.*

3.2 Study identification

Relevant studies will be identified by searching the following databases using predefined search strategies: Cochrane Central Register of Controlled Trials (CENTRAL); Medical Literature Analysis and Retrieval System Online (MEDLINE); and Excerpta Medica database (Embase). It should be noted that CENTRAL database does not contain any single-arm (uncontrolled) trials. Therefore, resources for identifying single-arm trials will be MEDLINE and Embase only. This search strategy is based on Sins et al.[4] and constructed

according to the criteria of interest (e.g. outcomes, population, intervention and study design) using MeSH or Emtree terms (thesaurus terms, headings and subheadings) and text words to retrieve potential references. Search strategies have been developed individually for CENTRAL, MEDLINE and Embase and are listed in Appendix A. Please note that the MEDLINE search strategy also aims to identify previously published SLRs and meta-analyses as an additional source to identify relevant primary studies of interest.

Considering the limited searches in Sins et al.[4] due to lack of a clinical trial registry search, a clinical trial registry search on ClinicalTrials.gov will be conducted to identify relevant primary studies of interest, especially unpublished and ongoing studies. This search is based on the search strategy of MEDLINE (**Appendix B**).

Sins et al.[4] completed their literature searches on 30th January 2017. Therefore, all searches on databases will be limited from the date 30th January 2017 onwards, except CENTRAL database. CENTRAL database lacks limit options by date and indexes for identifying date of reference created. Thus, the limit on CENTRAL database will be performed by restricting the publication year from 2017 onwards.

Although it is possible to restrict searches by language (English), it is highly advisable that the search strategy retains high sensitivity (the proportion of references for the desired topic that are retrieved), especially as the estimated number of recalls is small. Therefore, there is no restriction on language at the search stage.

3.3 Study selection

Two reviewers, working independently, will review all abstracts and proceedings identified by the search according to the selection criteria, with the exception of outcome criteria, which will only be applied during the screening of full-text publications. All studies identified as eligible studies during abstract screening will then be screened at a full-text stage by the same two reviewers. Reasons for exclusion will be recorded. The full-text studies identified at this stage will be included for the data extraction. Following reconciliation between the two investigators, a third reviewer will be included to reach consensus on any remaining discrepancies. The process of study identification and selection will be summarized with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.[5]

3.4 Data extraction

Two reviewers, working independently, will extract data on study characteristics, interventions, patient characteristics, and outcomes for the final list of included studies. Following reconciliation between the two reviewers, a third reviewer will be included to reach consensus on any remaining discrepancies. Data will be stored and managed in a Microsoft Excel workbook.

3.4.1 Study characteristics

The following study characteristics will be extracted:

- Study name
- Study year
- Study authors
- Study design
- Study inclusion criteria
- Study exclusion criteria
- Location of study (countries)
- Year of study initiation and study close
- Follow-up period
- Outcomes
- Patient flow
- Study- and analyses populations (e.g. ITT, mITT, etc.)

3.4.2 Intervention characteristics

The following intervention characteristics will be extracted:

- Treatment regimen
- Treatment dose
- Method of administration
- Frequency of administration
- Duration of treatment
- Concomitant/background therapies
- Compliance/Adherence

3.4.3 Patient characteristics

The following patient characteristics at baseline will be extracted:

- Age
- Gender
- Race and ethnicity
- Other relevant socio-demographics
- Concomitant hydroxycarbamide/hydroxyurea
- Fetal hemoglobin
- Genetic status (HbSS, HbSβo, HbSC, Hbsβ+, other)
- Painful crisis

- Hospital admission frequency
- Painful crisis including home crisis
- Transfusions
- Previous SCD related complications
- Acute chest syndrome
- Avascular osteonecrosis
- Stroke
- Other comorbidities

3.4.4 Outcomes

The following outcomes will be extracted:

- Number of VOCs
- Time to the first VOC
- Duration of VOCs
- % of patients with 0 VOCs/ year
- Number of SCD-related pain days
- Duration of SCD-related pain days
- Number of Hospital Admissions for VOC
- time to first hospital admission for a VOC
- Intensity of pain
- Serious complications
- Organ damage
- Survival
- Quality of life
- Adverse events

For each outcome of interest, the upper & Lower limits of scales along with definition will be reported. For dichotomous outcomes, the number of patients with the event and the number of patients in each treatment arm will be extracted. For continuous outcomes, the change from baseline in all intervention groups will be extracted. If the change from baseline is not provided, the score at end of follow-up and the baseline score will be extracted. For event rates, the number of events, the number of patients in each treatment arm and follow-up or exposure time will be extracted. For time-to-event outcomes, hazard ratios and associated information regarding uncertainty will be extraction. Kaplan Meir curves will be extracted in terms of the proportion of patients who had an event over time using DigitizeIt® in addition to the number of patients at risk over time.

3.4.5 Study quality

Two independent reviewers will assess study quality. Following reconciliation between the two investigators, a third investigator will be included to reach consensus on any remaining discrepancies.

The Cochrane Collaboration's Risk of Bias tool will be used to assess risk of bias in included RCTs (**Appendix C**).[6] This instrument is used to evaluate six key domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. The risk of bias instrument can be used to assign summary assessments of within-study bias, low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for one or more key domains), or high risk of bias (high risk of bias for one or more domains).

The Newcastle-Ottawa Scale will be used to assess the quality of single arm studies (**Appendix C**).[7] This instrument is used to evaluate the quality of observational studies based on 1) study group and selection, 2) comparability of the groups within studies, and 3) the ascertainment of either the exposure or outcomes of interest for case-control or cohort studies. Ranking of the study quality will be done by using a 'star system' in which a study can be given a maximum of one star for each numbered item within the "Selection" and "Exposure" categories and a maximum of two stars for "Comparability" category. Two independent reviewers will assess study quality. Following reconciliation between the two investigators, a third investigator will be included to reach consensus on any remaining discrepancies.

4 Discussion

This SLR will involve highly sensitive searches in the peer-reviewed literature as well as searches of recent conferences and clinical trial registrations to identify unpublished completed trials with results available. The review processes will be guided by the pre-defined eligibility criteria established in the review protocol. Data quality will be ensured through the involvement of two independent researchers in the study selection and data extraction phases of the project. The primary outcomes will include median time to the first VOC, median time to the second VOC, median rate of VOCs per year, and overall survival (OS), which reflect the primary outcomes as assessed in the Sins, et al. review as well as many clinical trials for this population. Results of the SLR will help to inform clinicians and decision makers and will provide the foundation to assess the feasibility of performing an NMA.

Despite the strengths of the proposed SLR, some limitations are applicable to all SLRs that should be acknowledged. While there is a clear justification to limit the search and selection to June 20, 2018 based on the scope to update the Sins review, there is always a risk select trials will not be identified that align with the selection criteria. Additionally, as the evidence base is continually growing, any trials published after the search date will not be captured. Further, any trials that are published close to the search date but are not yet indexed in the databases at the time of the search will not be captured by the search of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials. Hand searches of other published reviews may help overcome these potential limitations.

As always, the SLR is also limited by the use of published data. There is a risk of publication bias as some clinical trials fail to be published while others are published only in abstract form, which presents limited information. However, an extensive search of conference abstracts will be performed, which may mitigate the impact on the results of the SLR. Posters or slides corresponding to the conference abstracts will be identified where available; however, often conferences do not provide complete information. Moreover, conference results should be interpreted with caution, as they do not undergo the same peer review process as fully published results. Finally, the search and selection will be restricted to trials published in English. Therefore, there is a risk that non-English publications will not be identified.

Appendix A: Literature search strategies

Table 2: Search strategy for MEDLINE

#	Searches	Concept
1	exp pain/	Outcomes
2	(pain or painfull).tw.	
3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	
4	exp length of stay/	
5	(hospital adj3 (admission or stay)).tw.	
6	(patient adj3 (admission or stay)).tw.	
7	or/1-6	
8	anemia, sickle cell/	Population
9	hemoglobin, sickle/	
10	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	
11	or/8-10	
12	exp antisickling agents/	Interventions
13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or endari or voxelotor or GBT440).mp.	
14	(8 or 9 or 10) and prevent vaso-occlusiv*.tw.	
15	or/12-14	
16	7 and 11 and 15	
17	meta analysis.pt.	Systematic review and meta-analysis studies
18	((meta adj analys*) or metaanalys or meta-analys*).ti,ab,sh.	
19	(systematic adj5 (review or overview*)).ti,ab,sh.	
20	or/17-19	
21	16 and 20	
22	clinical trial/	RCTs
23	(clinic adj5 trial*).ti,ab,sh.	

24	single blind method/	
25	double blind method/	
26	random allocation/	
27	placebos/	
28	(placebo or random*).ti,ab,sh.	
29	randomized controlled trial/	
30	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	
31	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	
32	randomi?ed control trial*.tw.	
33	or/22-32	
34	16 and 33	
35	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	Single arm trials
36	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	
37	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	
38	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	
39	Clinical Trial, Phase I.pt.	
40	Clinical Trial, Phase II.pt.	
41	Clinical Trial, Phase III.pt.	
42	(registry or registries).ti,ab,kf,hw.	
43	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	
44	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	
45	(nonrandom* or non-random*).ti,ab,kf.	
46	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	
47	(all adj3 received).ab.	
48	or/35-47	
49	16 and 48	

50	limit 21 to ed=20170130-20180620	Date limit on rSLR and meta-analysis studies
51	limit 34 to ed=20170130-20180620	Date limit on RCTs
52	limit 49 to ed=20170130-20180620	Date limit on single arm trials

Table 3: Search strategy for EMBASE

#	Searches	
1	exp pain/	Outcomes
2	(pain or painfull).tw.	
3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	
4	exp "length of stay"/	
5	(hospital adj3 (admission or stay)).tw.	
6	(patient adj3 (admission or stay)).tw.	
7	or/1-6	
8	sickle cell anemia/	Population
9	hemoglobin S/	
10	(sickle cell or sickle h$emoglobin or drepanocyt* or drepanotic or drepanocytemia or h$emoglobin-s or Hb-S or sickle an$emia or meniscocytosis).mp.	
11	or/8-10	
12	antisickling agent/	Intervention
13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or endari or voxelotor or GBT440).mp.	
14	(8 or 9 or 10) and prevent vaso-occlusiv*.tw.	
15	or/12-14	
16	7 and 11 and 15	
17	randomized controlled trial/	RCTs

18	(RCT or randomi#ed or randomi#ation).ab,ti,kw,hw.	
19	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or subsitut* or treat*)).ab,kw.	
20	trial.ti.	
21	crossover procedure/	
22	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dumm*)).ti,ab,kw,hw.	
23	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	
24	or/17-23	
25	16 and 24	
26	prospective study/ or retrospective study/ or longitudinal study/ or cohort analysis/ or cross-sectional study/ or case control study/ or population based case control study/	Single-arm trials
27	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 study).ti,ab,kw.	
28	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	
29	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab,kw.	
30	(registry or registries).ti,ab,kw,hw.	
31	(nonrandom* or non-random*).ti,ab,kw.	
32	((control* adj2 before adj2 after) or CBA study).ti,ab,kw.	
33	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kw.	
34	(all adj3 received).ab.	
35	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 1 clinical trial/	
36	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kw.	
37	or/26-36	
38	16 and 37	
39	limit 25 to em=201705-201825	Date limit on RCTs
49	limit 38 to em=201705-201825	Date limit on single arm trials

Table 4: Search strategy for Cochrane Register of Controlled Trials

#	Searches	
#1	MeSH descriptor: [Pain] explode all trees	Outcomes
#2	(pain or painfull):ti,ab,kw	
#3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises):ti,ab,kw	
#4	MeSH descriptor: [Length of Stay] explode all trees	
#5	(hospital near/3 (admission or stay)):ti,ab,kw	
#6	(patient near/3 (admission or stay)):ti,ab,kw	
#7	#1 or #2 or #3 or #4 or #5 or #6	
#8	MeSH descriptor: [Anemia, Sickle Cell] this term only	Population
#9	MeSH descriptor: [Hemoglobin, Sickle] this term only	
#10	(sickle cell or sickle h*emoglobin or drepanocyt* or drepanotic or drepanocytemia or h*emoglobin-s or Hb-S or sickle an*emia or meniscocytosis):ti,ab,kw	
#11	#8 or #9 or #10	
#12	MeSH descriptor: [Antisickling Agents] explode all trees	Interventions
#13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or endari or voxelotor or GBT440):ti,ab,kw	
#14	(#8 or #9 or #10) and prevent vaso-occlusiv*	
#15	#11 or #12 or #13	
#16	#7 and #11 and #14	

Appendix B: ClinicalTrials.gov search

Table 6: Search strategy for ClinicalTrials.gov*

#	Searches	Search column
#1	Anemia, Sickle Cell OR Sickle Beta Thalassemia OR Sickle Cell Anemia OR Sickle Cell trait	Condition or disease
#2	SCD OR SCA OR Sickle	Other terms
#3	Drug OR Placebo OR Crizanlizumab OR Hydroxyurea OR Endari OR Voxelotor OR GBT440 OR hydroxycarbamide	Intervention/treatment
#4	pain OR hospitalisation OR hospitalization OR (hospital AND (admission OR stay)) OR crisis OR VOC OR ((vaso OR vein OR vena OR venous) AND (occlusive OR occlusive OR interruption OR obstruction)) OR survival OR quality of life	Outcome Measures
	#1 or #2 or #3 or #4	

*Advanced Search option without any restrictions except search strings listed.

Appendix C: Risk of bias and quality assessment

Table 5: Cochrane risk of bias assessment tool[6]

Domain	Support for judgment	5
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to the knowledge of the allocated interventions by participants and personnel during the study.
Detection bias		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to the knowledge of the allocated interventions by outcome assessors.
Attrition bias		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Table 6: Newcastle-Ottawa quality assessment scale cohort studies[7]

Domain	Response
Selection	
1. Representativeness of the exposed cohort	a. Truly representative of the average _____ (describe) in the community* b. Somewhat representative of the average _____ in the community* c. Selected group of users (e.g. nurses, volunteers) d. No description of the derivation of the cohort
2. Selection of the non-exposed cohort	a. Drawn from the same community as the exposed cohort* b. Drawn from a different source c. No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure	a. Secure record (e.g. surgical records)* b. Structured interview* c. Written self-report d. No description
4. Demonstration that outcome of interest was not present at start of study	a. Yes* b. No
Comparability	
1. Comparability of cohorts on the basis of the design or analysis	a. Study controls for _____ (select the most important factor)* b. Study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor)*
Outcomes	
1. Assessment of outcome	a. Independent blind assessment* b. Record linkage* c. Self-report d. No description
2. Was follow-up long enough for outcomes to occur	a. Yes (select an adequate follow up period for outcome of interest)* b. No
3. Adequacy of follow up of cohorts	a. Complete follow up - all subjects accounted for* b. Subjects lost to follow up unlikely to introduce bias - small number lost - >____% (select an adequate %) follow up, or description provided of those lost)* c. Follow up rate <____% (select an adequate %) and no description of those lost d. No statement

Note: A study can be awarded a maximum of one star for each numbered item within the selection and outcomes categories. A maximum of two stars can be given for comparability.

References

1. National Heart Lung and Blood Institute. Sickle Cell Disease. 2018; https://www.nhlbi.nih.gov/health-topics/sickle-cell-disease.
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3. McClish DK, Penberthy LT, Bovbjerg VE, et al. Health related quality of life in sickle cell patients: the PiSCES project. *Health Qual Life Outcomes.* 2005;3:50.
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7. Wells GS, O'Connell D, Peterson J, Welch V, Losos M. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed October 1, 2016.

Appendix F. Systematic literature review protocol for transfusions.

Search protocol

Objective

This search protocol aims to supplement new evidence on the treatment effects of transfusion used for preventing crises in sickle cell disease (SCD) patients in adults and adolescents for previous systematic literature review (led by Thomas Statistical Consultants). The search strategy and concept are modified from a recent systematic review by Sins et al.[1] and Fortin et al[2]. The strategy has been developed to fulfil updated eligibility criteria (Table 1) and retrieve single-arm trials.

Table 1. Eligibility criteria

Criteria	Description
Population	Trials that included SCD patients aged 16 and above
Interventions	x Red blood cell transfusions x Other types of transfusions
Comparators	x Placebo or best medical care x Interventions included in previous systematic review
Outcomes	x Pain, crisis and VOC (frequency, intensity and duration in one event) x Hospital admission, including emergency department (ED) and nurse visits x SCD complications, including acute chest syndromes x Analgesic use x Adverse events*
Study design	x Randomized controlled trials (RCTs) x Single-arm studies
Language	x Only studies published in English

*In addition to efficacy outcomes, adverse events are of interest for the review, but will not be used as study selection criteria

Resources

Electronic databases

Studies will be identified by searching the following electronic databases:

- x Cochrane Central Register of Controlled Trials (CENTRAL)
- x Medical Literature Analysis and Retrieval System Online (MEDLINE)
- x Excerpta Medica database (Embase)

Hand-searches

[1] Sins JWR, Mager DJ, Davis S, Biemond BJ, Fijnvandraat K: **Pharmacotherapeutical strategies in the prevention of acute, vaso-occlusive pain in sickle cell disease: a systematic review**. *Blood advances* 2017, **1**(19):1598-1616.

[2] 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, Issue 8. Art. No.: CD012082. DOI: 10.1002/14651858.CD012082.pub2.

- x ClinicalTrial.gov

Search strategy

Search strategies have been developed individually for CENTRAL, MEDLINE, Embase and ClinicalTrial.gov and their results are listed in Appendix 1-4. The concept of a search strategy is elaborated using MEDLINE as an example (Table 2). The search strategy was constructed according to the criteria (e.g. outcomes, population, intervention and study design) using MeSH or Emtree terms (thesaurus terms, headings and subheadings) and text words to retrieve potential references.

Table 2. Search strings and concepts

No	Searches	Results	
1	anemia, sickle cell/	19329	Population
2	hemoglobin, sickle/	3011	
3	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	27120	
4	1 or 2 or 3	27602	
5	Blood Transfusion/	48056	Intervention
6	Erythrocyte Transfusion/	8033	
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	90906	
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	47785	
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	35184	
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	26829	
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1217	
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	24060	
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	183648	
14	Blood Component Transfusion/	3477	
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	16726	

16	14 not 15	3229	
17	ERYTHROCYTES/	128578	
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	216650	
19	17 or 18	258199	
20	16 and 19	834	
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	13177	
22	(((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	3326	
23	13 or 20 or 21 or 22	188025	
24	exp pain/	362648	
25	(pain or painfull).tw.	547392	
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	66169	Outcome
27	exp length of stay/	77857	
28	(hospital adj3 (admission or stay)).tw.	104873	
29	(patient adj3 (admission or stay)).tw.	6507	
30	or/24-29	901074	
31	4 and 23 and 30	848	
32	clinical trial/	512148	
33	(clinic adj5 trial*).ti,ab,sh.	1010	
34	single blind method/	25632	
35	double blind method/	147368	
36	random allocation/	95709	
37	placebos/	34063	RCT filter
38	(placebo or random*).ti,ab,sh.	1263924	
39	randomized controlled trial/	467730	
40	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	786522	
41	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	145215	
42	randomi?ed control trial*.tw.	6481	
43	or/32-42	1565168	

44	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	2187051	Single-arm studies filter
45	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	1071161	
46	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	615678	
47	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	340559	
48	Clinical Trial, Phase I.pt.	18409	
49	Clinical Trial, Phase II.pt.	29604	
50	Clinical Trial, Phase III.pt.	14110	
51	(registry or registries).ti,ab,kf,hw.	139501	
52	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	53439	
53	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	114108	
54	(nonrandom* or non-random*).ti,ab,kf.	34084	
55	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	2644	
56	(all adj3 received).ab.	41192	
57	or/44-56	3114626	
58	31 and 43	120	
59	31 and 57	278	

Search results

The numbers of references retrieved by search strategies from three databases are listed below. The search date was from the earliest date to 29th Aug 2018 in all databases. In total, there were 1,631references retrieved.

CENTRAL

- Number of references related to controlled trials: 332

MEDLINE

- Number of references related to randomised controlled trials: 120
- Number of references related to single-arm studies: 279

Embase

- Number of references related to randomised controlled trials: 245
- Number of references related to single-arm studies: 599

ClinicalTrial.gov

- Number of references: 56

Deduplication

Duplicates were identified firstly by 'find duplicates' function in Endnote X8 and then double-checked manually by sorting author, title, volume and issue. After that, all references were de-duplicate against references retrieved from previous systematic review. This left 825 references from the electronic databases to be screened.

In terms of references from ClinicalTrial.gov, there were only 16 references left to be screened after deduplication.

In total, there are 841 references to go through during the title and abstract screening stage.

Appendix 1. Search strategy and results for CENTRAL database

Search Strategy:

#	Searches	Results
#1	MeSH descriptor: [Anemia, Sickle Cell] this term only	583
#2	MeSH descriptor: [Hemoglobin, Sickle] this term only	19
#3	(sickle cell or sickle h*emoglobin or drepanocyt* or drepanotic or drepanocytemia or h*emoglobin-s or Hb-S or sickle an*emia or meniscocytosis):ti,ab,kw	4790
#4	#1 or #2 or #3	4790
#5	MeSH descriptor: [Blood Transfusion] this term only	1766
#6	MeSH descriptor: [Erythrocyte Transfusion] explode all trees	564
#7	((blood or erythrocyte* or "red cell*" or "red blood cell*" or RBC*) near/5 (transfus* or infus* or unit*))	14775
#8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) near/5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program* or therapy)):ab	30189
#9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)):ti	3612
#10	("allogeneic blood" or (unit* near/2 blood) or "allogenic blood" or (blood near/2 exposure) or "donor blood" or "blood product*" or "blood component*" or "blood support")	3365
#11	hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*	107
#12	(red cell* or erythrocyte* or blood or RBC*) and transfus*:ti	2434
#13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	41927
#14	MeSH descriptor: [Blood Component Transfusion] this term only	115
#15	MeSH descriptor: [Erythrocytes] this term only	1478
#16	(red cell* or red blood cell* or erythrocyte* or RBC*)	12756
#17	#14 and (#15 or #16)	39
#18	#13 or #17	41927
#19	MeSH descriptor: [Pain] explode all trees	42323
#20	(pain or painfull):ti,ab,kw	124349

#21	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises):ti,ab,kw	4404
#22	MeSH descriptor: [Length of Stay] explode all trees	6488
#23	(hospital near/3 (admission or stay)):ti,ab,kw	20854
#24	(patient near/3 (admission or stay)):ti,ab,kw	1779
#25	#19 or #20 or #21 or #22 or #23 or #24	153780
#26	#4 and #18 and #25	332

Of 332 results:

- Cochrane reviews: 35
- Cochrane Protocol: 1
- Trials: 296
- Editorials: 0
- Special collections: 0
- Clinical Answers: 0

Appendix 2. Search strategy and results for MEDLINE

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to August 29, 2018
Search Strategy:

#	Searches	Results
1	anemia, sickle cell/	19329
2	hemoglobin, sickle/	3011
3	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	27120
4	1 or 2 or 3	27602
5	Blood Transfusion/	48056
6	Erythrocyte Transfusion/	8033
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	90906
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	47785
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	35184
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	26829
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1217
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	24060
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	183648
14	Blood Component Transfusion/	3477
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	16726
16	14 not 15	3229
17	ERYTHROCYTES/	128578
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	216650

19	17 or 18	258199
20	16 and 19	834
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	13177
22	(((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	3326
23	13 or 20 or 21 or 22	188025
24	exp pain/	362648
25	(pain or painfull).tw.	547392
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	66169
27	exp length of stay/	77857
28	(hospital adj3 (admission or stay)).tw.	104873
29	(patient adj3 (admission or stay)).tw.	6507
30	or/24-29	901074
31	4 and 23 and 30	848
32	clinical trial/	512148
33	(clinic adj5 trial*).ti,ab,sh.	1010
34	single blind method/	25632
35	double blind method/	147368
36	random allocation/	95709
37	placebos/	34063
38	(placebo or random*).ti,ab,sh.	1263924
39	randomized controlled trial/	467730
40	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	786522
41	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	145215
42	randomi?ed control trial*.tw.	6481
43	or/32-42	1565168
44	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	2187051
45	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	1071161

46	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	615678
47	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	340559
48	Clinical Trial, Phase I.pt.	18409
49	Clinical Trial, Phase II.pt.	29604
50	Clinical Trial, Phase III.pt.	14110
51	(registry or registries).ti,ab,kf,hw.	139501
52	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	53439
53	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	114108
54	(nonrandom* or non-random*).ti,ab,kf.	34084
55	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	2644
56	(all adj3 received).ab.	41192
57	or/44-56	3114626
58	31 and 43	120
59	31 and 57	278

Appendix 3. Search strategy and results for Embase database

Database(s): **Embase** 1974 to 2018 Week 35
Search Strategy:

#	Searches	Results
1	exp Anemia, Sickle Cell/	32009
2	(h?emoglobin s or h?emoglobin sc or h?emoglobin se or h?emoglobin ss or h?emoglobin c or h?emoglobin d or Hb s or Hb sc or Hb se or Hb ss or Hb c or Hb d or sc disease*).tw.	5794
3	(sickle cell or sicklemia or sickled or sickling or meniscocyt* or drepanocyt*).tw.	29569
4	1 or 2 or 3	38361
5	Blood Transfusion/	108332
6	Erythrocyte Transfusion/	23021
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	135137
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	77239
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	38387
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	43111
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1555
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	28985
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	273982
14	Blood Component Transfusion/	2629
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	19765
16	14 not 15	2279
17	ERYTHROCYTES/	112741
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	256379

19	17 or 18	278120
20	16 and 19	523
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	22304
22	(((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	4095
23	13 or 20 or 21 or 22	279695
24	exp pain/	1146280
25	(pain or painfull).tw.	789805
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	82887
27	exp length of stay/	150699
28	(hospital adj3 (admission or stay)).tw.	169748
29	(patient adj3 (admission or stay)).tw.	12514
30	or/24-29	1690290
31	4 and 23 and 30	2325
32	randomized controlled trial/	508600
33	(RCT or randomi#ed or randomi#ation).ab,ti,kw,hw.	1062285
34	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or subsitut* or treat*)).ab,kw.	560662
35	trial.ti.	248694
36	crossover procedure/	56042
37	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dumm*)).ti,ab,kw,hw.	276112
38	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	99658
39	or/32-38	1386841
40	prospective study/ or retrospective study/ or longitudinal study/ or cohort analysis/ or cross-sectional study/ or case control study/ or population based case control study/	1771952
41	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 study).ti,ab,kw.	1282224
42	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	790240
43	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab,kw.	500633

44	(registry or registries).ti,ab,kw,hw.	183687
45	(nonrandom* or non-random*).ti,ab,kw.	42777
46	((control* adj2 before adj2 after) or CBA study).ti,ab,kw.	3333
47	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kw.	80316
48	(all adj3 received).ab.	75969
49	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 1 clinical trial/	126474
50	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kw.	205403
51	or/40-50	3180246
52	31 and 39	245
53	31 and 51	599

Appendix 4. Search strategy and results for ClinicalTrial.gov

#	Searches	Search column
#1	Anemia, Sickle Cell OR Sickle Beta Thalassemia OR Sickle Cell Anemia OR Sickle Ce	Condition or disease
#2	SCD OR SCA OR Sickle	Other terms
#3	Transfusion OR blood OR RBC OR hemaOR it OR erythrocyte	Intervention/treatment
#4	pain OR hospitalisation OR hospitalization OR (hospital AND (admission OR stay)) OR OR VOC OR ((vaso OR vein OR vena OR venous) AND (occlusive OR occlusive OR interruption OR obstruction)) OR survival OR Quality of life	Outcome Measures
	#1 or #2 or #3 or #4	

*Advanced Search option without any restrictions except search strings listed.

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Crizanlizumab and comparators for adults with sickle-cell disease: a systematic review and network meta-analysis

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Title: Crizanlizumab and comparators for adults with sickle-cell disease: a systematic review and network meta-analysis

Running title: Crizanlizumab for adults with sickle-cell disease

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ABSTRACT

Objectives: Treatment options for preventing vaso-occlusive crises (VOC) among patients with sickle cell disease (SCD) are limited, especially if hydroxyurea treatment has failed or is contraindicated. A systematic literature review (SLR) and network meta-analysis (NMA) were conducted to evaluate the efficacy and safety of crizanlizumab for older adolescent and adult (≥16 years old) SCD patients.

Methods: The SLR included randomized controlled trials (RCT) and uncontrolled studies. Bayesian NMA of VOC, all-cause hospitalization days, and adverse events were conducted.

Results: The SLR identified 51 studies and 9 RCTs on 14 treatments that met the NMA inclusion criteria. The NMA found crizanlizumab 5.0 mg/kg was associated with a reduction in VOC (hazard ratio 0.55, 95% credible interval (0.43, 0.69); Bayesian probability of superiority >0.99), all-cause hospitalization days (0.58 (0.50, 0.68); >0.99), and no evidence of difference on adverse events (0.91 (0.59, 1.43); 0.66) or serious adverse events (0.93 (0.47, 1.87); 0.59) compared with placebo. The hazard ratio for reduction in VOC for crizanlizumab relative to L-glutamine was 0.67 (0.50, 0.88); >0.99). These results were sensitive to assumptions regarding whether patient age is an effect modifier.

Conclusions: This NMA provides preliminary evidence comparing the efficacy of crizanlizumab with other treatments for VOC prevention.

PATIENT AND PUBLIC INVOLVEMENT

- No patient or public involvement in this study.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This SLR was comprehensive in terms of outcomes and interventions and was focused on the target population of crizanlizumab.
- To include a diverse range of outcome summaries, a shared parameter Bayesian NMA was employed, as recommended by NICE.
- Risk of bias was assessed using the best practice Cochrane collaboration tool.
- It was not possible to adjust for differences in statistical analysis across RCTs.
- The strength of comparisons on outcomes other than vaso-occlusive crises (VOC) were weak, and VOC may not be the key outcome for patients.

INTRODUCTION

Sickle Cell Disease (SCD) affects approximately 100,000 people in the US.[1] The disease is caused by an autosomal-recessive single gene defect in the beta chain of hemoglobin (HbA), which results in sickle cell hemoglobin (HbS). Sickled cells break down prematurely, and are associated with varying degrees of anemia. Interactions of red blood cells, white blood cells, platelets and endothelial cells are an important contributor to the pathophysiology of sickle cell disease.[2-7] For instance, endothelial cells lining the vasculature are activated and have increased expression of adhesion molecules in SCD patients; this plays a central role in the development of vaso-occlusion.[3 8 9] Ultimately, obstruction of small blood capillaries cause painful crises, damage to major organs, and increased vulnerability to severe infections. Over the past several decades, life expectancy has improved, however, the disease continues to be associated with early mortality and high morbidity.[10] The aim of treatment is to aid disease and chronic pain management, reduce severity and/or prevent complications, and manage acute pain during crises.[11]

There is no widely available cure for SCD and few effective treatments. Hydroxyurea and L-glutamine (Endari), the only two FDA-approved drugs for SCD, are indicated for the prevention of vaso-occlusive crises (VOC).[12] In a two-year pediatric study, per patient health care costs for children on hydroxyurea were $9450, compared with $13716 for those who did not receive this treatment.[13] Despite the National Heart, Lung, and Blood Institute's (NHLBI) recommendations, hydroxyurea is not regularly prescribed and adherence to the therapy is poor.[14] Further, there are no current clinical guidelines outlining when to integrate L-glutamine into care. Regular blood transfusions can also be used as a preventive measure, but they may also lead to abnormally high levels of iron in the blood, which can cause long-term organ damage and reactions due to a mismatch between the donors and recipients.[14] Voxelotor has shown an ability to increase haemoglobin levels in patients with SCD[15] and in November 2019 was FDA-approved. [16]

Crizanlizumab is a new, FDA-approved[17] drug for the prevention of vaso-occlusive crises. A phase II multicenter, randomized, placebo-controlled, double-blind, 12-month study was completed to evaluate crizanlizumab 5.0 mg/kg and 2.5 mg/kg versus placebo.[18] This study found that the median rate of crises per year was 1.63 with crizanlizumab 5.0 mg/kg versus 2.98 with placebo (indicating a 45.3% lower rate with high-dose crizanlizumab 5.0 mg/kg, *P=0.01*). The median time to the first VOC was also significantly longer with high-dose crizanlizumab 5.0 mg/kg than with placebo (4.07 vs. 1.38 months, *P=0.001*), as was the median time to the second VOC (10.32 vs. 5.09 months, *P=0.02*). In addition, the median rate of uncomplicated crises per year was 1.08 with crizanlizumab 5.0 mg/kg, as compared with 2.91 with placebo (indicating a 62.9% lower rate with crizanlizumab 5.0 mg/kg, *P=0.02*).

The comparative efficacy and safety of crizanlizumab has been evaluated against placebo, however head-to-head randomized controlled trial (RCT) evidence is lacking for comparisons to treatments of interest. Network meta-analysis (NMA) is a statistical method that allows for the simultaneous evaluation of all treatments within a therapeutic area and allows for indirect comparisons between treatments where head-to-head evidence may not be available. Specifically, NMA can be used to combine direct and indirect evidence regarding any interventions that form a network of RCTs where each trial has at least one intervention (active or placebo) in common with another trial and all RCTs are sufficiently similar.[19 20] To minimize risk of bias, RCTs should be identified through a comprehensive systematic literature review (SLR) using pre-defined criteria.[21]

This study conducts a SLR and NMA to assess the comparative efficacy and safety of crizanlizumab against relevant competing interventions for older adolescent and adult (≥16 years old) patients with SCD.

METHODS

Systematic literature reviews

The SLR protocol was finalised on 25 June 2018 and the SLR was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22] A PRISMA NMA checklist can be found in Appendix A. The SLR approach updated and expanded an earlier published SLR by Sins et al.[23] by including non-controlled studies and included additional interventions. Inclusion and exclusion criteria for studies are summarised in Table 1 below. Relevant studies were identified by searching the following databases: Cochrane Central Register of Controlled Trials (CENTRAL); Medical Literature Analysis and Retrieval System Online (MEDLINE); and Excerpta Medica database (Embase). We also searched a trial registry, *ClinicalTrials.gov.* The search strategies were derived from Sins et al.[23] and can be found in Appendix B along with the complete search protocols in Appendices C and D. As blood transfusion was not included by Sins et al.,[23] we conducted a separate search for blood transfusion from inception of databases to 30th August 2018. For non-transfusion studies, the search date was from 1st January 2017 to 21st June 2018 to bridge the findings of Sins et al. [23]

Table 1: Study selection criteria to identify trials for the systematic literature review

Criteria	Description
Population	Studies included adult patients with sickle cell disease
Interventions	• Crizanlizumab • L-glutamine • Voxelotor (GBT440) • Red blood cell transfusions • Other types of transfusions • Any pharmacological interventions for preventing crisis, pain and/or vaso-occlusive crisis (VOC)
Comparators	• Placebo or best supportive care • Any of the listed interventions of interest • Any treatment that facilitates an anchored indirect comparison
Outcomes	Primary outcomes: • Pain, crisis and VOC (frequency, intensity and duration in one event) Secondary outcome: • Hospital admission, including emergency department (ED) and nurse visits • SCD complications, including acute chest syndromes (ACS) • Analgesic use • Adverse events*

Study design	• Randomized controlled trials (RCTs) • Single-arm trials when RCTs are not available for the interventions of interest
Language	English

**In addition to efficacy outcomes, adverse events are of interest for the review, but will not be used as study selection criteria.*

Results of searches were managed using Endnote and a Microsoft Excel spreadsheet. Two reviewers screened and selected records independently against inclusion and exclusion criteria using titles and abstracts. Full-texts of potential eligible records were retrieved and screened to assess the eligibility for data extraction. Disagreements were resolved by discussion and consensus. Following reconciliation between the two investigators, a third investigator was included to reach consensus for any remaining discrepancies. The Cochrane Collaboration's Risk of Bias tool was used to assess risk of bias in included RCTs. [24] The Newcastle-Ottawa Scale was used to assess the quality of non-controlled studies.[25]

The primary outcome of this review was sickle cell pain crisis (SCPC), also known as a VOC leading to a healthcare visit. A variety of definitions for VOC was observed in the included studies. We consulted several medical experts and chose the definition of VOC used in the pivotal Phase II RCT of crizanlizumab.[18] In this trial, a VOC was defined as an acute episode of pain, with no medically determined cause other than a vaso-occlusive event that resulted in a medical facility visit and treatment with oral or parenteral opioids or with a parenteral nonsteroidal anti-inflammatory drug. In addition to outcomes specifically named as VOC, the outcomes of pain crisis and Sickle Cell Disease Crisis (SCDC) were extracted and included with the VOC set if found to use a comparable definition.

Other outcomes identified as of interest and/or extracted included pain-related outcomes, acute chest syndrome (ACS), all-cause hospitalizations, transfusions, analgesic use, death, adverse events, and serious adverse events. In addition to study and intervention characteristics, the patient characteristics were extracted to qualitatively assess comparability of different study populations.

Network meta-analysis

This paper adopts the Bayesian statistical framework to conduct the NMA. This is different to the frequentist framework as the data, represented as a likelihood, are used to update a prior distribution on uncertain parameters to provide a posterior distribution[26]. Bayesian NMA is conducted using Markov Chain Monte Carlo (MCMC) estimation which is a technique to sample from the posterior distribution of a specified likelihood and prior. The Bayesian framework is recommended by NICE and published textbooks for NMA due to its flexibility and in this study it allows the synthesis of different data types, which would be difficult in the frequentist setting[27 28]. The key outputs of a Bayesian analysis are 95% credible intervals (CrI) and Bayesian probabilities. The 95% CrI is the 95th percentile of the MCMC samples from the posterior distribution and represents a region where there is 95% probability of containing the true value of some parameter, for example a hazard ratio. The Bayesian probability for a parameter is the proportion of the MCMC distribution that lies above or below a certain threshold; in this analysis the interest lies in Bayeisan probabilities of superiority which are the probability that the hazard ratios are greater than 1.

Quantitative synthesis through this Bayesian NMA approach was planned for reported or derived time-to-event outcomes of VOC, all-cause hospitalization days, adverse events, and serious adverse

events, in line with those reported by the Phase II RCT on crizanlizumab.[18] International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Society for Medical Decision (MDM), and UK National Institute for Health and Care Excellence (NICE) guidelines were followed in design of the NMA model.[27 29-31] As the pivotal study on crizanlizumab was conducted within an older adolescent and adult (≥16 years old) population, the NMA was conducted only on studies that included patients ≥16 years old with SCD. Whilst the pivotal study for L-glutamine (Niihara 2018) included patients aged <16 years old, a decision was made to include the study to enable a comparison with crizanlizumab. The primary comparison examines the outcomes in the whole population. A sensitivity analysis, was subsequently run using the results with Endari in a subgroup of patients aged >18 years old (reported in Niihara 2018).. Evidence networks were generated with nodes corresponding to treatments and edges connecting nodes if at least one RCT comparing corresponding treatments was identified.[32] An extended network including RCTs with a mixture of child, adolescent and adult populations was investigated for additional direct or indirect evidence on any comparison with crizanlizumab 5.0 mg/kg.

Following NICE guidelines, we employed a shared parameter model for hazard ratios to synthesise studies summarising outcomes in different formats and accounting for differences in trial duration.[27] Summaries that could be included were total number of events, percentage of patients with events, mean numbers of events, mean or median rates, numbers of patients with at least one event, and risk or hazard ratio of event. Likelihood and link function for each summary followed MDM and NICE guidelines.[27 31] Total number of events are modelled with a Poisson likelihood and log link, numbers of patients with at least one event are modelled using a Binomial likelihood and complementary log log link, while risk and hazard ratios are modelled on a log scale with a Normal likelihood and identify link. In line with NICE recommendations, a Bayesian perspective with vague priors was adopted.[27 31] Sensitivity to priors was explored with details in Appendix B; the base case prior has a standard deviation of 100 while the precise prior sensitivity has a standard deviation of 3.16 on log scale of baseline and treatment effects. Fixed and random effect were considered with choice being made on basis of model fit; meta-regressions were also explored to assess heterogeneity due to trial duration, proportion female, mean age, proportion homozygous hemoglobin S (HbSS) genotype, proportion hydroxyurea use, and proportion black or African-American.[33] Different doses of the same drug were analysed independently. If a connected evidence network could be formed using only RCTs, single-arm study evidence was discarded. The reference treatment in all analyses was placebo. If feasible, inconsistency between direct and indirect evidence was planned to be tested by node-splitting and an independent means inconsistency model.[19] All analyses were conducted using the MCMC software of OpenBUGS version 3.2.3.[34] Two MCMC chains with 400,000 iterations for burn-in and 30,000 iterations for posterior sampling were used. Convergence was assessed by visual inspection and the Gelman-Rubin statistic.[34 35] Further details of the modelling methods are provided in Appendix E.

We generated hazard ratios with 95% CrI of high-dose crizanlizumab 5.0 mg/kg relative to each comparator. We estimated the Bayesian probability that crizanlizumab was superior (lower hazard of event) or inferior (higher hazard of event). These probabilities are the Bayesian equivalent of one-sided p-values. In line with the recommendations of the American Statistical Association, we did not adopt a strict threshold for interpreting these Bayesian probabilities,[36] but instead reported the probability itself. Probabilities are interpreted to suggest evidence in favour of a hypothesis if it lay lower than 5% or above 95%, and weak evidence if the probability was between 5-10% or 90-95%.[37]

RESULTS

Systematic literature review results

We retrieved 3388 records from electronic databases, *ClinicalTrials.gov* and Sins 2017. After removing duplicates and irrelevant records, we screened 250 full-text articles. Fifty one studies (67 references) were included to perform evidence evaluation for the NMA (Figure 1). Full details and references for the 51 studies are included in Appendix B. We also identified fourteen additional ongoing clinical RCTs or completed RCTs without publication, which investigated effects of non-hydroxyurea treatments on SCD patients.[38-51]

Of 51 studies, duration of follow-up was reported in 41 studies and, among RCTs in the ≥16 years old population, duration ranged from 30 days in Wun 2013[52] to 52 weeks in Ataga 2017.[18] This range represents substantial variation in follow-up, but the methods used for NMA model trial follow-up compare annualized hazards in order to adjust for this difference.

The proportion of female patients varied across RCTs, ranging from 0.44 in Glassberg 2017[53] to 0.60 in Sins 2017,[54] so qualitatively similar proportions. Across all 51 studies, the proportion of females varied from 0.23 in Gupta 1995[55] to 1.00 in de Abood 1997,[56] representing a more substantial difference. In the ≥16 years old population RCTs, age ranged from 20.5 years in Pace 2003[57] to 35.5 years in Ataga 2008.[58] Across all 51 studies, the mean age ranged from 4.8 years in Adegoke 2013[59] to 48.8 years in Bridges 2017.[60] The proportion with HbSS genotype ranged from 0.60 in Wun 2013[52] to 1.00 in several studies that restricted enrolment to patients with HbSS disease alone, including Ataga 2008[58] in the ≥16 years old population. Although HbSS is indicative of absolute outcomes (prognostic factor), there is no known evidence that it is an effect modifier, so the NMA remains feasible.[33] Proportion of patients reported as black or African American ranged from 0.53 in NCT02482298[61] to 1.00 in Styles 2010.[62] Several studies excluded patients with history of hydroxyurea usage, including Bao 2008[63] in the ≥16 years old population. In the ≥16 years old population, this otherwise varied from 0.42 in Sins 2017[54] to 0.67 in Niihara 2018,[12] making it somewhat comparable.

Construction of evidence networks

Of the 51 studies identified, there were 17 non-controlled studies that were excluded from the NMA due to lack of common comparators and potential bias. Of the 34 remaining RCTs , only 8 were conducted solely in older adolescent and adult (≥16 years old) patients.[18 52-54 57 58 61 62]. As the only RCT identified on L-glutamine, Niihara 2018[12] was included in the network. This gave 9 RCTs in the ≥16 years old population evidence networks. Five of these studies used a VOC definition comparable to that in Ataga 2017[12 18 57 58 62] (details in Appendix E). The only study that examined transfusions was a conference abstract by Vichinsky. As the authors did not specify the definition of VOC or a placebo control, this study was excluded from the NMA[64] Appendix F shows the characteristics of included studies in the NMA. Analysed evidence networks are provided in Figure 2.

In addition to crizanlizumab 5.0 mg/kg and 2.5 mg/kg, multiple doses of other drugs were included in the networks. Ticagrelor was studied as both twice daily 45mg (high-dose) and 10mg (low-dose);[61] N-acetylcysteine (NAC) as 600mg (low-dose), 1200mg (mid-dose), and 2400mg (high-dose);[57] Senicapoc with a loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance,[62] and as a low-dose and high-dose formulation corresponding to single loading doses of 100mg and 150mg, respectively, and maintenance 6mg and 10mg daily, respectively.[58]

Cochrane risk of bias assessment for the 9 RCTs included in NMA is reported in full in Appendix E. Risk of bias was low in all categories for three of these studies (two studying senicapoc and one mometasome), and was low in all except incomplete outcome data in Ataga 2017.[18] Three studies were at unclear risk of bias due to random sequence generation and allocation concealment (studying ticagrelor, L-glutamine, and NAC doses).[12 57 61] Sins 2017 (studying NAC) was at low risk of bias for all categories except incomplete outcome data, on which it was at high risk of bias.[54]. Wun 2013 (studying prasugrel) was at unclear risk of bias on random sequence generation, allocation concealment, and blinding but low risk of bias on remaining categories.[52]

Network meta-analysis results

A fixed effects NMA approach was used for the primary analyses. The NMA models converged well and fit, assessed by comparing residual deviance to total number of data points, was good for all fixed effects analyses. Random effects analyses did not converge as only one RCT was available on each treatment contrast. Meta-regression to explore covariate effects did not reveal evidence of effect medication but convergence was poor for these models. Fit statistics and model assessment details are provided in Appendix E. Inconsistency could not be tested as there were no treatment contrasts on which both direct and indirect evidence were available.[19]

We discuss in turn the results of the NMA on VOC, all-cause hospitalization days, adverse events, and serious adverse events. Forest plots of hazard ratios with 95% CI of crizanlizumab vs all comparators are provided in Figure 3. Bayesian probabilities that crizanlizumab 5.0 mg/kg is superior or inferior are also provided in this figure. Pairwise results for all treatment comparisons are provided in Appendix E.

We found evidence that crizanlizumab 5.0 mg/kg had a lower hazard of VOC than placebo L-glutamine (hazard ratio 0.55, 95% CrI (0.43, 0.69); Bayesian probability crizanlizumab 5.0 mg/kg superior 0.9999), L-glutamine (0.67 (0.51, 0.88); 0.9982), and senicapoc (0.46 (0.32, 0.67); >0.9999). We found only weak evidence that hazard of VOC was lower on crizanlizumab 5.0 mg/kg than crizanlizumab 2.5 mg/kg (0.81 (0.63, 1.05); 0.9452) or low-dose NAC (0.48 (0.18, 1.21); 0.9396). We found no evidence of a difference between crizanlizumab 5.0 mg/kg and mid-dose NAC (0.81 (0.29, 2.18); 0.6619), high-dose NAC (1.91 (0.57, 7.58); 0.1507), high-dose senicapoc (0.57 (0.15, 2.17); 0.8010), or low-dose senicapoc (0.53 (0.14, 1.95); 0.8334). Results are summarized in Table 2 below. Cumulative ranking plots ('rankograms') are provided in Appendix B for the interested reader for each of the outcomes of interest. These are plots of the cumulative probability that each treatment is ranked in the top 1, 2, 3, etc. treatments.

Table 2. Bayesian probabilities that crizanlizumab is superior on each outcome analyzed*

	VOC	All-cause hospitalization	Adverse events	Serious adverse events
Placebo	>0.9999	>0.9999	0.6558	0.5857
L-glutamine	0.9982	0.0731	0.2480	0.2854
Crizanlizumab 2.5mg/kg	0.9452	>0.9999	0.5743	0.8134
Mometasome	-	0.7496	0.9399	-
Low-Dose NAC	0.9396	0.0166	0.6996	0.9744
Mid-Dose NAC	0.6619	-	-	-
High-Dose NAC	0.1507	-	-	-
Prasugrel	-	-	-	0.5242
Senicapoc	>0.9999	-	0.7176	-

High-Dose Senicapoc	0.8010	-	-	-
Low-Dose Senicapoc	0.8334	-	-	-
High-dose Ticagrelor	-	-	-	0.4247
Low-dose Ticagrelor	-	-	-	0.6181

*Proportion of MCMC samples for which crizanlizumab vs comparator hazard ratio is above (inferior) or below (superior) 1. Entry '-' indicates comparator not included in outcome specific evidence network.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelor=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

In a sensitivity analysis using a rate ratio of 0.64 with 95% confidence interval (0.45, 0.89) in a subgroup of patients aged >18 years old reported on page 231 of the publication Niihara 2018[12], we found no evidence that crizanlizumab had a lower hazard of VOC than L-glutamine (0.86 (0.57, 1.29); 0.7707). Full results of this analysis are provided in Appendix E.

We found evidence that crizanlizumab 5.0 mg/kg had a lower hazard of all-cause hospitalization days than placebo (0.58 (0.50, 0.68); >0.9999), and crizanlizumab 2.5 mg/kg (0.58 (0.50, 0.68); >0.9999), but found evidence that hazard was higher than on low-dose NAC (2.08 (1.06, 4.66); 0.0166). We found weak evidence that hazard of all-cause hospitalization days was higher on crizanlizumab 5.0 mg/kg than on L-glutamine (1.73 (0.82, 3.76); 0.0731) and no evidence of a difference with mometasome (0.89 (0.63, 1.26); 0.7496). Note that all-cause hospitalization includes admission for VOC but also for adverse events and non-SCD related causes.

The hazard of adverse events—both serious and overall—for crizanlizumab was generally similar or weakly better than other treatments. The exception is that there was weak evidence that crizanlizumab 5.0 mg/kg had a lower hazard than mometasome (0.51 (0.21, 1.19); 0.9399). We found no evidence of a difference in hazard of adverse events between crizanlizumab 5.0 mg/kg and placebo (0.91 (0.59, 1.43); 0.6558), L-glutamine (1.31 (0.62, 3.08); 0.2480), crizanlizumab 2.5 mg/kg (0.96 (0.61, 1.48); 0.5743), low-dose NAC (0.84 (0.45, 1.60); 0.6996), or senicapoc (0.86 (0.52, 1.44); 0.7176). Similarly, the hazard of serious adverse events on crizanlizumab 5.0 mg/kg were lower than on low-dose NAC (0.20 (0.02, 1.00); 0.9744). There was no evidence of a difference on adverse event rates between crizanlizumab 5.0 mg/kg and placebo (0.93 (0.47, 1.87); 0.5857), L-glutamine (1.24 (0.58, 2.70); 0.2854), crizanlizumab 2.5 mg/kg (0.75 (0.39, 1.43); 0.8134), high-dose ticagrelor (1.14 (0.27, 4.81); 0.4247), or low-dose ticagrelor (0.81 (0.21, 3.17); 0.6181).

Cumulative ranking plots ('rankograms') are provided in Appendix B for the interested reader. These are plots of the cumulative probability that each treatment is ranked in the top 1, 2, 3, etc. treatments. For Crisis, qualitatively, high-dose NAC was most likely to have the top rank (i.e., fewest events) rank but was closely followed by crizanlizumab 5.0 mg/kg. For adverse events, L-glutamine had the best (fewest events) rank followed crizanlizumab 5.0 mg/kg and for serious adverse events L-glutamine was again best ranked while crizanlizumab 5.0 mg/kg was middle ranking. For all-cause hospitalization days, NAC had the best rank (fewest hospitalizations) and was followed by L-glutamine and crizanlizumab 5.0 mg/kg.

A sensitivity analysis assuming more precise priors was conducted and details are provided in Appendix B. There was little or no impact on results. For example, the hazard ratio of VOC for

crizanlizumab 5.0 mg/kg compared with L-glutamine was (0.67 (0.51, 0.88); 0.9982) with precise priors and (0.67 (0.51, 0.88); 0.9982) in the base case with vague priors. Similarly, the hazard ratio of AE for crizanlizumab 5.0 mg/kg compared with L-glutamine was (1.29 (0.62, 2.93); 0.2480) with precise priors and (1.31 (0.62, 3.08); 0.2480) in the base case.

DISCUSSION

Previous SLRs and meta-analyses of treatments for SCD have demonstrated hydroxyurea to be effective in reducing VOC rates.[65 66] However, patients receiving hydroxyurea therapy can continue to have crises, end-organ damage, and a decreased life expectancy.[67] Crizanlizumab and L-glutamine are promising treatment options for SCD patients not well managed on hydroxyurea, but no direct comparison across these treatments has been conducted.[14 18 68] Our SLR and NMA is the first looking at the comparative efficacy of new treatments for older adolescent and adult (≥16 years old) SCD patients not well managed on hydroxyurea and is therefore of vital importance to this patient population.

Our baseline analysis found that crizanlizumab 5.0 mg/kg reduced VOC compared to L-glutamine, placebo, and senicapoc, and weak evidence of reduction compared to crizanlizumab 2.5 mg/kg and low-dose NAC. These results, however, were sensitive to whether the L-glutamine efficacy was measured for all patients or only those aged >18 years.

We found that crizanlizumab 5.0 mg/kg reduced all-cause hospitalization days compared to placebo and crizanlizumab 2.5 mg/kg. Conversely, we found evidence that low-dose NAC reduced hospitalization compared to crizanlizumab 5.0 mg/kg, and weak evidence that L-glutamine reduced hospitalization compared to crizanlizumab 5.0 mg/kg.

Our analysis found high-dose crizanlizumab 5.0 mg/kg had a lower hazard of adverse events compared to mometasome and of serious adverse events compared to low-dose NAC. There was no evidence of a difference between 5 mg/kg crizanlizumab on safety with other treatments.

Strengths

This SLR was comprehensive in terms of outcomes and interventions and was focused on the target population of crizanlizumab, that of older adolescent and adult (≥16 years old) SCD patients not well managed, or having failed previous treatment, with hydroxyurea. Our review followed the PRISMA guidelines and checklist.[22] Risk of bias was assessed using the best practice Cochrane collaboration tool.[24] To be comprehensive, we searched for both RCT and single-arm evidence but used only RCT evidence in the NMA. Our NMA combines direct head-to-head RCT evidence to enable indirect comparisons of interventions (e.g. crizanlizumab 5.0 mg/kg versus L-glutamine) that have not been compared directly; it thus goes beyond the published results of individual studies. Our analysis followed published and international guidelines on indirect comparisons and network meta-analysis.[27 29-31] On the outcome of VOC, we ensured only studies with a definition compatible with that of the principal crizanlizumab study were analysed. [18] To include a diverse range of outcome summaries, such as total number of events and numbers of patients with at least one event, a shared parameter Bayesian NMA was employed, as recommended by NICE.[27]

Limitations

There were several limitations to this SLR and NMA. There was at most only one RCT on each of the treatment contrasts. A similar definition of VOC was used across RCTs but the shared parameter NMA combined RCTs without adjusting for differences in statistical analyses, such as methods for managing drop-outs, used. Differences in RCT follow-up (e.g. 30 days in Wun 2013[52] and 52 weeks in

Ataga 2017)[18] limit comparability of annualized hazard rates across treatments. The strength of evidence for comparisons on hospitalization, adverse events, and serious adverse events was weak. Furthermore, we could not include transfusions in the NMA as the only available RCT in an adult population —Vichinsky 2010[64]— used an unspecified standard of care rather than a placebo control, did not describe the definition of VOC that was used, and was published only as an abstract.

Our NMA model generated results on a hazard ratio scale and thus used a complementary log-log link for the binomial likelihood when analyzing numbers of patients with at least one event. Although such data could have been modelled using a logit link, and thus generated odds ratios, this would have made it difficult to link to hazard ratio data, or total event data, reported by other studies. However, recent research has found hazards and odds ratios to be similar in NMA if the numbers of events are low, as they are in our study.[69]

Due to a lack of evidence, the NMA was not able to estimate the relative impact of crizanlizumab treatment on the rate of complicated VOC or organ damage, both of which are important health outcomes for patients and physicians. The heterogeneity variance of random effects models was not identifiable as only one study was available on each contrast. Published informative priors could be considered.[70] However, the heterogeneity variance would be entirely defined by this prior and its validity would depend on the relevance of a non-SCD clinical area as no NMA has been published previously in SCD. Inconsistency in the network could not be assessed as there were no loops in the evidence networks; it was necessary to assume consistency to enable comparisons with crizanlizumab. As there was no additional indirect evidence to be synthesized with the direct evidence, the NMA does not go beyond individual study results on pairwise comparisons for which there is direct head-to-head evidence (e.g. crizanlizumab 5.0 mg/kg versus placebo). In such cases, individual study results should remain the primary source of comparative data.

A previous SLR in non-hydroxyurea SCD treatments did not conduct quantitative synthesis due to concerns regarding heterogeneity.[23] Although we considered meta-regression on trial duration, proportion female, mean age, proportion HbSS genotype, proportion hydroxyurea use, and proportion black or African-American there was insufficient evidence as there was only one RCT on each treatment contrast. We were also lacking information on the amount of VOCs in the year preceding randomization/treatment start for several of the treatments included in the analysis, a factor known to be prognostic. We therefore had to assume differences in characteristics would not modify treatment effects, even in parameters expected to influence the frequency of VOCs. Although we conducted a sensitivity analysis using results among >18 year olds from Niihara 2018, that study itself concluded that there was "no significant interaction between trial group assignment and age".[71] On the other hand, if age is an effect modifier, the baseline results should be interpreted cautiously. Future real-world evidence studies may be useful to explore effect modifiers and identify patient types that benefit most from crizanlizumab and other treatments.

Further, caution should be taken when interpreting these results in relation to switching patients from hydroxyurea to crizanlizumab or L-glutamine. Our analysis does not purport to compare crizanlizumab, or indeed L-glutamine or blood transfusions, with hydroxyurea but is instead focused solely on patients who are not well managed on hydroxyurea. Before more evidence is available, physicians should consider treatment with hydroxyurea before consideration of second line treatments.[72]

Conclusion

Our baseline analysis showed from an SLR and NMA that crizanlizumab reduced crises and hospital days compared with placebo and other treatments with an acceptable adverse event profile in older adolescent and adult (≥16 years old) SCD patients when compared to other non-hydroxyurea treatments. The VOC results, however, were sensitive to assumptions regarding whether patient age is an effect modifier.

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DATA SHARING STATEMENT

All necessary data, coda, and initial values for our OpenBUGS models are provided in the network meta-analysis.

AUTHORSHIP CONTRIBUTIONS

HT drafted the manuscript and designed and conducted the network meta-analysis. NS ensured medical relevance for the review and analysis and provided context for the results. JJ advised on statistical aspects of the analysis. GJ and JS provided oversight to the whole project. LZ provided project management and administrative support. MB provided subject-matter expertise on the review and analysis. HYC led the systematic review. SG validated the network meta-analysis. All authors reviewed and edited the manuscript.

DISCLOSURES OF CONFLICTS OF INTEREST

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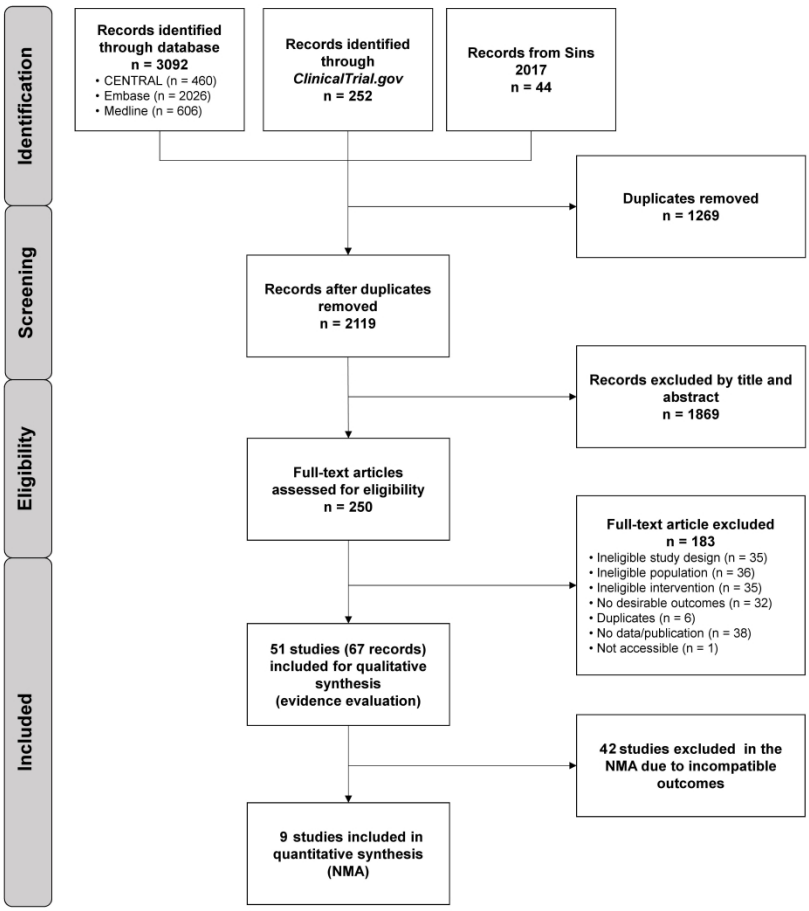


Figure 1. SCD Prisma Flow Chart

209x297mm (600 x 600 DPI)

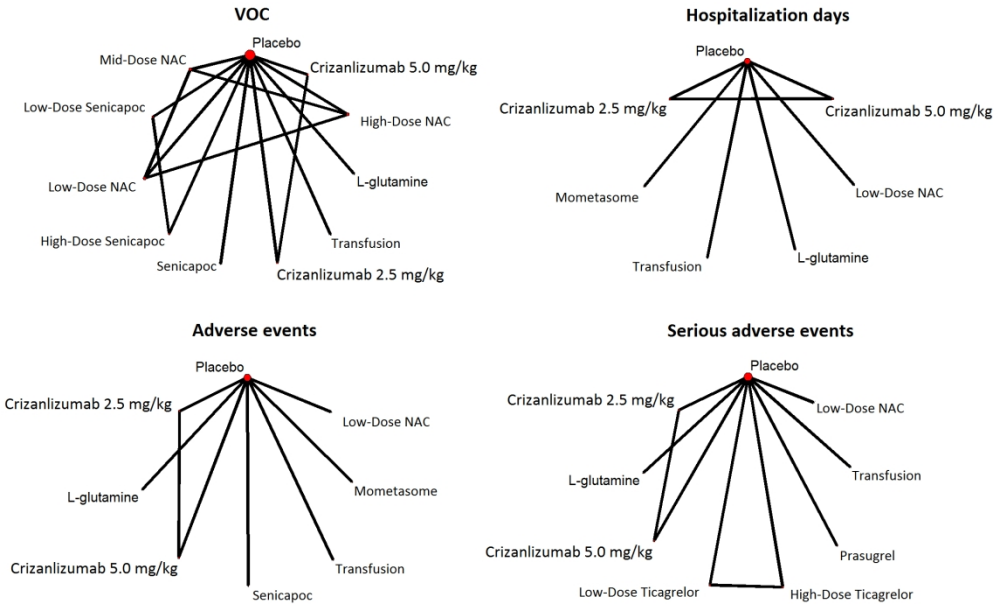


Figure 2. Evidence networks

* Each node represent a treatment and nodes are connected by an edge if at least trial has compared the relevant treatments. Any two treatments can be compared if their corresponding nodes can be connected by a path of one or more edges.

High-dose Crizanlizumab=5mg/kg 14 times over 52 weeks. Low-Dose Crizanlizumab=2.5mg/kg 14 times over 52 weeks. High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelor=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

5 RCTs on crisis = Ataga 2017 (crizanlizumab vs placebo), Niihara 2018 (L-glutamine vs placebo), Ataga 2011 (senicapoc vs. placebo), Ataga 2008 (senicapoc low-dose, senicapoc high-dose vs. placebo), and Pace 2003 (NAC low, mid, and high dose vs. placebo). 4 RCTs on all-cause hospitalization days = Ataga 2017 (crizanlizumab vs placebo), Niihara 2018 (L-glutamine vs placebo), Glassberg 2017 (mometasome vs. placebo), and Sins 2017 (NAC vs. placebo). 5 RCTs on adverse events = Glassberg 2017 (mometasome vs placebo), Ataga 2017 (crizanlizumab vs placebo), Ataga 2011 (senicapoc vs placebo), Sins 2017 (NAC vs placebo), and Niihara 2018 (L-glutamine vs placebo). 5 RCTs on serious adverse events = Ataga 2017 (crizanlizumab vs placebo), Sins 2017 (NAC vs placebo), Wun 2013 (prasugrel vs placebo), NCT02482298 (TICAGRELOR vs placebo), and Niihara 2018 (L-glutamine vs placebo).

291x185mm (192 x 192 DPI)

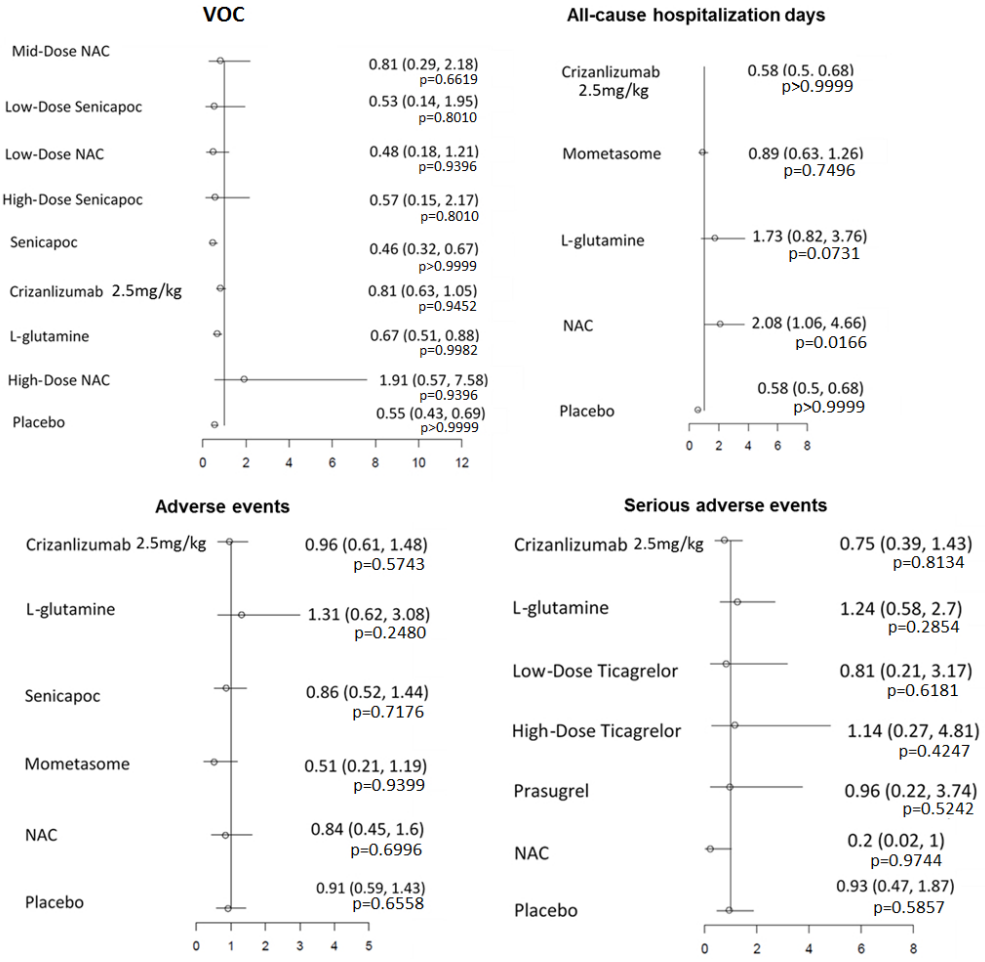


Figure 3. Forest plot

*Hazard ratio less than 1 suggests lower hazard of event on the crizanlizumab. Bayesian probabilities of superiority are proportion of MCMC samples for which crizanlizumab vs comparator hazard ratio is above (inferior) or below (superior) 1.

High-dose Crizanlizumab=5mg/kg 14 times over 52 weeks. Low-Dose Crizanlizumab=2.5mg/kg 14 times over 52 weeks. High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelor=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Appendix A. PRISMA Checklist

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**Page 1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**Page 2 (but used 'objectives' rather than 'background' to align with BMJ Open style guide.**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**Page 3**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**Page 4 (Table 1)**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Appendix D and E.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as	**Page 4 &5(Table 1&2)**

		criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**Page 4**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Page 4 and Appendix A, D, and E**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**Page 4&5**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**Page 4 (Table 1, appendix)**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**Page 4 (Table 1)**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***Page 5***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**Page 4**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**Page 4&5**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	**Page 5 and Appendix B**
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Page 5 and Appendix B

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**Page 4**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	**Page 5, and appendix B**
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 5 (Figure 1)
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Figure 2**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**Page 6**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2, Appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Page 6 and Appendix A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**Table 2**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	**Figure 3 and appendix**

Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	***Page 7 (no independent loops of evidence on which to test for inconsistency)***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Appendix A
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	***Page 6, 9, and Appendix B***
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Page 7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	Page 8 and 9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***Page 10***

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Box. Terminology: Reviews With Networks of Multiple Treatments

Different terms have been used to identify systematic reviews that incorporate a network of multiple treatment comparisons. A brief overview of common terms follows.

Indirect treatment comparison: Comparison of 2 interventions for which studies against a common comparator, such as placebo or a standard treatment, are available (i.e., indirect information). The direct treatment effects of each intervention against the common comparator (i.e., treatment effects from a comparison of interventions made within a study) may be used to estimate an indirect treatment comparison between the 2 interventions (**Appendix Figure 1, A**). An indirect treatment comparison (ITC) may also involve multiple links. For example, in **Appendix Figure 1, B**, treatments B and D may be compared indirectly on the basis of studies encompassing comparisons of B versus C, A versus C, and A versus D.

Network meta-analysis or *mixed treatment comparison*: These terms, which are often used interchangeably, refer to situations involving the simultaneous comparison of 3 or more interventions. Any network of treatments consisting of strictly unclosed loops can be thought of as a series of ITCs (**Appendix Figure 1, A and B**). In mixed treatment comparisons, both direct and indirect information is available to inform the effect size estimates for at least some of the comparisons; visually, this is shown by closed loops in a network graph (**Appendix Figure 1, C**). Closed loops are not required to be present for every comparison under study. "Network meta-analysis" is

an inclusive term that incorporates the scenarios of both indirect and mixed treatment comparisons.

Network geometry evaluation: The description of characteristics of the network of interventions, which may include use of numerical summary statistics. This does not involve quantitative synthesis to compare treatments. This evaluation describes the current evidence available for the competing interventions to identify gaps and potential bias. Network geometry is described further in **Appendix Box 4**.

Appendix Box 1. The Assumption of Transitivity for Network Meta-Analysis

Methods for indirect treatment comparisons and network meta-analysis enable learning about the relative treatment effects of, for example, treatments A and B through use of studies where these interventions are compared against a common therapy, C.

When planning a network meta-analysis, it is important to assess patient and study characteristics across the studies that compare pairs of treatments. These characteristics are commonly referred to as *effect modifiers* and include traits such as average patient age, gender distribution, disease severity, and a wide range of other plausible features.

For network meta-analysis to produce valid results, it is important that the distribution of effect modifiers is similar, for example, across studies of A versus B and A versus C. This balance increases the plausibility of reliable findings from an indirect comparison of B versus C through the common comparator A. When this balance is present, the assumption of transitivity can be judged to hold.

Authors of network meta-analyses should present systematic (and even tabulated) information regarding patient and study characteristics whenever available. This information helps readers to empirically evaluate the validity of the assumption of transitivity by reviewing the distribution of potential effect modifiers across trials.

Appendix Box 2. Differences in Approach to Fitting Network Meta-Analyses

Network meta-analysis can be performed within either a frequentist or a Bayesian framework. Frequentist and Bayesian approaches to statistics differ in their definitions of probability. Thus far, the majority of published network meta-analyses have used a Bayesian approach.

Bayesian analyses return the posterior probability distribution of all the model parameters given the data and prior beliefs (e.g., from external information) about the values of the parameters. They fully encapsulate the uncertainty in the parameter of interest and thus can make direct probability statements about these parameters (e.g., the probability that one intervention is superior to another).

Frequentist analyses calculate the probability that the observed data would have occurred under their sampling distribution for hypothesized values of the parameters. This approach to parameter estimation is more indirect than the Bayesian approach.

Bayesian methods have been criticized for their perceived complexity and the potential for subjectivity to be introduced by choice of a prior distribution that may affect study findings. Others argue that explicit use of a prior distribution makes transparent how individuals can interpret the same data differently. Despite these challenges, Bayesian methods offer considerable flexibility for statistical modeling. In-depth introductions to Bayesian methods and discussion of these and other issues can be found elsewhere.

Appendix Box 3. Network Meta-Analysis and Assessment of Consistency

Network meta-analysis often involves the combination of direct and indirect evidence. In the simplest case, we wish to compare treatments A and B and have 2 sources of information: direct evidence via studies comparing A versus B, and indirect evidence via groups of studies comparing A and B with a common intervention, C. Together, this evidence forms a closed loop, ABC.

Direct and indirect evidence for a comparison of interventions should be combined only when their findings are similar in magnitude and interpretation. For example, for a comparison of mortality rates between A and B, an odds ratio determined from studies of A versus B should be similar to the odds ratio comparing A versus B estimated indirectly based on studies of A versus C and B versus C. This assumption of comparability of direct and indirect evidence is referred to as *consistency* of treatment effects.

When a treatment network contains a closed loop of interventions, it is possible to examine statistically whether there is agreement between the direct and indirect estimates of intervention effect.

Different methods to evaluate potential differences in relative treatment effects estimated by direct and indirect comparisons are grouped as *local approaches* and *global approaches.* Local approaches (e.g., the Bucher method or the node-splitting method) assess the presence of inconsistency for a particular pairwise comparison in the network, whereas global approaches (e.g., inconsistency models, I^2 measure for inconsistency) consider the potential for inconsistency in the network as a whole.

Tests for inconsistency can have limited power to detect a true difference between direct and indirect evidence. When multiple loops are being tested for inconsistency, one or a few may show inconsistency simply by chance. Further discussions of consistency and related concepts are available elsewhere.
Inconsistency in a treatment network can indicate lack of transitivity (see **Appendix Box 1**).

Appendix Box 4. Network Geometry and Considerations for Bias

The term *network geometry* is used to refer to the architecture of the treatment comparisons that have been made for the condition under study. This includes what treatments are involved in the comparisons in a network, in what abundance they are present, the respective numbers of patients randomly assigned to each treatment, and whether particular treatments and comparisons may have been preferred or avoided.

Networks may take on different shapes. Poorly connected networks depend extensively on indirect comparisons. Meta-analyses of such networks may be less reliable than those from networks where most treatments have been compared against each other.

Qualitative description of network geometry should be provided and accompanied by a network graph. Quantitative metrics assessing features of network geometry, such as *diversity* (related to the number of treatments assessed and the balance of evidence among them), *co-occurrence* (related to whether comparisons between certain treatments are more or less common), and *homophily* (related to the extent of comparisons between treatments in the same class versus competing classes), can also be mentioned.

Although common, established steps for reviewing network geometry do not yet exist, however examples of in-depth evaluations have been described related to treatments for tropical diseases and basal cell carcinoma and may be of interest to readers. An example based on 75 trials of treatments for pulmonary arterial hypertension (**Appendix Figure 3**) suggests that head-to-head studies of active therapies may prove useful to further strengthen confidence in interpretation of summary estimates of treatment comparisons.

Appendix Box 5. Probabilities and Rankings in Network Meta-Analysis

Systematic reviews incorporating network meta-analyses can provide information about the hierarchy of competing interventions in terms of treatment rankings.

The term *treatment ranking probabilities* refers to the probabilities estimated for each treatment in a network of achieving a particular placement in an ordering of treatment effects from best to worst. A network of 10 treatments provides a total of 100 ranking probabilities—that is, for each intervention, the chance of being ranked first, second, third, fourth, fifth, and so forth).

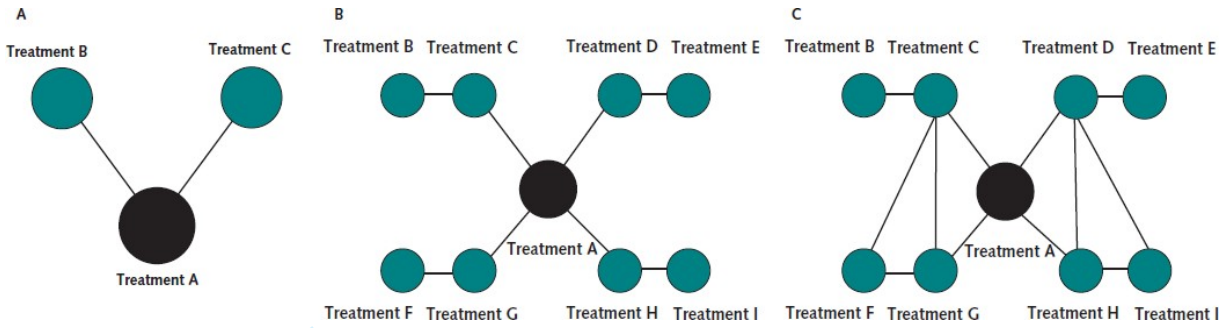
Several techniques are feasible to summarize relative rankings, and include graphical tools as well as different approaches for estimating ranking probabilities. **Appendix Figure 6** shows 2 approaches to presenting such information, on the basis of a comparison of adjuvant interventions for resected pancreatic adenocarcinoma.

Robust reporting of rankings also includes specifying median ranks with uncertainty intervals, cumulative probability curves, and the surface under the cumulative ranking (SUCRA) curve.

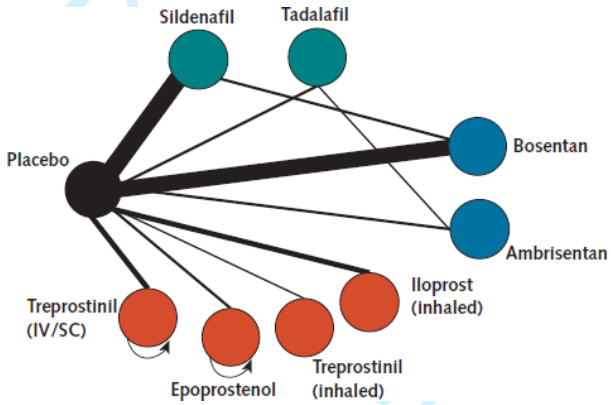
Rankings can be reported along with corresponding estimates of pairwise comparisons between interventions. Rankings should be reported with probability estimates to minimize misinterpretation from focusing too much on the most likely rank.

Rankings may exaggerate small differences in relative effects, especially if they are based on limited information. An objective assessment of the strength of information in the network and the magnitude of absolute benefits should accompany rankings to minimize potential biases.

Appendix Figure 1A-1C

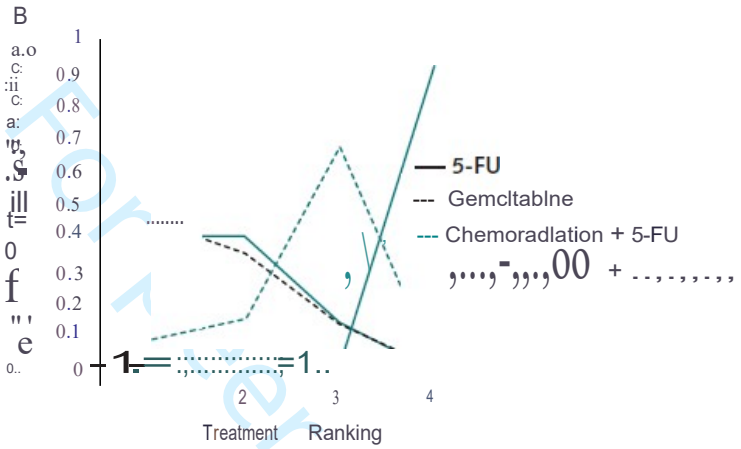


Appendix Figure 3



Appendix Figure 6

Ranking	Treatment and Coores ondlng Ranking Probabilities Grade 3 or 4 ematologlc Toxicity			
	5-FU	Gemcltablne	Chemoradlalton + 5-FU	Chemoradlatlon + gemcltablne
1	0.42	0.42	0.15	0.01
2	0.46	0.36	0.15	0,02
3	0.10	0.17	0.68	0.04
4	0,02	0.05	0,02	0.93



Appendix B: Additional details of Systematic literature review

A.1 Literature search strategies for non-transfusions SLR

Table 1: Search strategy for non-transfusions search of MEDLINE

#	Searches	Concept
1	exp pain/	Outcomes
2	(pain or painfull).tw.	
3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	
4	exp length of stay/	
5	(hospital adj3 (admission or stay)).tw.	
6	(patient adj3 (admission or stay)).tw.	
7	or/1-6	
8	anemia, sickle cell/	Population
9	hemoglobin, sickle/	
10	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	
11	or/8-10	
12	exp antisickling agents/	Interventions
13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or L-glutamine or voxelotor or GBT440).mp.	
14	(8 or 9 or 10) and prevent vaso-occlusiv*.tw.	
15	or/12-14	
16	7 and 11 and 15	
17	meta analysis.pt.	Systematic review and meta-analysis studies
18	((meta adj analys*) or metaanalys or meta-analys*).ti,ab,sh.	
19	(systematic adj5 (review or overview*)).ti,ab,sh.	
20	or/17-19	
21	16 and 20	
22	clinical trial/	RCTs
23	(clinic adj5 trial*).ti,ab,sh.	

#	Searches	Concept
24	single blind method/	
25	double blind method/	
26	random allocation/	
27	placebos/	
28	(placebo or random*).ti,ab,sh.	
29	randomized controlled trial/	
30	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	
31	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	
32	randomi?ed control trial*.tw.	
33	or/22-32	
34	16 and 33	
35	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	Single arm trials
36	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	
37	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	
38	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	
39	Clinical Trial, Phase I.pt.	
40	Clinical Trial, Phase II.pt.	
41	Clinical Trial, Phase III.pt.	
42	(registry or registries).ti,ab,kf,hw.	
43	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	
44	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	
45	(nonrandom* or non-random*).ti,ab,kf.	
46	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	
47	(all adj3 received).ab.	
48	or/35-47	
49	16 and 48	

#	Searches	Concept
50	limit 21 to ed=20170130-20180620	Date limit on rSLR and meta-analysis studies
51	limit 34 to ed=20170130-20180620	Date limit on RCTs
52	limit 49 to ed=20170130-20180620	Date limit on single arm trials

Table 2: Search strategy for non-transfusions search of EMBASE

#	Searches	
1	exp pain/	Outcomes
2	(pain or painfull).tw.	
3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	
4	exp "length of stay"/	
5	(hospital adj3 (admission or stay)).tw.	
6	(patient adj3 (admission or stay)).tw.	
7	or/1-6	
8	sickle cell anemia/	Population
9	hemoglobin S/	
10	(sickle cell or sickle h$emoglobin or drepanocyt* or drepanotic or drepanocytemia or h$emoglobin-s or Hb-S or sickle an$emia or meniscocytosis).mp.	
11	or/8-10	
12	antisickling agent/	Intervention
13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or L-glutamine or voxelotor or GBT440).mp.	
14	(8 or 9 or 10) and prevent vaso-occlusiv*.tw.	
15	or/12-14	
16	7 and 11 and 15	
17	randomized controlled trial/	RCTs
18	(RCT or randomi#ed or randomi#ation).ab,ti,kw,hw.	

#	Searches	
19	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or subsitut* or treat*)).ab,kw.	
20	trial.ti.	
21	crossover procedure/	
22	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dumm*)).ti,ab,kw,hw.	
23	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	
24	or/17-23	
25	16 and 24	
26	prospective study/ or retrospective study/ or longitudinal study/ or cohort analysis/ or cross-sectional study/ or case control study/ or population based case control study/	Single-arm trials
27	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 study).ti,ab,kw.	
28	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	
29	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab,kw.	
30	(registry or registries).ti,ab,kw,hw.	
31	(nonrandom* or non-random*).ti,ab,kw.	
32	((control* adj2 before adj2 after) or CBA study).ti,ab,kw.	
33	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kw.	
34	(all adj3 received).ab.	
35	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 1 clinical trial/	
36	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kw.	
37	or/26-36	
38	16 and 37	
39	limit 25 to em=201705-201825	Date limit on RCTs
49	limit 38 to em=201705-201825	Date limit on single arm trials

Table 3: Search strategy for non-transfusions search of Cochrane Register of Controlled Trials

#	Searches	
#1	MeSH descriptor: [Pain] explode all trees	Outcomes
#2	(pain or painfull):ti,ab,kw	
#3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises):ti,ab,kw	
#4	MeSH descriptor: [Length of Stay] explode all trees	
#5	(hospital near/3 (admission or stay)):ti,ab,kw	
#6	(patient near/3 (admission or stay)):ti,ab,kw	
#7	#1 or #2 or #3 or #4 or #5 or #6	
#8	MeSH descriptor: [Anemia, Sickle Cell] this term only	Population
#9	MeSH descriptor: [Hemoglobin, Sickle] this term only	
#10	(sickle cell or sickle h*emoglobin or drepanocyt* or drepanotic or drepanocytemia or h*emoglobin-s or Hb-S or sickle an*emia or meniscocytosis):ti,ab,kw	
#11	#8 or #9 or #10	
#12	MeSH descriptor: [Antisickling Agents] explode all trees	Interventions
#13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or L-glutamine or voxelotor or GBT440):ti,ab,kw	
#14	(#8 or #9 or #10) and prevent vaso-occlusiv*	
#15	#11 or #12 or #13	
#16	#7 and #11 and #14	

Table 6: Search strategy for non-transfusions search of ClinicalTrials.gov*

#	Searches	Search column
#1	Anemia, Sickle Cell OR Sickle Beta Thalassemia OR Sickle Cell Anemia OR Sickle Cell trait	Condition or disease
#2	SCD OR SCA OR Sickle	Other terms
#3	Drug OR Placebo OR Crizanlizumab OR Hydroxyurea OR L-glutamine OR Voxelotor OR GBT440 OR hydroxycarbamide	Intervention/treatment
#4	pain OR hospitalisation OR hospitalization OR (hospital AND (admission OR stay)) OR crisis OR VOC OR ((vaso OR vein OR vena OR venous) AND (occlusive OR occlusive OR interruption OR obstruction)) OR survival OR quality of life	Outcome Measures
	#1 or #2 or #3 or #4	

*Advanced Search option without any restrictions except search strings listed.

A.2 Literature search strategies for transfusions SLR

Table 4: Search strategy for transfusions search on CENTRAL database

#	Searches	Results
#1	MeSH descriptor: [Anemia, Sickle Cell] this term only	583
#2	MeSH descriptor: [Hemoglobin, Sickle] this term only	19
#3	(sickle cell or sickle h*emoglobin or drepanocyt* or drepanotic or drepanocytemia or h*emoglobin-s or Hb-S or sickle an*emia or meniscocytosis):ti,ab,kw	4790
#4	#1 or #2 or #3	4790
#5	MeSH descriptor: [Blood Transfusion] this term only	1766
#6	MeSH descriptor: [Erythrocyte Transfusion] explode all trees	564
#7	((blood or erythrocyte* or "red cell*" or "red blood cell*" or RBC*) near/5 (transfus* or infus* or unit*))	14775
#8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) near/5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program* or therapy)):ab	30189
#9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)):ti	3612
#10	("allogeneic blood" or (unit* near/2 blood) or "allogenic blood" or (blood near/2 exposure) or "donor blood" or "blood product*" or "blood component*" or "blood support")	3365
#11	hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*	107
#12	(red cell* or erythrocyte* or blood or RBC*) and transfus*:ti	2434
#13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	41927
#14	MeSH descriptor: [Blood Component Transfusion] this term only	115
#15	MeSH descriptor: [Erythrocytes] this term only	1478
#16	(red cell* or red blood cell* or erythrocyte* or RBC*)	12756
#17	#14 and (#15 or #16)	39
#18	#13 or #17	41927
#19	MeSH descriptor: [Pain] explode all trees	42323
#20	(pain or painfull):ti,ab,kw	124349

#	Searches	Results
#21	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises):ti,ab,kw	4404
#22	MeSH descriptor: [Length of Stay] explode all trees	6488
#23	(hospital near/3 (admission or stay)):ti,ab,kw	20854
#24	(patient near/3 (admission or stay)):ti,ab,kw	1779
#25	#19 or #20 or #21 or #22 or #23 or #24	153780
#26	#4 and #18 and #25	332

Table 5: Search strategy for transfusions search on MEDLINE database

#	Searches	Results
1	anemia, sickle cell/	19329
2	hemoglobin, sickle/	3011
3	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	27120
4	1 or 2 or 3	27602
5	Blood Transfusion/	48056
6	Erythrocyte Transfusion/	8033
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	90906
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	47785
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	35184
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	26829
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1217
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	24060
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	183648
14	Blood Component Transfusion/	3477
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	16726

#	Searches	Results
16	14 not 15	3229
17	ERYTHROCYTES/	128578
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	216650
19	17 or 18	258199
20	16 and 19	834
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	13177
22	(((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	3326
23	13 or 20 or 21 or 22	188025
24	exp pain/	362648
25	(pain or painfull).tw.	547392
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso - occlusiv* or crisis or crises).tw.	66169
27	exp length of stay/	77857
28	(hospital adj3 (admission or stay)).tw.	104873
29	(patient adj3 (admission or stay)).tw.	6507
30	or/24-29	901074
31	4 and 23 and 30	848
32	clinical trial/	512148
33	(clinic adj5 trial*).ti,ab,sh.	1010
34	single blind method/	25632
35	double blind method/	147368
36	random allocation/	95709
37	placebos/	34063
38	(placebo or random*).ti,ab,sh.	1263924
39	randomized controlled trial/	467730
40	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	786522
41	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	145215
42	randomi?ed control trial*.tw.	6481
43	or/32-42	1565168

#	Searches	Results
44	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	2187051
45	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	1071161
46	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	615678
47	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	340559
48	Clinical Trial, Phase I.pt.	18409
49	Clinical Trial, Phase II.pt.	29604
50	Clinical Trial, Phase III.pt.	14110
51	(registry or registries).ti,ab,kf,hw.	139501
52	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	53439
53	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	114108
54	(nonrandom* or non-random*).ti,ab,kf.	34084
55	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	2644
56	(all adj3 received).ab.	41192
57	or/44-56	3114626
58	31 and 43	120
59	31 and 57	278

Table 6: Search strategy for transfusions search on EMBASE database

#	Searches	Results
1	exp Anemia, Sickle Cell/	32009
2	(h?emoglobin s or h?emoglobin sc or h?emoglobin se or h?emoglobin ss or h?emoglobin c or h?emoglobin d or Hb s or Hb sc or Hb se or Hb ss or Hb c or Hb d or sc disease*).tw.	5794
3	(sickle cell or sicklemia or sickled or sickling or meniscocyt* or drepanocyt*).tw.	29569
4	1 or 2 or 3	38361
5	Blood Transfusion/	108332
6	Erythrocyte Transfusion/	23021
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	135137
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	77239
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	38387
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	43111
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1555
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	28985
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	273982
14	Blood Component Transfusion/	2629
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	19765
16	14 not 15	2279
17	ERYTHROCYTES/	112741
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	256379
19	17 or 18	278120
20	16 and 19	523
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	22304
22	(((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	4095
23	13 or 20 or 21 or 22	279695

#	Searches	Results
24	exp pain/	1146280
25	(pain or painfull).tw.	789805
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	82887
27	exp length of stay/	150699
28	(hospital adj3 (admission or stay)).tw.	169748
29	(patient adj3 (admission or stay)).tw.	12514
30	or/24-29	1690290
31	4 and 23 and 30	2325
32	randomized controlled trial/	508600
33	(RCT or randomi#ed or randomi#ation).ab,ti,kw,hw.	1062285
34	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or subsitut* or treat*)).ab,kw.	560662
35	trial.ti.	248694
36	crossover procedure/	56042
37	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dumm*)).ti,ab,kw,hw.	276112
38	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	99658
39	or/32-38	1386841
40	prospective study/ or retrospective study/ or longitudinal study/ or cohort analysis/ or cross - sectional study/ or case control study/ or population based case control study/	1771952
41	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 study).ti,ab,kw.	1282224
42	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	790240
43	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab,kw.	500633
44	(registry or registries).ti,ab,kw,hw.	183687
45	(nonrandom* or non-random*).ti,ab,kw.	42777
46	((control* adj2 before adj2 after) or CBA study).ti,ab,kw.	3333
47	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kw.	80316
48	(all adj3 received).ab.	75969

#	Searches	Results
49	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 1 clinical trial/	126474
50	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kw.	205403
51	or/40-50	3180246
52	31 and 39	245
53	31 and 51	599

Table 7: Search strategy for transfusions search on clinicaltrials.gov database

#	Searches	Search column
#1	Anemia, Sickle Cell OR Sickle Beta Thalassemia OR Sickle Cell Anemia OR Sickle Cell trait	Condition or disease
#2	SCD OR SCA OR Sickle	Other terms
#3	Transfusion OR blood OR RBC OR hematocrit OR erythrocyte	Intervention/treatment
#4	pain OR hospitalisation OR hospitalization OR (hospital AND (admission OR stay)) OR crisis OR VOC OR ((vaso OR vein OR vena OR venous) AND (occlusive OR occlusive OR interruption OR obstruction)) OR survival OR quality of life	Outcome Measures
	#1 or #2 or #3 or #4	

*Advanced Search option without any restrictions except search strings listed.

A.3 Additional results from systematic literature review

Table 8: Cochrane risk of bias assessment of randomized controlled trials included in the feasibility assessment

Trial ID	Random sequence generation	Allocation concealment	Blinding (personnal)	Blinding (outcome assessor)	Incomplete outcome data	Selective reporting	Other bias
Arruda 2013	Low	Low	Unclear	Unclear	Low	Unclear	None
Ataga 2008	Low	Low	Low	Low	Low	Low	Industry funded; Any conflict of interest of authors
Ataga 2011	Low	Low	Low	Low	Low	Low	Industry funded; Any conflict of

Trial ID	Random sequence generation	Allocation concealment	Blinding (personnal)	Blinding (outcome assessor)	Incomplete outcome data	Selective reporting	Other bias
							interest of authors
Ataga 2017	Low	Low	Low	Low	Unclear	Low	Industry funded; Any conflict of interest of authors
Bao 2008	Unclear	Unclear	Low	Low	Low	Low	None
Cabannes 1984	Low	Low	Low	Low	Unclear	Low	Baseline imbalances or not assessed
Deceulaer 1982	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Baseline imbalances or not assessed; Industry funded
Diop 2011	Low	Low	Low	Low	Low	Low	None
Glassberg 2017	Low	Low	Low	Low	Low	Low	None
NCT02482298	Unclear	Unclear	Low	Low	Low	Low	Industry funded
Niihara 2018	Unclear	Unclear	Low	Low	High	Low	Industry funded
Pace 2003	Unclear	Unclear	Low	Low	High	Low	Industry funded
Schlaeger 2017	Low	Low	Low	Low	Low	Low	None
Sins 2017	Low	Low	Low	Low	High	Low	None
Tomer 2001	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Baseline imbalances
Wun 2013	Unclear	Unclear	Unclear	Low	Low	Low	Industry funded
Adegoke 2013	Low	Unclear	High	High	High	Unclear	No placebo used in control group
Alvim 2005	Unclear	Unclear	Unclear	Unclear	Low	Unclear	None
Charnigo 2017	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Subset of a RCT database
Daak 2013	Low	Low	Low	Low	Low	Low	Industry funded
Daak 2018	Unclear	Unclear	Low	Low	Low	Unclear	Baseline imbalances or not assessed
de Abood 1997	High	High	High	High	Unclear	Unclear	Baseline imbalances or not assessed; No placebo used in control group
Eke 2003	Low	Low	High	High	Low	Low	Baseline imbalances or not assessed

Trial ID	Random sequence generation	Allocation concealment	Blinding (personnal)	Blinding (outcome assessor)	Incomplete outcome data	Selective reporting	Other bias
Gail 1982	Low	Low	Low	Low	Low	Unclear	None
Gupta 1995	Low	Unclear	Low	Low	Unclear	Unclear	None
Heeney 2016	Low	Low	Low	Low	Low	Low	Industry funded; Any conflict of interest of authors
Isaacs 1972	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Baseline imbalances or not assessed; Industry funded
Mann 1974	Unclear	Unclear	High	High	Low	Unclear	Risk of carry-over effect in crossover study; No placebo used in control group
Manrique 1987	Unclear	Unclear	Unclear	Unclear	Low	High	None
Oski 1968	Unclear	Unclear	Low	Low	Low	Unclear	Industry funded; Risk of carry-over effect in crossover study
Reid 2014	Unclear	Low	Low	Low	High	Low	Industry funded; Any conflict of interest of authors
Vinchinsky 2010	Unclear	Unclear	High	High	Unclear	Unclear	Industry funded
Wambebe 2001	Low	Low	Low	Unclear	Unclear	Unclear	Risk of carry-over effect in crossover study
Zago 1984	Unclear	Unclear	Unclear	Unclear	High	Unclear	Risk of carry-over effect in crossover study

** Note: Trial bolded were base case studies; Trials shaded in grey were not included in the final network meta-analyses.*

Table 9: Newcastle-Ottawa quality assessment of non-randomized controlled trials included in the feasibility assessment

Al Hashmi 2017	---	★	★	---	★	---	---	---	★	4
Brandalise 2017	---	★	★	---	★	★	★	---	★	6
Bridges 2017	---	★	★	---	---	---	---	---	★	3
Bumma 2017	---	★	★	---	★	---	---	---	---	3
Colombatti 2018	★	★	★	---	★	---	---	★	★	6
Di Maggio 2018	★	★	★	---	★	★	---	★	★	7
Hoppe 2017	★	★	---	---	★		---	---	---	3
Keikhaei 2015	★	★	★	---		---	---	---	★	4
Kwiatkowski 2017	★	★	---	---	---	---	---	★	★	4
LeBlanc 2016	---	★	★	★	---	---	---	★	★	5
Lemonne 2017	---	★	★	---	---	---	★	★	★	5
NCT01476696	---	★	---	---	---	---	---	---	★	2
Quarmyne 2017	★	★	★	---	★	---	---	★	---	5
Rigano 2018	★	★	★	---	★	★	---	★	★	7
Sethy 2018	★	★	★	---	---		---	★	★	5
Styles 2010	---	★	★	★	---	---	---	---	---	3
Youssry 2017	★	★	★	---	★	★	---	★	★	7

Figure 1: Cochrane assessment of randomized controlled trials included in the feasibility assessment

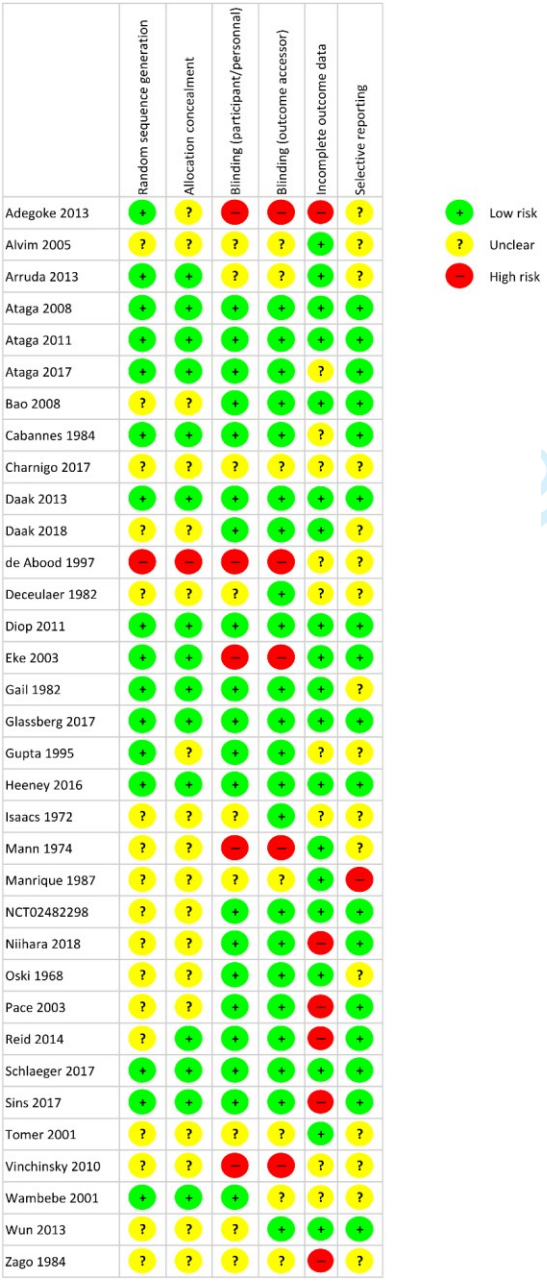


Table 10: Study characteristics of trials included in the feasibility assessment

Trial	Registry number	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Blinding	Design	Follow-up	Country
Adegoke 2013	---	Lime juice + Routine oral drugs	Control (Routine oral drugs)	---	---	Open	RCT	6 months	Nigeria
Alvim 2005	---	Piracetam	Placebo	---	---	Double-blind	RCT, crossover	1 year (6 months, then crossover with 2 weeks washout period)	Saudi Arabia
Arruda 2013	---	Placebo	Vitamins C and E	---	---	Double-blind	RCT	180 days	Brazil
Ataga 2008	NCT00040677	Senicapoc (high-dose)	Senicapoc (low-dose)	Placebo	---	Double-blind	RCT	12 week	US
Ataga 2011	NCT00102791	Senicapoc	Placebo	---	---	Double-blind	RCT	52 weeks	United States, Jamaica, Brazil, France, Trinidad and the United Kingdom.
Ataga 2017	NCT01895361	Crizanlizumab (high-dose)	Crizanlizumab (low-dose)	Placebo	---	Double-blind	RCT (Phase 2)	52 weeks	Brazil, Jamaica, USA
Bao 2008	---	Zinc	Placebo	---	---	Double-blind	RCT	3 months	US
Cabannes 1984	---	Ticlopidine	Placebo	---	---	Double-blind	RCT	6 months	Africa
Charnigo 2017	---	PF-04447943	Placebo	---	---	---	RCT (Phase 1b)	29 days	---
Daak 2013	ISRCTN80844630	Omega-3	Placebo	---	---	Double-blind	RCT	1 year	Sudan
Daak 2018	---	AltemiaTM	Placebo	---	---	Double-blind	RCT (Phase 2)	2 months	USA

Trial	Registry number	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Blinding	Design	Follow-up	Country
de Abood 1997	---	DMPA	Levonorgestrel + ethinyl estradiol	Surgical sterilized (injectable)	---	Double-blind	RCT	12 months	Spain
Deceulaer 1982	---	Medroxyprogesterone acetate	Placebo	---	---	Double-blind	RCT, crossover	2 years (9 months, then crossover after 6 months washout)	Jamaica
Diop 2011	---	Sulfadoxine-pyrimethamine	Placebo	---	---	Open	RCT	3 months	Senegal
Eke 2003	---	Placebo (Vitamin c)	Proguanil	---	---	Open	RCT (Phase 2)	9 months	Nigeria
Gail 1982	---	Urea	Control	---	---	Double-blind	RCT (Phase 2)	Average: 13.7 months	Ghana
Glassberg 2017	NCT02061202	Mometasone furoate	Placebo	---	---	Triple-blind	RCT	16 weeks	US
Gupta 1995	---	Zinc	Placebo	---	---	Double-blind	RCT (Phase 2)	1.5 years	India
Heeney 2016	NCT01794000	Prasugrel	Placebo	---	---	Double-blind	RCT (Phase 3)	A minimum of 9 months and a maximum of 24 months	Americas, Europe, Asia and Africa
Isaacs 1972	---	Steroid (Testoserone/ Progesterone)	Saline	---	---	---	RCT, crossover (preliminary report before crossover)	4-6 months	Nigeria
Mann 1974	---	Folic acid	Folic acid + Sodium bicarbonate	---	---	---	RCT, crossover	2 years (crossover after 1 year, no washout)	UK
Manrique 1987	---	Pentoxifylline	Placebo	---	---	---	RCT (Phase 2)	6 weeks	Brazil
NCT02482298	NCT02482298	Ticagrelor 45 mg	Ticagrelor 10 mg	Placebo	---	Double-blind	RCT	12 weeks	USA, Egypt, France, Italy,

Trial	Registry number	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Blinding	Design	Follow-up	Country
									Kenya, Lebanon, UK, Turkey
Niihara 2018	NCT01179217	L-glutamine	Placebo	---	---	Double-blind	RCT (Phase 3)	48 weeks	USA
Oski 1968	---	Promazine hydrochloride	Placebo	---	---	Double-blind	RCT, crossover	3 months	USA
Pace 2003	---	NAC (high-dose)	NAC (mid-dose)	NAC (low-dose)	Placebo	Double-blind	RCT	7 months	USA
Reid 2014	NCT01601340	HQK-1001	Placebo	---	---	Double-blind	RCT	48 weeks	United States, Lebanon, Egypt, Jamaica and Canada
Schlaeger 2017	---	Pregabalin	Placebo	---	---	Double-blind	RCT	3 months	USA
Sins 2017	NCT01849016	NAC	Placebo	---	---	Double-blind	RCT	6 months	Netherlands, Belgium, UK
Styles 2010	---	GMI-1070	---	---	---	---	Single-arm	1 month	USA
Tomer 2001	---	mehaden fish oil	Placebo (olive oil)	---	---	Double-blind	RCT	12 months	US
Vichinsky 2010	---	Transfusion	Standard of care	---	---	---	RCT	---	USA
Wambebe 2001	---	Niprisan	Placebo	---	---	Phase 2	RCT, crossover (Phase 2)	13 months (6 months per treatment, 1-month washout in-between)	Nigeria
Wun 2013	NCT01167023	Prasugrel	Placebo	---	---	Double-blind	RCT (Phase 2)	30 days	United States and Canada
Zago 1984	---	Aspirin	Placebo	---	---	---	RCT, crossover (Phase 2)	10 months (5 months per treatment)	Brazil

Trial	Registry number	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Blinding	Design	Follow-up	Country
Al Hashmi 2017	---	Hydroxyurea	---	---	---	---	Single-arm	6 months	Oman
Brandalise 2017	---	Methotrexate	---	---	---	---	Single-arm	12 weeks	Brazil
Bridges 2017	---	GBT440	---	---	---	---	Single-arm	10 weeks	Unclear
Bumma 2017	---	Scheduled outpatient red cell exchange programme	---	---	---	---	Single-arm	1 year	---
Colombatti 2018	NCT02709681	Hydroxyurea	---	---	---	---	Single-arm	1 years	Italy
Di Maggio 2018	---	Hydroxyurea	---	---	---	---	Single-arm	Mean: 6.6 years	Italy
Hoppe 2017	NCT00508027	Simvastatin	---	---	---	---	Single-arm	3 months	USA
Keikhaei 2015	---	Hydroxyurea	---	---	---	---	Single-arm	1 year	Iran
Kwiatkowski 2017	---	Deferiprone	---	---	---	---	Single-arm	1 year	USA
LeBlanc 2016	NCT02709681	Methadone	---	---	---	---	Single-arm	Mean: 2.1 years	USA
Lemonne 2017	---	Hydroxyurea	---	---	---	---	Single-arm	2 years	Guadeloupe
NCT01476696	NCT01476696	Prasugrel	---	---	---	---	Single-arm (Phase 2 part B)	28 days	USA
Quarmyne 2017	---	Hydroxyurea	---	---	---	---	Single-arm	3 months	USA
Rigano 2018	---	Hydroxyurea	---	---	---	---	Single-arm	Median: 7 years	Italy
Sethy 2018	---	Hydroxyurea	---	---	---	---	Single-arm	12 months	India
Youssry 2017	---	Hydroxyurea	---	---	---	---	Single-arm	up to 120 months	Egypt

Note: Trial bolded were base case studies; Trials shaded in grey were not included in the final network meta-analyses.

Table 11: Eligibility criteria of RCTs included in the feasibility assessment

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Adegoke 2013	Lime juice + Routine oral drugs (folic acid, vitamin B complex and proguanil) vs Control (Routine oral drugs (folic acid, vitamin B complex and proguanil))	---	---	Steady state (no painful episode, anemic crisis, or infection on the day of recruitment)	No hydroxyurea treatment	---	Not on any other alternative medicine commonly used by some patients with SCA in Nigeria such as Aloe vera gel, Moringa oleifera, Solamine syrup, and Ciklavit (Cajanus cajal) suspension as well as Discriovite suspension and or Nicosan (Niprisan) capsule
Alvim 2005	Piracetam vs Placebo	5-20 years	---	---	No hydroxyurea treatment	Regular blood transfusion programmes	---
Arruda 2013	Placebo vs Vitamins C and E	≥ 18 years	HbSS or HbSβ^0	---	---	---	Other investigational drugs in the last 12 months

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Ataga 2008	Senicapoc (high-dose) vs Senicapoc (low-dose) vs Placebo	18-60 years	HbSS	≥ 1 nacute sickle-related painful episode that had required hospitalization, but none in the 4 weeks prior to screening	Stable dose for a minimum of 3 months at study enrollment.	Received a transfusion within 30 days of enrollment or undergone an exchange transfusion within 60 days of enrollment	One or more nonallowed medications within 30 days of enrollment (eg, amiodarone, chlorperazine, disopyramide, dofedilide, haloperidol, procainamide, quinidine, risperidone, sotalol, thioridazine, trifluoperazine, warfarin sodium, and erythropoietin)
Ataga 2011	Senicapoc vs Placebo	16-65 years	HbSS, HbSC, HbSβ^0, HbSβ$^+$	≥ 2 acute sickle-related painful crises in the previous 12 months	Received hydroxyurea for the preceding 12 months and their dose was stabilized for at least 3 months prior to the study	Participated in a chronic transfusion programme	Received previous treatment with senicapoc
Ataga 2017	Crizanlizumab (high-dose) vs Crizanlizumab (low-dose) vs Placebo	16-65 years	HbSS, HbSC, HbSβ^0, HbSβ$^+$	2-10 SCD-related pain crises in the 12 months before enrollment	---	Undergoing long-term red-cell transfusion therapy	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Bao 2008	Zinc vs Placebo	---	HbSS	---	No hydroxyurea treatment	receiving > 6 transfusions per year	---
Cabannes 1984	Ticlopidine vs Placebo	---	---	---	---	---	Received no antisickling treatment for 2 months before admission
Charnigo 2017	PF-04447943 vs Placebo	---	SCD	---	---	---	---
Daak 2013	Omega-3 vs Placebo	---	---	Steady state, defined as no evidence of fever, infection, or crisis for .4 wk before the start of the study	No hydroxyurea treatment	Prescence of blood transfusion	---
Daak 2018	AltemiaTM vs Placebo	5–17 years	---	2-10 documented sickle cell crises during the 12 months prior to screening	Either not received, or were on a stable regimen of hydroxyurea	---	---
de Abood 1997	DMPA vs Levonorgestrel + ethinyl estradiol vs Surgical sterilized (injectable)	---	---	---	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Deceulaer 1982	Medroxyprogesterone acetate vs Placebo	---	---	---	---	---	---
Diop 2011	Sulfadoxine-pyrimethamine vs Placebo	---	---	---	---	---	---
Eke 2003	Placebo (Vitamin c) vs Proguanil	1-16 years	HbSS	---	---	---	---
Gail 1982	Urea vs Control	---	HbSS	---	---	---	---
Glassberg 2017	Mometasone furoate vs Placebo	≥ 15 years	HbSS or HbSβ^0	< 15 ED visits for SCD pain over the prior 12 months	---	---	---
Gupta 1995	Zinc vs Placebo	> 5 years	HbSS	---	---	---	Patients on drug therapy for some other disease
Heeney 2016	Prasugrel vs Placebo	2-18 years	HbSS, HbSβ^0	≥2 VOC in the year prior to screening	---	History of chronic RBC transfusion for prevention of stroke or current chronic treatment with RBC for any reason.	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Isaacs 1972	Steroid (Testoserone/Progesterone) vs Saline	---	HbSS	Moderately severe pain at least once in 3 months (with little or no fever or exacerbations of jaundice)	---	---	---
Mann 1974	Folic acid vs Folic acid + Sodium bicarbonate	5-17 years	HbSS, HbSC, HbSβ	Previously suffered painful crises	---	---	---
Manrique 1987	Pentoxifylline vs Placebo	---	HbSS	---	---	---	---
NCT02482298 2017	Ticagrelor 45 mg vs Ticagrelor 10 mg vs Placebo	18-30 years	HbSS, HbSβ^0	---	Dose must have been stable for 3 months	Treatment with chronic red blood cell transfusion therapy.	Chronic treatment with anticoagulants or antiplatelet drugs
Niihara 2018	L-glutamine vs Placebo	> 5 years	HbSS, HbSβ^0	≥ 2 pain crises (no upper limit) documented during the previous year	Stable dose within 3 months and continue during the trial	Received any blood products within 3 weeks before screening	Received treatment with l-glutamine within 30 days before the screening
Oski 1968	Promazine hydrochloride vs Placebo	---	---	≥2 painful episodes during	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
				the 2 year period prior to study.			
Pace 2003	NAC (high-dose) vs NAC (mid-dose) vs NAC (low-dose) vs Placebo	> 15 years	HbSS, HbSβ^0	With dense cells greater than 6% and 2 or more VOC episodes per year for the 2 years prior to enrollment	---	Chronic transfusions	Investigational drug therapy
Reid 2014	HQK-1001 vs Placebo	12-60 years	HbSS, HbSβ	≥ 1 acute SCD-related complication or leg ulcers in 12 months	No current (i.e., within 3 months prior to enrolment) hydroxyurea treatment	Regular transfusion program or transfusion in the preceding 3 months unless Hb A had decreased to less than 20%	---
Schlaeger 2017	Pregabalin vs Placebo	18-82 years	---	Pain now score ≥ 4 on a 0-10 scale at registration	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Sins 2017	NAC vs Placebo	≥ 12 years	HbSS, HbSC, HbSβ^0, HbSβ$^+$	≥ 1 VOC per year in the past 3 years	Stable dose for 6 months piror to study	Chronic blood transfusion or transfusion in the preceding 3 months	Use of pain medication for sickle-cell related pains on more than 15 days per month in the past 6 months
Styles 2010	GMI-1070	18-50 years	HbSS and HBSB0thal	---	---	---	---
Tomer 2001	mehaden fish oil vs Placebo (olive oil)	≥ 18 years	---	Frequent pain episodes (≥3 events/year)	Not on hydroxyurea	---	---
Vichinsky 2010	Transfusions vs standard of care	21-55 years	---	---	30% on hydroxyurea on transfusion, 50% on hydroxyurea on standard of care	---	---
Wambebe 2001	Niprisan vs Placebo	2-45 years	HbSS	≥ 3 painful or vaso-occlusive crises in the previous year	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Wun 2013	Prasugrel vs Placebo	18 to 55 years	HbSS, HbSC, HbSβ^0, HbSβ^+	Did not have a diagnosis of acute VOC within 30 days of the study screening visit	Stable dose 30 days prior to randomization	---	---
Zago 1984	Aspirin vs Placebo	---	---	---	---	---	---
Al Hashmi 2017	Hydroxyurea	≥ 18 years	---	> 3 admissions with VOC/year, history of acute chest syndrome, history of priapism, history of splenic sequestration crises	On hydroxyurea 5-10mg/kg/day	Blood transfusion during the study	---
Brandalise 2017	Methotrexate	---	---	> 3 severe VOC episodes/year, that were refractory to opioids for periods longer than 3 weeks duration.	Under chronic hydroxyurea treatment	---	---
Bridges 2017	GBT440	---	SCD and severe anemia, i.e.	---	---	---	---

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
			HB < 6.5 g/dL				
Bumma 2017	Scheduled outpatient red cell exchange programme	---	---	---	---	---	---
Colombatti 2018	Hydroxyurea	---	---	2-3 vaso-occlusive crisis and/or hospitalizations in the last year	---	---	---
Di Maggio 2018	Hydroxyurea	---	---	>3 painful VOC per year and/or >2 Acute Chest Syndrome	New to hydroxyurea treatment	---	---
Hoppe 2017	Simvastatin	>10 years	HbSS or HbSβ^0	≥ 3 vaso-occlusive pain episodes in the preceding year	At a stable dose for ≥ 3 months	Red cell transfusion within the 30 days prior to enrolment	Current treatment with statins, amiodarone or other drugs with known metabolic interactions with statins (e.g. cytochrome P450 3A4 metabolism)
Keikhaei 2015	Hydroxyurea	6-18 years	SCD	---	---	---	Treatment other than hydroxyurea

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Kwiatkowski 2017	Deferiprone	---	---	---	---	---	---
LeBlanc 2016	Methadone	---	---	> 5 pain events per year	---	---	---
Lemonne 2017	Hydroxyurea	---	---	Absence of acute episodes (infection, VOC, ACS, stroke, priapisrn) at least one month before inclusion into the study.	---	No blood transftisions in the previous three months	---
NCT01476696	Prasugrel	≥2 to <18 years of age and ≥ 12 kg body weigh t	HbSS, HbSβ^0	---	A stable dose for the 60 days prior to enrolment	Treatment with packed RBC or whole blood transfusion therapy within 30 days prior to dosing	Any nonsteroidal anti-inflammatory drug (NSAID) use within 5 days prior to screening or Any aspirin, warfarin, thienopyridine, or other antiplatelet medication use within 10 days prior to dosing or Anticipated use of aspirin, warfarin, thienopyridine, or other antiplatelet medication during the study period

Trial	Interventions	Age	Genotype	History of pain/crises/complications	Status of hydroxyurea treatment	Prior transfusion (exclusion criteria)	Concurrent medications (exclusion criteria)
Quarmyne 2017	Hydroxyurea	---	HbSS, $HbS\beta^0$	---	---	Concurrent chronic transfusion	---
Rigano 2018	Hydroxyurea	---	---	2–3 VOC and/or acute chest syndrome in the year prior	Received hydroxyurea therapy	---	---
Sethy 2018	Hydroxyurea	≥ 18 years	HbSS	> 2 attacks of VOC per year and/or rate of transfusion 1–2 units/month	---	---	---
Youssry 2017	Hydroxyurea	---	---	---	On hydroxyurea ≥3 consecutive months	Chronic blood transfusion protocol	---

** - VOC: vaso-occlusive crisis; SCD: sickle cell disease; ED: emergency department; Note: Trial bolded were base case studies; Trials shaded in grey were not included in the final network meta-analyses.*

A.4 Outcome definitions

Table 12: Definitions of crisis used in 5 RCTs included in adult network

Study	Treatments	Crisis
Ataga 2017	Placebo, High-dose Crizanlizumab, Low-dose Crizanlizumab	Sickle cell–related pain crises were defined as acute episodes of pain, with no medically determined 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 nonsteroidal anti-inflammatory drug. The acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism were also considered to be crisis events.
Ataga 2011	Placebo, senicapoc	A painful crisis was defined as an episode of acute pain with no cause other than a vaso-occlusive event that required a medical facility visit and treatment with oral or parenteral narcotics, or parenteral non-steroidal anti-inflammatory drugs. Included in the definition of painful crisis were acute chest syndrome, hepatic sequestration, splenic sequestration, priapism, stroke and death (with the exception of homicide, suicide, or accidental death). To ensure consistency across sites, all protocol-defined sickle-related painful crises identified by the Investigators that resulted in a visit to a medical facility were adjudicated by an independent, blinded, Crisis Review Committee (CRC).
Ataga 2008	Placebo, senicapoc (low-dose), senicapoc (high-dose)	An independent, blinded crisis review committee adjudicated all sickle cell painful crises and related adverse event data (Document S1). A painful crisis was defined as a period of severe pain (with no explanation other than SCD) lasting 4 or more hours in duration, requiring a visit to a health care facility, and requiring parenteral opiate or other narcotic for relief
Pace 2003	Placebo, NAC (low-dose) 600 mg/day, NAC (mid-dose) 1200mg/day, NAC (high-dose) 2400mg/day	Defined as a visit to a medical facility that lasted more than 4 hr for acute pain related to vaso-occlusion requiring parenteral narcotics. The occurrence of acute chest syndrome, priapism, splenic, or hepatic sequestration was also counted as a VOC episode. Acute chest syndrome included those subjects with chest wall pain and a new infiltrate on chest X ray.
Niihara 2018	Placebo, L-glutamine	A pain crisis was defined as pain leading to treatment with a parenterally administered narcotic or ketorolac in an emergency department (ED) (or outpatient treatment center) or during hospitalization.

A.5 Additional risk of bias results

Overall, the RCTs were considered to have low risk of bias based on assessment using the Cochrane Collaboration's tool. Almost 50% were at unclear risk of bias due to allocation concealment, selective reporting, and random sequence generation. Also, 10-15% were at high risk of bias due to incomplete outcome data, blinding of outcome assessor, and blinding of personnel. Full results are in the appendix.

Overall, the single-arm studies were at high risk of bias due on several domains of the Newcastle-Ottawa scaleFigure 4): 93.7% at high risk of bias due to outcome of interest not being present at start, 87.5% at high risk of bias due to assessment of outcome, and 75% at high risk of bias due to comparability on additional factors. Also, almost 50% were at high risk of bias due to representativeness of exposed cohort, comparability on basic factors, or the follow-up not being long enough. This high risk of bias further discourages use of the single-arm studies for analysis.

Figure 2: Cochrane risk of bias assessment of 9 randomized controlled studies included in network meta-analysis

Figure 3: Cochrane risk of bias assessment across all studies included in review presented as percentages across studies.

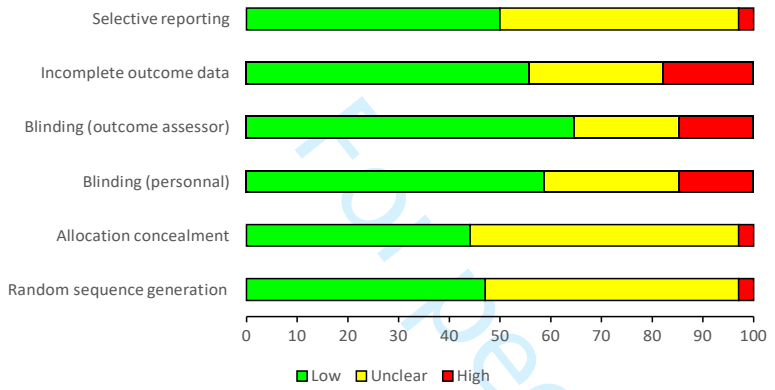
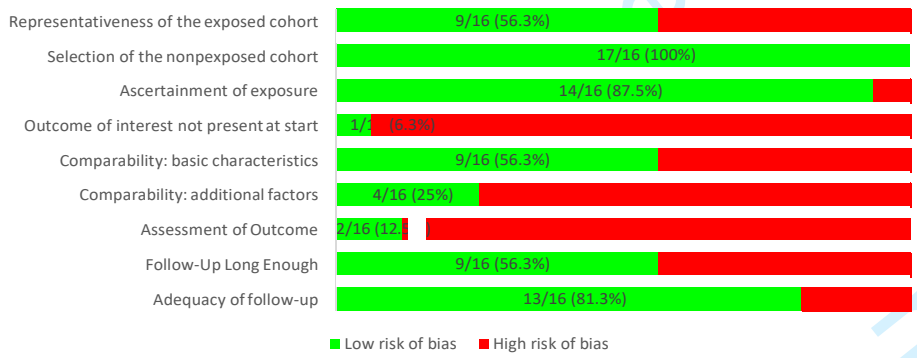


Figure 4: Newcastle-Ottawa quality assessment of non-randomized trials presented as percentages across studies.



A.6 Table of characteristics and references for of all studies identified by SLR

Author/Year/Country Ref/Enrolment /NCT registry	Design Total N of PT (N of female); N of arm	Main in/exclusion criteria	Participants					Interventions			Sponsor	Pub type
			Age (years)† Race (n, %)†	Total N of SCD types (n, %)	Total N of HU use (n, %)	Baseline pain/crisis/VOC (n or %) †	Other baseline characteristics (n or %) †	Group	Duration	Other concomitant therapy		
Schlaeger 2017 USA [1]	RCT, double-blind Single centre 22 (16); 2	1. 18-82 years 2. history of SCD pain that was not well controlled (pain now score ≥ 4 on a 0-10 scale at registration) Exclusion: renal impairment	Adults Mean (SD): 33.1 (9.9) African american: 11 (100%)	HbSS: 15 (68%) HbSC: 6 (27%) HbSβ: 1 (5%)	NR	NR	NR	1. Pregabalin 75mg BID oral (n=11) 2. Placebo (n=11)	3 months	NR	NR	JA
Hoppe 2017 USA [2] NCT00508027	Single-arm Single centre 24 (13); 1	1. >10 years 2. history of ≥ 3 vaso-occlusive pain episodes requiring treatment with a prescribed oral or parenteral analgesic in the preceding year 3. Patients receiving treatment with HU at a stable dose for ≥3 months were eligible	Adults and children Overall mean: 18.5 (range 10-34)	HbSS: 17 (89%) HbSβ⁰: 2 (11%)	10 (53%)	NR	NR	Simvastatin (n=19*) OD oral Dose adjusted by weight: 40 mg (weight >60 kg); 30 mg (weight 45–60 kg); 25 mg (weight 35–44 kg)	3 months	NR	DDCF, NHL BI and NCRR	JA
Glassberg 2017 USA [3] Feb 2014 to Oct 2016 NCT02061202	RCT, triple-blind Single centre 54 (23); 2	1. HbSS or HbSβ⁰ 2. ≥15 years 3. self-report of cough or wheeze over the preceding two months Exclusion: Diagnosis of asthma, incareration, pregnancy, ≥15 ED visits for SCD pain over the prior 12 months and discharge from the hospital within the previous 7 days	Adults and adolescents Mean (SD): 30(8.56)	HbSS: 50 (96%) HbSβ⁰: 2 (4%)	34 (65%)	NR	Prior ED Utilization (past 12 months) 0-5 visits: 71% 6-10 visits: 24% 11-15 visits: 6%	1. Mometasone furoate 220mcg OD inhale (n=35*) 2. Placebo (n=17*) In addition to standard SCD care	16 weeks	NR	NHLBI	JA

Ataga 2017 Brazil, Jamaica, USA [4-8] Aug 2013 to Jan 2015 NCT01895361	RCT, double-blind Multicentre 198 (109); 3	1. HbSS, HbSC, HbSβ^0, HbSβ$^+$ 2. 16-65 years 3. two to ten SCD-related pain crises in the 12 months before the enrolment Exclusion: long-term red-cell transfusion	Adults and adolescents Median: 26 (range 16-56) Black, or African American: 60 (90%) White: 4 (6%) Other: 3 (4%)	HbSS: 141 (71%) HbSC: 32 (16%) HbSβ^0: 12 (6%) HbSβ$^+$: 10 5%) Other: 3 (2%)	123 (62%)	N of SCD-related pain crises during previous 12 months 2-4: 63% 5-10: 37%	NR	1. High-dose Crizanlizumab 5 mg/kg IV (n=67) 2. Low-dose Crizanlizumab 2.5 mg/kg IV (n=66) 3. Placebo (n=65) Two doses 2 weeks apart (loading dose) and then every 4 weeks. A total of 14 doses for 50 weeks	52 weeks	NR	Selexys Pharmaceuticals, NHLBI and OOPD	JA, JA supp
Lemonne 2017 Guadeloupe [9]	Single-arm Single centre 28 (13); 1	1. at the beginning of the HU therapy 2. patients were at steady state, i.e., no blood transfusions in the previous three months and absence of acute episodes (infection, VOC, ACS, stroke, priapisrn) at least one month before inclusion into the study. Exclusion: renal insufficiency, hepatic insufficiency or human immunodeficiency virus infection	Adults Overall mean: 37.0(SD 11.6)	All SCA (50% with α-thalassemia)	N/A	Frequent hospitalized VOC: 14 (50%) N of ACS ≥ 1: 10 (36%)	NR	HU Therapy (n=28)	2 years	NR	Region of Guadeloupe.	JA
Quarmyne 2017 USA [10] 2009-2011	Single-arm Retrospective 134 (74); 1	1. HbSS, HbSβ^0 2. started HU in 2009-2011 Exclusion: concurrent chronic transfusion and hydroxyurea therapy, underwent bone marrow transplant, no follow-up data	Adults and Children Overall Median: 7.5 ≤5 years: 39% 6-10 years: 33% 11-15 years: 20% >15 years: 8%	NR	None	NR	NR	HU oral (n=78*) Dose: 20 mg/kg/day (initially), followed by dose escalation every 2 months to 25–30 mg/kg/day or maximum tolerated dose if lower	~3 months	NR	NCATS, NIH and the Abraham J. & Phyllis Katz Foundation.	JA
Daak 2018 USA [11]	RCT, double-blind Multicentre 67(NR); 2	1. 5–17 years 2. two and ten (inclusive) documented SCC during the 12 months prior to screening 3. either not received, or were on a stable regimen of hydroxyurea (HU)	Children and Adolescents NR	NR	51 (76%)	NR	NR	1. AltemiaTM (n=50) 2. Placebo (n=17)	2 months	NR	NR	CA
Bridges 2017 Unclear	Single-arm	Patients with SCD and severe anaemia, i.e. Hb < 6.5 g/dL	Adults	HbSS:6 (86%) HbSβ: 1 (14%)	NR	Baseline VOC admission (total n): 15	Baseline transfusions (total n): 24	GBT440 900mg OD (n=7)	10 weeks	NR	NR	CA

[12]	Single centre 7(4); 1		Overall mean: 48.6(SD 15.8)									
Charnigo 2017 Unclear **[13]**	RCT (phase 1b) Retrospective 29 (NR); 2	Stable SCD patients	NR	NR	NR	NR	NR	1. PF-04447943 25mg or 5mg BID oral (n=22) 2. Placebo (n=7)	29 days	NR	Pfizer	CA
Sins 2017 Netherlands, Belgium, UK [14, 15] Apr 2013 to Nov 2015 NCT01849016	RCT, double-blind Multicentre 96 (40); 2	1. HbSS, HbSC, HbSβ^0, HbSβ$^+$ 2. ≥ 12 years 3. History of at least 1.0 VOC per year in the past 3 years Exclusion: Chronic blood transfusion or transfusion in the preceding 3 months, VOC in the last 4 weeks, pregnancy, active gastric/duodenal ulcers, HU treatment with unstable dose in the last 3 months or started on HU shorter than 6 months prior to study, use of pain medication for SCD-related pains on more than 15 days per month in the past 6 months, poor compliance	Adults Mean (SD): 28.4(8.9) Latin-America/Caribbean: 17 (43%) Africa :23 (57%)	HbSS/HbSβ^0: 46 (69%) HbSC/HbSβ$^+$:21 (31%)	28 ((42%)	N of VOC over past three years Median: 11 (IQR 6-20)	Number of hospital admission over past three years Median: 3 (IQR 1-6)	1. Placebo (n=40*) 2. NAC 600mg BID oral (n=27*)	6 months	NR	ZonMw, the Academic Medical Centre, JANIVO Stichting, Egbers Stichting,	JA
Niihara 2018 US [16-20] Jun 2010 to Dec 2013 NCT01179217	RCT, double-blind (phase 3) Multicentre 230 (124); 2	1. > 5 years 2. had had at least two pain crises (no upper limit) documented during the previous year 3. HU at stable dose within 3 months and continue during the trial	Adults and children Mean (SD): 21.4(12.42) Black: 144 (95%) Hispanic: 4 (3%) Other: 4 (3%)	SCA: 207 (90%) HbSβ^0: 21 (9%) HbSβ^{+}: 2 (1%)	153 (66.5%)	N of SCD pain crises in the year before trial 0-1: 0.7% 2-5: 84.2% 6-9: 9.9% ≥ 10: 5.3%	NR	1. L-glutamine 0.3 g/kg BID oral (n=152) 2. placebo (n=78) Maximum dose: 30mg	48 weeks	NR	Emmaus Medical	JA
Sethy 2018 India **[21]** 2013 to 2016	Single-arm Single site 142 (46); 1	1. HbSS 2. ≥ 18 years 3. > 2 attacks of VOC per year and/or rate of transfusion 1–2 units/month were included in the study Exclusion: pregnancy, human immunodeficiency virus infection or medications that could potentially enhance HU toxicity, abnormal serum Cr/ALT levels	Adults	All HbSS	N/A	64% presented with repeated VOC, 13% with transfusion dependency and 23% with both the above features	NR	HU 10 mg/kg/day oral (n=128*)	12 months	All the patients were advised to take folic acid (5 mg/day) and ensure adequate fluid intake	NR	JA

Di Maggio 2018 Italy [22] January 2000 to April 2014	Single-arm Retrospective 140 (71); 1	1. start HU treatment 2. >3 painful vaso-occlusive crises per year and/or >2 Acute Chest Syndrome	Adults and children Median(range): 35 (0.4-61)	HbSS: 25 (18%) HbSβ^0: 54 (39%) HbSβ$^+$: 56 (40%) HbSα-β: 4 (3%) HbSLepore: 1 (0.7%)	90 (64%)	NR	NR	HU oral (n=140) Starting dose: 10 mg/kg daily Titration: increased at a rate of 5 mg/kg/week	Mean follow-up: 6.6 years	NR	NR	JA, JA supp
Youssry 2017 Egypt [23]	Single-arm Retrospective 60 (37); 1	Patients who were on HU therapy for at least 3 consecutive months Exclusion: Chronic blood transfusion, chronic disabling hepatic/renal disease	Adults and children Mean: 12.8 (SD 5.5) (range 4 to 24)	HbSS: 27 (45%) HbSβ: 33 (55%)	N/A	NR	NR	HU 15-30mg/kg/day oral (n=60)	Up to 120 months	NR	NR	JA
Bumma 2017 USA [24] 1/1/2000 to 1/15/2016	Single-arm Retrospective 104 (60); 1	NR	Adults and Adolescents Median (range): 24(15-62)	HbSS: 89 (86%)	13%	NR	NR	Scheduled outpatient red cell exchange (n=104)	1 year	NR	NR	CA
Kwiatkowski 2017 USA [25]	Single-arm Registry data 291 (166); 0	Inclusion on a patient registry has been maintained for all US patients who receive deferiprone	Adults and children Mean: 29.5 (SD15.7) ≤ 18years: 79	NR	NR	NR	NR	Deferiprone oral (n=291)	Mean: 1.3 years (range 0-4.1)	NR	NR	CA
Rigano 2018 Italy [26]	Single-arm Retrospective cohort 652 (302); 1	1. On HU therapy 2. The indication for HU initiation was 2–3 vaso-occlusive crisis and/or acute chest syndrome in the year prior	Adults and children Mean: 24.5 (SD 15) Median: 24 (range 1-67) Caucasian: 400/621 Africa: 221/621	HbSS: 277 (47%) HbSβ^0: 167 (28%) HbSβ$^+$: 131 (20%) Other: 19 (3%) Total N: 594	N/A	NR	NR	HU oral (n=628*) 10 mg/kg/day, and adjusted or escalated according to tolerance	Median duration: 7 years (range <1-29)	Folic acid was concomitantly used in 71.3% of patients (n/N = 388/448).	NR	JA

Al Hashmi 2017 Oman [27]	Single-arm Single centre 18 (6); 1	1. Aged ≥ 18 years 2. on HU 5-10mg/kg/day 3. history of more than three admissions with vaso-occlusive crises /year, history of acute chest syndrome, history of priapism, history of splenic sequestration crises Exclusion: pregnancy, blood transfusion during the study, follow-up of < 6 months	Adults	NR	N/A	NR	NR	HU 5-10mg/kg/day oral (n=18)	At least 6 months	NR	NR	CA
Colombatti 2018 Italy [28]	Single arm Multicentre 204 (20); 1	1. On HU therapy	Children and adolescents Overall mean: 7.68 (range 11-221 months) Nigeria: 65 (32%) Ghana: 32 (16%) Senegal: 12 (6%) Italy and Albania: 37 (18%) Central America and India: 10 (5%) Unknown: 10 (5%)	HbSS:172 (84%) HbSβ^0: 22 (11%) HbSC: 8 (4%) HbSβ$^+$: 3 (1.5%) Other: 1 (0.5%)	N/A	NR	NR	HU therapy (varied by centre) (n=204)	1 year	NR	NR	JA
Brandalise 2017 Brazil [29] RBR-2s9xvn	Single arm Single centre 14 (5); 1	1. Under chronic hydroxyurea treatment 2. >3 severe VOC episodes/year, that were refractory to opioids for periods longer than 3 weeks duration Exclusion: pregnancy, concomitant infection	Adults Overall median: 23.5 (range 18-32)	HbSS:11(79%) HbSC:3 (11%)	14 (100%)	Previous VOC/month: 3.3 (95% CI 2.0-5.0) (excluding one PT with 19.3 VOC/month)	Avascular necrosis: 7	MTX 10mg weekly IM (n=14)	12 weeks	NR	Boldrini Children's Center and UNIEMP Institute.	JA
Keikhaei 2015 Iran Cohort [30] 2013 to 2014	Single-arm Single centre 48 (24); 1	1. admitted to Shafa Hospital, Ahvaz, Iran, from 2013 to 2014 2. aged 6-18	Children and adolescents Overall mean 13.7 (range 6 to 18)	NR	NR	NR	NR	HU 10 mg/kg/day oral (n=48)	1 year	NR	Ahvaz Jundishapur University of Medical Sciences	JA

LeBlanc 2016 USA [31] NCT02709681	Single-arm Retrospective cohort study 16 (6); 1	More than 5 pain events per year	Adults and adolescents Mean: 15.5 (SD 2.8)	HbSS: 14 (88%) HbSβ⁰: 1 (6%) HbSC: 1 (6%)	NR	NR	ED visit/month: Mean 0.31 (SD 0.27) Hospitalization/month: 0.19 Chronic transfusions: 10	Methadone oral (n=16) Flexible dose	Mean: 2.1 years	NR	NR	CA
Heeney 2016 Americas, Europe, Asia and Africa [32, 33] May 2013 to Jun 2015 NCT01794000	RCT, double-blind (phase 3) Multicentre 341 (173); 2	1. HbSS, HbSβ⁰ 2. At least 2 VOC in the year prior to screening 3. TCD within the last year for patients ≤16 years of age 4. Children aged 2 to <18 years 5. Body weight ≥12 kg Exclusion: abnormal/conditional TCD, chronic transfusion, hepatic/renal dysfunction, history of transient ischemic attach or haemorrha, severe head traumatic stroke, chronic treatment with NSAID, use of anticoagulants or other antiplatelet drugs	Children and adolescents Mean:10.6 (SD 4.3) White: 58/169 Black: 109/169 Multiple: 2/169	NR	153 (45%)	N of VOCs in previous year: Mean 4.0 (SD 7.9)	NR	1. Placebo (n=170) 2. Prasugrel oral (n=171) Individual dose-adjustment strategy: Initial dose: 0.08 mg/kg; maintenance: 0.04-0.12 mg/kg (maximum 10mg) by a targeted level of platelet reactivity	9 to 24 months	No anticoagulants or antiplatelet drugs during the study No NSAID drugs	Daiichi Sankyo and Eli Lilly	JA
Reid 2014 United States, Lebanon, Egypt, Jamaica and Canada [34] Aug 2012 to May 2013 NCT01601340	RCT, double-blind (phase 2, terminated early) Multicentre 76 (49); 2	1. HbSS or HbSβ 2. Aged 12-60 years 3. at least one acute SCD-related complication or leg ulcers in 12 months prior to enrolment 4. no current (i.e., within 3 months prior to enrolment) HU treatment Exclusion: regular transfusion, an acute vaso-occlusive event within 3 weeks, pulmonary hypertension requiring oxygen therapy, symptomatic untreated peptic ulcer or gastroesophageal reflux disease, history of pancreatitis, abnormal ALT/AST levels, HIV infection	Adults and children Mean: 27.8 (range 12-55) Black or African-American: 24 (63%) White :14 (37%)	HbSS: 60 (79%) HbSβ⁰: 16 (21%)	N/A	N of pain crises in the 12 months before enrolment 0-1: 13 >2: 25	NR	1. HQK-1001 15 mg/kg BID oral (n=38) 2. placebo (n=38)	48 weeks	Folic acid daily	HemaQuest Pharmaceuticals	JA

Adegoke 2013 Nigeria **[35]** Jul to Dec 2011	RCT, open Multicentre 113 (56); 2	Steady state (no painful episode, anemic crisis, or infection on the day of recruitment) Exclusion: alternative medicine (Aloe vera gel, Moringa oleifera, Solamine syrup, and Ciklavit (Cajanus cajal) suspension), hydroxyurea, Discriovite suspension, Niprisan	Children and adolescents Mean: 4.55 (SD 3.57)	NR	NR	N of previous significant painful episodes Mean: 3.27 (SD 3.93)	N of previous Transfusion Mean: 1.29 (SD 0.77) N of Previous hospitalization Mean: 2.12 (SD 2.67)	1. Lime juice + Routine oral drugs (folic acid, vitamin B complex and proguanil) BID oral (n=58) 2. Control (Routine oral drugs (folic acid, vitamin B complex and proguanil)) BID (n=55) Adjusted by body weight: ≤10kg: 5 ml; 11-20 kg: 10 ml; ≥20 kg: 15 mg	6 months	NR	NR	JA
Arruda 2013 Brazil **[36]** Sep to Dec 2010	RCT, double-blind Single centre 83 (53); 2	1. HbSS or HbSβ^0 Exclusion: hospitalized patients, pregancy, untreated iron overload, other investigational drugs in the last 12 months or contraindications to Vitamin C/E	Adults Overall median: 27 (range 18-68)	HbSS: 73 (88%)	NR	NR	Chronic use of NSAIDs: 52 Chronic use of opioids: 16 Transfused patients (past 12 months): 18	1. Placebo (n=39) 2. Vitamins C 1400 mg/day and E 800 mg/day oral (n=44)	6 months	NR	FAPESP and CNPq	JA
Wun 2013 United States and Canada **[37-39]** 26 Aug 2010 to 13 Jun 2011 NCT01167023	RCT, double-blind (phase 2) Multicentre 62 (30); 2	1. HbSS, HbSC, HbSβ^0, HbSβ$^+$ 2. aged 18 to 55 years 3. did not have a diagnosis of acute VOC within 30 days of the study screening visit 4. NSAIDs for treatment of pain were not permitted in the 5 days prior to randomization or for ≥5 consecutive days during the study period. 5. HU was permitted in patients already on a stable dose 30 days prior to randomization Exclusion: hepatic/renal dysfunction, HCt < 18%, risk of excessive bleeding, history of bleeding disorders, haemorrhagic or ischemic stroke, retinal haemorrhage, TIA or intracranial haemorrhage	Adults Mean:31.5	HbSS: 37 (61%) HbSC: 15 (25%) HbSβ^0: 3 (5%) HbSβ þ+: 6 (8%)	NR	Vaso-occlusive crisis: 61% Pain intensity: Mean: 1.8 vs 2.4	Acute chest syndrome: 22.0% (prasugrel) vs 9.5% (placebo) Pulmonary hypertension: 17.1% (prasugrel) vs 9.5% (placebo)	1. Prasugrel 5 mg/day oral (n=41) 2. placebo (n=19*)	30 days	NR	Daiichi Sankyo Co., Ltd. and Eli Lilly and Company.	JA
Daak 2013 Sudan **[40]** Apr 2009 to May 2010	RCT, double-blind Single centre 140 (61); 2	Steady state, defined as no evidence of fever, infection, or crisis for >4 week before the start of the study Exclusion: other chronic diseases, transfusion within 4 months,	Children and adolescents Mean (SD): 7.8(5.5)	All HbSS	NR	NR	Crisis-induced hospitalization (N/year) No. admission: 9.8%	1. Placebo (n=61*) 2. Omega-3 (n=67*)	1 year	All of the patients were receiving regular folate supplementation, and those ,5	Marie Curie Transfer of Knowledge Programme, Efamol, and the Kitchner	JA

ISRCTN80844630		hydroxyurea treatment, history of overt stroke, pregnancy					1-2: 43.7% 3-5: 24.1% > 5: 22.4%			y of age were receiving standard oral prophylactic penicillin.	Memorial Trust Fund and University of Khartoum	
Ataga 2011 United States, Jamaica, Brazil, France, Trinidad and the United Kingdom. **[41]** **Feb 2005 to Apr 2007** **NCT00102791**	RCT, double-blind (phase 3, terminated early) Multicentre 297 (160); 2	1. HbSS, HbSC, HbSβ^0, HbSβ$^+$ 2. aged 16-65 years 3. at least two acute sickle-related painful crises in the previous 12 months 4. Patients were permitted to receive concomitant therapy with HU if they had received HU for the preceding 12 months and their dose was stabilized for at least 3 months prior to the study Exclusion: unstable cardiovascular, neurological, endocrine, hepatic, or renal disorders, Hb < 40 or > 110 g/L, chronic transfusion, cancer diagnosis within 5 years, or hepatitis B/C or HIV infection	Adults and adolescents Mean: 28.5(SD 9.9) Black: 134 (92%) Multiracial: 6 (4%) Caucasian: 3 (2%) Other: 2 (2%)	HbSS: 245 (85%) HbSC: 16 (6%) HbSβ^0: 21(7%) HbSβ$^+$: 4 (1%) Other: 3 (1%)	163 (56%)	SCD crises history in past 12 months (%) 2-4: 59% >5: 41%	NR	1. Senicapoc 20mg/d BID (loading) and then 10mg/dOD oral (n=145*) 2. placebo (n=144*)	52 weeks	NR	Icagen (Research Triangle Park)	JA
Diop 2011 Senegal **[42, 43]** Sep 2007 to Feb 2008	RCT, open Single centre 60 (31); 2	1. Follow-up at least 2 years before in the clinic with records of standardized clinical and laboratory Exclusion: allergic to sulfonamide	Adults and adolescents Mean: 23.2 (SD 6.9)	All SCA	NR	N of VOC/year: Mean 0.8 (SD 1.25)	N of SCD with chronic complications: 8	1. Sulfadoxine-pyrimethamine (S: 25 mg/kg/P: 1.25 mg/kg) OD oral (n=30) 2. Placebo (n=30) The treatment was given once during the following months: September, October, and November	3 months	1. Folic acid, paracetamol during pains 2. Artemisinin-based combination therapy or injectable quinine for malaria attacks	NR	JA

Alvim 2005 Saudi Arabia **[44, 45]** Sep 1998 to Dec 1999	RCT, crossover, double-blind 73 (40); 2	Exclusion: renal, hepatic, cardiac or coagulation disorders secondary or not to SCD, regular transfusion, hydroxyurea use, age > 20 or < 5 years, cognitive dysfunction	Adults and children Median: 12.1 (range 5 to 20)	HbSS: 42 (58%) HbSC: 26 (36%) HbSβ⁰: 5 (7%)	NR	NR	History of transfusion: once: 13; 2-5 times: 19; More than 5: 18 Splenectomy: 5 Cholecystectomy: 5 Osteomyelitis: 11 Acute splenic sequestration: 12 Aplastic crisis: 1 Avascular necrosis of femoral head: 4	1. Piracetam 4.8 g/m^2/day QID (n=73*) 2. Placebo (n=73*)	6 months, then crossover with 2 weeks washout period	NR	FAPEMIG, CNPq	JA
Bao 2008 US **[46]**	RCT, double-blind Single centre 36 (14); 2	Exclusion: non-ambulatory, receiving more than 6 transfusions per year or taking hydroxyurea, history of substance abuse, neurological or psychiatric deficits that could affect compliance, use of immunosuppressive drugs, HIV and hepatitis B	Adults Overall mean: 32.9 (SD 9.7) (range 18-47) All black	HbSS: 32 (89%) HbSC: 3 (8%) HbSβ: 1 (3%)	None	N of sickle pain episode 3-month prior to the study: 5 (placebo); 3 (zinc)	NR	1. Placebo (n=18) 2. Zinc 25mg TID (n=18)	3 months	NR	NR	JA
Ataga 2008 **US** **[47]** **Feb 2002 and Jan 2004** **NCT00040677**	RCT, double-blind (phase 2) Multicentre 90 (45); 3	1. HbSS 2. Aged 18-60 years 3. at least one prior acute sickle-related painful episode (commonly referred to as painful crisis) that had required hospitalization, but none in the 4 weeks prior to screening Exclusion: Hb< 40 g/L or > 100 g/L, received a transfusion within 30 days or underwent an exchange transfusion within 60 days, hepatitis B, HIV, cancer diagnosis within 5 years, mediations (eg, amiodarone, chlorperazine, disopyramide, dofedilide, haloperidol, procainamide, quinidine, risperidone, sotalol, thioridazine, trifluoperazine, warfarin sodium, and erythropoietin)	Adults Mean: 33.6(range 19-55)	All HbSS	24 (27%)	Hospitalizations due to painful episodes in previous 12 months: None: 12 (39%) 1: 6 (19%) 2-3: 6 (19%) ≥3: 7 (23%)	NR	1. Placebo (n=30) 2. Senicapoc (low-dose): 100 mg (loading dose); 6 mg/d (maintenance) oral OD (n=29) 3. Senicapoc (high-dose): 150 mg (loading dose); 10 mg/d (maintenance) oral OD (n=31)	12 weeks	NR	Icagen (Research Triangle Park, NC)	JA

Eke 2003 Nigeria [48]	RCT, open (phase 2) Single centre 101 (48); 3	1. HbSS 2. Aged 1-16 years 3. Stable condition Exclusion: loss to 2 consecutive follow-up, pregnancy	Children and Adolescents Mean: 8.1 (SD 4.3) (Range 2-16)	HbSS: 101 (100%)	NR	NR	Total N of malarial parasites: 20 (equally distributed)	1. Pyrimethamine 0.5 mg/kg once weekly oral (n=36*) 2. Proguanil 1.5 mg/kg OD oral (n=32*) 3. Placebo (Vitamin c 7 mg/kg) OD oral (n=29*)	9 months	NR	Combating Childhood Communicable Diseases (Atlanta, Georgia)	JA
Pace 2003 US [49]	RCT, double-blind Single centre 21 (10); 4	1. HbSS or HbSβ^0 2. Aged above 15 years 3. With dense cells greater than 6% and 2 or more VOC episodes per year for the 2 years prior to enrollment. Exclusion: pregnancy, narcotic addition, chronic transfusions, history of stroke, HIV, investigational drug	Adults and Adolescents Mean:17.9 (SD1.2)	NR	NR	N of VOC episodes Mean: 5 (SD 2)	NR	1. Placebo (n=5) 2. NAC (low-dose) 600 mg/day (n=5) 3. NAC (mid-dose) 1200mg/day (n=5) 4. NAC (high-dose) 2400mg/day (n=6) All doses were divided by 3 to be taken	7 months	NR	Zambon Corp.	JA
Wambebe 2001 Nigeria [50, 65]	RCT, cross-over, double-blind (Phase 2) 82 (46); 2	1. HbSS 2. Aged 2-45 years 3. at least 3 painful or vaso-occlusive crises in the previous year Exclusion: HIV, hepatitis, pregnancy	Adults and children Overall (years) < 9: 1 (1%) 10-19: 67 (82%) 20-29: 11 (13%) 30-39: 3 (4%)	All HbSS	NR	Mild to Moderate Pains (Mean): 18.38 Severe Pains: 12.67	NR	1. Niprisan 12 mg/kg OD (n= 70*) 2. Placebo (n=70*)	6 months, then crossover without washout	NR	NR	JA
Tomer 2001 US [51, 52]	RCT, double-blind Single centre 13 (NR); 2	1. Frequent pain episodes (≥3 events/year) 2. Not on HU	Adults NR	NR	None	Frequency of pain episodes in 12 months: 7.8	NR	1. Mehaden fish oil: 0.25 g/kg/day OD oral daily (n=5*) 2. Placebo (n=5*)	12 months	NR	NR	JA
de Abood 1997 Spain [53]	RCT, double-blind Single centre 43 (43); 3	1. HbSS 2. history of at least one painful crisis per month were included	Adults Overall range: 17-39	All HbSS	NR	NR	NR	1. DMPA 150mg per month for first three months, then usual dose of 150mg every 3 months oral (n=13) 2. levonorgestrel/ethinyl estradiol (0.15/0.03 mg) OD oral (n=14) 3. Surgically sterilized (n=16) [not eligible]	12 months	NR	Special Programme of Human Reproduction of WHO	JA

Gupta 1995 India **[54]**	RCT, double-blind Phase 2 145 (34); 0	1. > 5 years 2. HbSS Exclusion: chronic persistent infection or exposed to extremes of temperature variation frequently, on drug therapy for some other disease, evidence of organ failure	Adults and children Mean: 16.4 (range12-27)	All HbSS	NR	NR	NR	1. Zinc: 220 mg TID oral (n=65*) 2. Placebo (n=65*)	1.5 years	NR	NR	JA
Manrique 1987 Brazil **[55]**	RCT Phase 2 60 (23); 2	HbSS Exclusion: acute infections	Adults and children Range: 7-34	All HbSS	NR	Overall pain events (n) None: 11 < 5 times: 7 < 10 times: 15 > 10 times: 11 Persistent: 14 Not clear: 2 Overall pain duration (days) None: 11 < 5 days: 12 < 10 days: 17 > 10 days: 4 Persistent: 14 Not clear: 2 All in 6 months observation period		1. Placebo (n=29*) 2. Pentoxifylline :(Adults: 1200mg; children: 400-600 mg, depending on body weight) oral (n=28*)	6 weeks	NR	NR	JA
Zago 1984 Brazil **[56]**	RCT, crossover 42 (NR); 2	NR	Adults and children Median: 12 (range 4 - 31)	HbSS: 25 (86%) HbSβ⁰: 4 (14%)	NR	NR	NR	1. Aspirin 17-45 mg/kg OD (n=29*) 2. Placebo (n=29*)	5 months, then crossover without washout	NR	NR	JA
Cabannes 1984 Africa **[57]**	RCT, double-blind Multicentre 140 (NR); 2	No antisickling treatment for two months before admission to the study Exclusion: other than HbSS; uncontrolled parasitic disease; malnutrition; a history of drug abuse; glaucoma, prostatis hypertrophy, urinary retention, hypersensitivity to ticlopidine or anticholingeric drugs, acute cerebro-vascular accidents, severe intercurrent infection, pulmonary oedema or renal failure	Adults and adolescents Overall range 15-45	All HbSS	NR	N of crises in 6 months before study: 223	NR	1. Ticlopidine 250mg BID if body weight <45kg; 250mg TID if body weight >45kg oral (n=70) 2. Placebo (n=70)	6 months	Acute crises treatment varied depends on regions but including transfusions, analgesic, antibiotics and anticoagulants	NR	JA

Gail 1982 Ghana [58] Sep 1976 to Sep 1978	RCT, double-blind Phase 2 79 (39); 2	HbSS Exclusion: other major illnesses	Adults and children Overall: < 5 years: 21 5-14 years: 28 > 14 years: 30	All HbSS	NR	Number of crises in the previous year 0-2: 18 > 2: 21	NR	1. Control (n=39) 2. Urea: 0.266 g/kg Low-dose: twice a week; High-dose: daily (n=40)	Average: 13.7 months	1. Folic acid (1 mg) and multivitamins daily 2.Chloroquine was given with urea or sucrose placebo	International Sickle Cell Anemia Research Institute and CSRPM	JA
Deceulaer 1982 Jamaica [59]	RCT, crossover, double-blind Single centre 25 (25); 2	HbSS	Adults Overall age range: 20-41	All HbSS	NR	NR	NR	1. placebo (n=10*) 2. medroxyprogesterone acetate 150mg every 3-month IM (n=13*)	2 years (9 months, then crossover after 6 months washout)	NR	NR	JA
Mann 1974 UK [60]	RCT, crossover Single centre 18 (12); 2	1. HbSS, HbSC, HbSβ 2. 5-17 years 3. Previously suffered painful crises	Children and adolescents Overall mean 8.4 (SD 3.2)	HbSS: 15 (83%) HbSC: 2 (11%) HbSβ: 1 (6%)	NR	NR	NR	1. Folic acid 5 mg daily oral (n=25) 2. Folic acid 5mg + Sodium bicarbonate 0.06-0.2 gm/kg/day initially, then 0.1-0.4 mg/kg/day oral (n=25)	2 years (1 year than crossover without washout	NR	United Birmingham Hospitals and Endowment Research Fund	JA
Isaacs 1972 Nigeria [61]	RCT, crossover (preliminary report before crossover) 44 (28); 2	1. HbSS 2. Moderately severe pain at least once in three months (with little or no fever or exacerbations of jaundice)	Adults and children Overall range 2-35	All HbSS	NR	NR	NR	1. Saline IM (n=44*) 2. Steroid (Testoserone/Progesterone) Male: testosterone 10 mg; Female: progesterone 10 mg every week IM (n=44*)	4-6 months	All patients were on regular folates and had high or normal serum-iron values	Glaxo Allenburys of Nigeria	Journal article
Oski 1968 USA [62]	RCT, crossover, double-blind 14 (5); 2	At least 2 painful episodes during the 2 year period prior to study	Adults and children NR	HbSS: 10 (71%) HbSC: 4 (29%)	NR	NR	NR	1. Promazine hydrochloride oral (n=14*) Based on weight: 2 tablets a day: 40-80 pounds; 3 tablets a day: 80-120 pounds; 4 tablets a day: > 120 pounds 2. Placebo (n=14*)	3 months	NR	NR	JA

NCT02482298 USA, Egypt, France, Italy, Kenya, Lebanon, UK, Turkey [63] Jul 2015 to Nov 2016	RCT, double-blind Multicentre 87 (47); 3	1. HbSS, HbSβ^0 2. Aged 18-30 3. If treated with hydroxyurea, the dose must have been stable for 3 months	Adults Mean: 21.6 (SD 3.42) Black Or African American: 17 (57%) White: 13 (43%)	NR	NR	NR	NR	1. Placebo (n =30) 2. Ticagrelor 10MG BID oral (n=27) 3. Ticagrelor 45mg BID oral (n=30)	12 weeks	NR	AstraZenec a	CT
NCT01476696 USA [64] Feb 2014 to Oct 2016 NCT01476696	Single-arm Phase 2 (Part B) 18 (NR); 1	1. HbSS, HbSβ 2. ≥2 to <18 years of age and ≥ 12 kg body weight 3. Participants on hydroxyurea must be on a stable dose for the 60 days prior to enrolment without signs of hematologic toxicity at screening	Children and adolescents NR (only reported overall, part A+B)	NR	NR	NR	NR	Prasugrel 0.06-0.12 mg/kg depending on their steady-state PD response oral (n=18)	14 ± 4 days	NR	Eli Lilly and Company	CT
Vichinsky 2010 [66]	RCT 36 (NR)	1. HbSS 2. Normal neurological exam, WAIS III PIQ score ≤ 90, hemoglobin ≤ 9 g/dL 3. Aged 21-55	Adults Mean: 29	All HbSS	HU: 14 (39%)	NR	Transfusion group had average of 5.6 transfusions (which differ from standard care group) ACS: 35%	1. Chronic transfusion (n = 20) maintaining a hemoglobin of 2 g/dL rise over baseline with matched red cells for D, C/c, E/e, and Kell antigens 2. Standard care (n = 16)	4 weeks	NR	NR	CT
Styles USA [67]	Single-arm Open-label ½ study Three centers 15 (0); 1	NR	Adults Mean: 32 (range 18-50) All African-American	HbSS: 13 HbSβ^0: 2	HU: 4 (26.7%)	VOC: 6 (past year)	ACS: 2 (past year) Transfusion: 2 (past year) Priapism: 1 (past year)	GMI-1070 20mg/kg (first dose) and 10 mg/kg after 10 hours	28 days	NR	NR	CT

†If not stated, only one arm data were shown as representative

*final number used for analysis or crossover design

ACS: Acute chest syndrome; ALT: Alanine transaminase; CA: Conference abstract; Cr: creatinine; CSRPM: Center for Scientific Research into Plant Medicine; CT: Clinical trial registry; DDCF: Doris Duke Charitable Foundation; ED: emergency department; HbSS: Homozygous sickle haemoglobin (HbS); HbSC: sickle haemoglobin S and haemoglobin C; HbSβ: sickle beta thalassemia, type '0' or '+'; HU: hydroxyurea; JA: Journal article; MTX: Methotrexate; NAD: N-acetylcysteine ;NCATS: National Center for Advancing Translational Sciences; NCRR: National Center for Research Resources; NHLBI: National Heart Lung and Blood Institute; NSAID: Nonsteroidal anti-inflammatory drugs; NR: Not reported; OOPD: FDA's Office of Orphan Products Development; PT: patient; SCD: sickle cell disease; TCD: transcranial Doppler; ZonMw: The Netherlands Organisation for Health Research and Development

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Appendix C Systematic review protocol main (non-transfusions)

Contents

Tables

Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
EMBASE	Excerpta Medica dataBASE
MEDLINE	Medical Literature Analysis and Retrieval System Online
PICOS	Population, Interventions, Comparisons, Outcomes, and Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RBC	Red blood cells
RCT	Randomized controlled trial
SCD	Sickle cell disease
SLR	Systematic literature review
VOC	Vaso-occlusive crisis

1 Introduction

Sickle cell disease (SCD) is a genetic blood disorder characterized by abnormality in the oxygen-carrying protein hemoglobin found in red blood cells (RBCs), depicted by RBCs having a rigid sickle-like shape.[1] Vaso-occlusive crises (VOCs) are the hallmark of SCD, with the disease being associated with serious complications, multi-organ failure, and an increased risk of death.[2] Quality of life is severely impaired for these patients due to recurrent chronic pain crises, regular use of analgesics, repeated hospitalization due to VOCs, and multiple organ failure.[3] The ability to modify the disease and prevent VOC episodes can decrease the risk of complications, organ damage, and the subsequent risk of death in SCD patients, as well as reduce health-resource utilization episodes.

There are limited treatment options are for SCD patients.[2] Hydroxyurea (HU) is the mainstay of treatment; however, majority of patients do not persist on HU, or will not take or cannot take HU, and among the HU-treated patients, some still continue to experience VOCs, fatal organ damage, and a shortened life span.[2] Novartis has developed crizanlizumab for the prevention of VOCs in SCD patients. In a recent randomized, double-blind, placebo-controlled Phase 2 trial, the safety and efficacy of crizanlizumab with or without hydroxyurea was assessed in SCD patients still experiencing ≥2VOCs/ year at time of enrollment.[2] Treatment with high-dose crizanlizumab resulted in a 45.3% reduction in annual rate of VOCs compared to placebo;[2] in addition, the median times to first and second VOC were 2-3 times as long for patients receiving crizanlizumab compared to those receiving placebo.[2]

2 Objective

The key parameters for the economic model relate to the treatment effects of the interventions used for the treatment of SCD. Treatment effects of the relevant alternative interventions of interest will be based on currently available published clinical trial evidence identified by means of a systematic literature review and synthesized with meta-analysis techniques. The current document defines the scope and process of the systematic literature review (SLR).

3 Methodology

3.1 Eligibility criteria

The SLR will focus on identifying clinical trials evaluating the treatment effects of relevant competing interventions for the treatment of SCD and will be an update of the recent review by Sins et al.[4] The scope will be expanded by incorporating recently published studies and including single arm trials when RCTs are not available for the relevant interventions of interest. Study eligibility criteria are defined in terms of the population, interventions, comparisons, outcomes, and study design (PICOS) outlined in **Table 1**, which will guide the identification and selection of studies considered relevant.

Table 1: Eligibility criteria

Criteria	Description
Population	*Inclusion criteria:* • Adult patients with sickle cell disease
Interventions	• Crizanlizumab • Hydroxyurea • Endari • Voxelotor (GBT440) • Any pharmacological interventions for preventing vaso-occlusive crisis (VOC)*
Comparators	• Placebo or best supportive care • Any of the listed interventions of interest • Any treatment that facilitates an anchored indirect comparison
Outcomes	• Any efficacy related outcome**
Study design	• RCTs • Single-arm trials when RCTs are not available for the interventions of interest
Language	• Only studies published in English

**We exclude interventions such as gene therapy, stem cell therapy and bone marrow transplantation, as these interventions aim to cure sickle cell disease in severe sickle cell disease patients*

***In addition to efficacy outcomes, adverse events are of interest for the review, but will not be used as study selection criteria.*

3.2 Study identification

Relevant studies will be identified by searching the following databases using predefined search strategies: Cochrane Central Register of Controlled Trials (CENTRAL); Medical Literature Analysis and Retrieval System Online (MEDLINE); and Excerpta Medica database (Embase). It should be noted that CENTRAL database does not contain any single-arm (uncontrolled) trials. Therefore, resources for identifying single-arm trials will be MEDLINE and Embase only. This search strategy is based on Sins et al.[4] and constructed

according to the criteria of interest (e.g. outcomes, population, intervention and study design) using MeSH or Emtree terms (thesaurus terms, headings and subheadings) and text words to retrieve potential references. Search strategies have been developed individually for CENTRAL, MEDLINE and Embase and are listed in Appendix A. Please note that the MEDLINE search strategy also aims to identify previously published SLRs and meta-analyses as an additional source to identify relevant primary studies of interest.

Considering the limited searches in Sins et al.[4] due to lack of a clinical trial registry search, a clinical trial registry search on ClinicalTrials.gov will be conducted to identify relevant primary studies of interest, especially unpublished and ongoing studies. This search is based on the search strategy of MEDLINE (**Appendix B**).

Sins et al.[4] completed their literature searches on 30th January 2017. Therefore, all searches on databases will be limited from the date 30th January 2017 onwards, except CENTRAL database. CENTRAL database lacks limit options by date and indexes for identifying date of reference created. Thus, the limit on CENTRAL database will be performed by restricting the publication year from 2017 onwards.

Although it is possible to restrict searches by language (English), it is highly advisable that the search strategy retains high sensitivity (the proportion of references for the desired topic that are retrieved), especially as the estimated number of recalls is small. Therefore, there is no restriction on language at the search stage.

3.3 Study selection

Two reviewers, working independently, will review all abstracts and proceedings identified by the search according to the selection criteria, with the exception of outcome criteria, which will only be applied during the screening of full-text publications. All studies identified as eligible studies during abstract screening will then be screened at a full-text stage by the same two reviewers. Reasons for exclusion will be recorded. The full-text studies identified at this stage will be included for the data extraction. Following reconciliation between the two investigators, a third reviewer will be included to reach consensus on any remaining discrepancies. The process of study identification and selection will be summarized with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.[5]

3.4 Data extraction

Two reviewers, working independently, will extract data on study characteristics, interventions, patient characteristics, and outcomes for the final list of included studies. Following reconciliation between the two reviewers, a third reviewer will be included to reach consensus on any remaining discrepancies. Data will be stored and managed in a Microsoft Excel workbook.

3.4.1 Study characteristics

The following study characteristics will be extracted:

- Study name
- Study year
- Study authors
- Study design
- Study inclusion criteria
- Study exclusion criteria
- Location of study (countries)
- Year of study initiation and study close
- Follow-up period
- Outcomes
- Patient flow
- Study- and analyses populations (e.g. ITT, mITT, etc.)

3.4.2 Intervention characteristics

The following intervention characteristics will be extracted:

- Treatment regimen
- Treatment dose
- Method of administration
- Frequency of administration
- Duration of treatment
- Concomitant/background therapies
- Compliance/Adherence

3.4.3 Patient characteristics

The following patient characteristics at baseline will be extracted:

- Age
- Gender
- Race and ethnicity
- Other relevant socio-demographics
- Concomitant hydroxycarbamide/hydroxyurea
- Fetal hemoglobin
- Genetic status (HbSS, HbSβo, HbSC, Hbsβ+, other)
- Painful crisis

- Hospital admission frequency
- Painful crisis including home crisis
- Transfusions
- Previous SCD related complications
- Acute chest syndrome
- Avascular osteonecrosis
- Stroke
- Other comorbidities

3.4.4 Outcomes

The following outcomes will be extracted:

- Number of VOCs
- Time to the first VOC
- Duration of VOCs
- % of patients with 0 VOCs/ year
- Number of SCD-related pain days
- Duration of SCD-related pain days
- Number of Hospital Admissions for VOC
- time to first hospital admission for a VOC
- Intensity of pain
- Serious complications
- Organ damage
- Survival
- Quality of life
- Adverse events

For each outcome of interest, the upper & Lower limits of scales along with definition will be reported. For dichotomous outcomes, the number of patients with the event and the number of patients in each treatment arm will be extracted. For continuous outcomes, the change from baseline in all intervention groups will be extracted. If the change from baseline is not provided, the score at end of follow-up and the baseline score will be extracted. For event rates, the number of events, the number of patients in each treatment arm and follow-up or exposure time will be extracted. For time-to-event outcomes, hazard ratios and associated information regarding uncertainty will be extraction. Kaplan Meir curves will be extracted in terms of the proportion of patients who had an event over time using DigitizeIt® in addition to the number of patients at risk over time.

3.4.5 Study quality

Two independent reviewers will assess study quality. Following reconciliation between the two investigators, a third investigator will be included to reach consensus on any remaining discrepancies.

The Cochrane Collaboration's Risk of Bias tool will be used to assess risk of bias in included RCTs (**Appendix C**).[6] This instrument is used to evaluate six key domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. The risk of bias instrument can be used to assign summary assessments of within-study bias, low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for one or more key domains), or high risk of bias (high risk of bias for one or more domains).

The Newcastle-Ottawa Scale will be used to assess the quality of single arm studies (**Appendix C**).[7] This instrument is used to evaluate the quality of observational studies based on 1) study group and selection, 2) comparability of the groups within studies, and 3) the ascertainment of either the exposure or outcomes of interest for case-control or cohort studies. Ranking of the study quality will be done by using a 'star system' in which a study can be given a maximum of one star for each numbered item within the "Selection" and "Exposure" categories and a maximum of two stars for "Comparability" category. Two independent reviewers will assess study quality. Following reconciliation between the two investigators, a third investigator will be included to reach consensus on any remaining discrepancies.

4 Discussion

This SLR will involve highly sensitive searches in the peer-reviewed literature as well as searches of recent conferences and clinical trial registrations to identify unpublished completed trials with results available. The review processes will be guided by the pre-defined eligibility criteria established in the review protocol. Data quality will be ensured through the involvement of two independent researchers in the study selection and data extraction phases of the project. The primary outcomes will include median time to the first VOC, median time to the second VOC, median rate of VOCs per year, and overall survival (OS), which reflect the primary outcomes as assessed in the Sins, et al. review as well as many clinical trials for this population. Results of the SLR will help to inform clinicians and decision makers and will provide the foundation to assess the feasibility of performing an NMA.

Despite the strengths of the proposed SLR, some limitations are applicable to all SLRs that should be acknowledged. While there is a clear justification to limit the search and selection to June 20, 2018 based on the scope to update the Sins review, there is always a risk select trials will not be identified that align with the selection criteria. Additionally, as the evidence base is continually growing, any trials published after the search date will not be captured. Further, any trials that are published close to the search date but are not yet indexed in the databases at the time of the search will not be captured by the search of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials. Hand searches of other published reviews may help overcome these potential limitations.

As always, the SLR is also limited by the use of published data. There is a risk of publication bias as some clinical trials fail to be published while others are published only in abstract form, which presents limited information. However, an extensive search of conference abstracts will be performed, which may mitigate the impact on the results of the SLR. Posters or slides corresponding to the conference abstracts will be identified where available; however, often conferences do not provide complete information. Moreover, conference results should be interpreted with caution, as they do not undergo the same peer review process as fully published results. Finally, the search and selection will be restricted to trials published in English. Therefore, there is a risk that non-English publications will not be identified.

Appendix A: Literature search strategies

Table 2: Search strategy for MEDLINE

#	Searches	Concept
1	exp pain/	Outcomes
2	(pain or painfull).tw.	
3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	
4	exp length of stay/	
5	(hospital adj3 (admission or stay)).tw.	
6	(patient adj3 (admission or stay)).tw.	
7	or/1-6	
8	anemia, sickle cell/	Population
9	hemoglobin, sickle/	
10	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	
11	or/8-10	
12	exp antisickling agents/	Interventions
13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or endari or voxelotor or GBT440).mp.	
14	(8 or 9 or 10) and prevent vaso-occlusiv*.tw.	
15	or/12-14	
16	7 and 11 and 15	
17	meta analysis.pt.	Systematic review and meta-analysis studies
18	((meta adj analys*) or metaanalys or meta-analys*).ti,ab,sh.	
19	(systematic adj5 (review or overview*)).ti,ab,sh.	
20	or/17-19	
21	16 and 20	
22	clinical trial/	RCTs
23	(clinic adj5 trial*).ti,ab,sh.	

24	single blind method/	
25	double blind method/	
26	random allocation/	
27	placebos/	
28	(placebo or random*).ti,ab,sh.	
29	randomized controlled trial/	
30	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	
31	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	
32	randomi?ed control trial*.tw.	
33	or/22-32	
34	16 and 33	
35	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	Single arm trials
36	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	
37	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	
38	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	
39	Clinical Trial, Phase I.pt.	
40	Clinical Trial, Phase II.pt.	
41	Clinical Trial, Phase III.pt.	
42	(registry or registries).ti,ab,kf,hw.	
43	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	
44	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	
45	(nonrandom* or non-random*).ti,ab,kf.	
46	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	
47	(all adj3 received).ab.	
48	or/35-47	
49	16 and 48	

50	limit 21 to ed=20170130-20180620	Date limit on rSLR and meta-analysis studies
51	limit 34 to ed=20170130-20180620	Date limit on RCTs
52	limit 49 to ed=20170130-20180620	Date limit on single arm trials

Table 3: Search strategy for EMBASE

#	Searches	
1	exp pain/	Outcomes
2	(pain or painfull).tw.	
3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	
4	exp "length of stay"/	
5	(hospital adj3 (admission or stay)).tw.	
6	(patient adj3 (admission or stay)).tw.	
7	or/1-6	
8	sickle cell anemia/	Population
9	hemoglobin S/	
10	(sickle cell or sickle h$emoglobin or drepanocyt* or drepanotic or drepanocytemia or h$emoglobin-s or Hb-S or sickle an$emia or meniscocytosis).mp.	
11	or/8-10	
12	antisickling agent/	Intervention
13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or endari or voxelotor or GBT440).mp.	
14	(8 or 9 or 10) and prevent vaso-occlusiv*.tw.	
15	or/12-14	
16	7 and 11 and 15	
17	randomized controlled trial/	RCTs

18	(RCT or randomi#ed or randomi#ation).ab,ti,kw,hw.	
19	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or subsitut* or treat*)).ab,kw.	
20	trial.ti.	
21	crossover procedure/	
22	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dumm*)).ti,ab,kw,hw.	
23	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	
24	or/17-23	
25	16 and 24	
26	prospective study/ or retrospective study/ or longitudinal study/ or cohort analysis/ or cross-sectional study/ or case control study/ or population based case control study/	Single-arm trials
27	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 study).ti,ab,kw.	
28	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	
29	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab,kw.	
30	(registry or registries).ti,ab,kw,hw.	
31	(nonrandom* or non-random*).ti,ab,kw.	
32	((control* adj2 before adj2 after) or CBA study).ti,ab,kw.	
33	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kw.	
34	(all adj3 received).ab.	
35	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 1 clinical trial/	
36	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kw.	
37	or/26-36	
38	16 and 37	
39	limit 25 to em=201705-201825	Date limit on RCTs
49	limit 38 to em=201705-201825	Date limit on single arm trials

Table 4: Search strategy for Cochrane Register of Controlled Trials

#	Searches	
#1	MeSH descriptor: [Pain] explode all trees	Outcomes
#2	(pain or painfull):ti,ab,kw	
#3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises):ti,ab,kw	
#4	MeSH descriptor: [Length of Stay] explode all trees	
#5	(hospital near/3 (admission or stay)):ti,ab,kw	
#6	(patient near/3 (admission or stay)):ti,ab,kw	
#7	#1 or #2 or #3 or #4 or #5 or #6	
#8	MeSH descriptor: [Anemia, Sickle Cell] this term only	Population
#9	MeSH descriptor: [Hemoglobin, Sickle] this term only	
#10	(sickle cell or sickle h*emoglobin or drepanocyt* or drepanotic or drepanocytemia or h*emoglobin-s or Hb-S or sickle an*emia or meniscocytosis):ti,ab,kw	
#11	#8 or #9 or #10	
#12	MeSH descriptor: [Antisickling Agents] explode all trees	Interventions
#13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or endari or voxelotor or GBT440):ti,ab,kw	
#14	(#8 or #9 or #10) and prevent vaso-occlusiv*	
#15	#11 or #12 or #13	
#16	#7 and #11 and #14	

Appendix B: ClinicalTrials.gov search

Table 6: Search strategy for ClinicalTrials.gov*

#	Searches	Search column
#1	Anemia, Sickle Cell OR Sickle Beta Thalassemia OR Sickle Cell Anemia OR Sickle Cell trait	Condition or disease
#2	SCD OR SCA OR Sickle	Other terms
#3	Drug OR Placebo OR Crizanlizumab OR Hydroxyurea OR Endari OR Voxelotor OR GBT440 OR hydroxycarbamide	Intervention/treatment
#4	pain OR hospitalisation OR hospitalization OR (hospital AND (admission OR stay)) OR crisis OR VOC OR ((vaso OR vein OR vena OR venous) AND (occlusive OR occlusive OR interruption OR obstruction)) OR survival OR quality of life	Outcome Measures
	#1 or #2 or #3 or #4	

*Advanced Search option without any restrictions except search strings listed.

Appendix C: Risk of bias and quality assessment

Table 5: Cochrane risk of bias assessment tool[6]

Domain	Support for judgment	Review authors' judgment
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to the knowledge of the allocated interventions by participants and personnel during the study.
Detection bias		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to the knowledge of the allocated interventions by outcome assessors.
Attrition bias		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Table 6: Newcastle-Ottawa quality assessment scale – cohort studies[7]

Domain	Response
Selection	
1. Representativeness of the exposed cohort	a. Truly representative of the average _____ (describe) in the community* b. Somewhat representative of the average _____ in the community* c. Selected group of users (e.g. nurses, volunteers) d. No description of the derivation of the cohort
2. Selection of the non-exposed cohort	a. Drawn from the same community as the exposed cohort* b. Drawn from a different source c. No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure	a. Secure record (e.g. surgical records)* b. Structured interview* c. Written self-report d. No description
4. Demonstration that outcome of interest was not present at start of study	a. Yes* b. No
Comparability	
1. Comparability of cohorts on the basis of the design or analysis	a. Study controls for _____ (select the most important factor)* b. Study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor)*
Outcomes	
1. Assessment of outcome	a. Independent blind assessment* b. Record linkage* c. Self-report d. No description
2. Was follow-up long enough for outcomes to occur	a. Yes (select an adequate follow up period for outcome of interest)* b. No
3. Adequacy of follow up of cohorts	a. Complete follow up - all subjects accounted for* b. Subjects lost to follow up unlikely to introduce bias - small number lost - > % (select an adequate %) follow up, or description provided of those lost)* c. Follow up rate < % (select an adequate %) and no description of those lost d. No statement

Note: A study can be awarded a maximum of one star for each numbered item within the selection and outcomes categories. A maximum of two stars can be given for comparability.

References

1. National Heart Lung and Blood Institute. Sickle Cell Disease. 2018; https://www.nhlbi.nih.gov/health-topics/sickle-cell-disease.
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Appendix D. Systematic literature review protocol for transfusions.

Search protocol

Objective

This search protocol aims to supplement new evidence on the treatment effects of transfusion used for preventing crises in sickle cell disease (SCD) patients in adults and adolescents for previous systematic literature review (led by Thomas Statistical Consultants). The search strategy and concept are modified from a recent systematic review by Sins et al.[1] and Fortin et al[2]. The strategy has been developed to fulfil updated eligibility criteria (Table 1) and retrieve single-arm trials.

Table 1. Eligibility criteria

Criteria	Description
Population	Trials that included SCD patients aged 16 and above
Interventions	• Red blood cell transfusions • Other types of transfusions
Comparators	• Placebo or best medical care • Interventions included in previous systematic review
Outcomes	• Pain, crisis and VOC (frequency, intensity and duration in one event) • Hospital admission, including emergency department (ED) and nurse visits • SCD complications, including acute chest syndromes • Analgesic use • Adverse events*
Study design	• Randomized controlled trials (RCTs) • Single-arm studies
Language	• Only studies published in English

*In addition to efficacy outcomes, adverse events are of interest for the review, but will not be used as study selection criteria

Resources

Electronic databases

Studies will be identified by searching the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- Medical Literature Analysis and Retrieval System Online (MEDLINE)
- Excerpta Medica database (Embase)

Hand-searches

[1] Sins JWR, Mager DJ, Davis S, Biemond BJ, Fijnvandraat K: **Pharmacotherapeutical strategies in the prevention of acute, vaso-occlusive pain in sickle cell disease: a systematic review**. *Blood advances* 2017, **1**(19):1598-1616.

[2] 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, Issue 8. Art. No.: CD012082. DOI: 10.1002/14651858.CD012082.pub2.

- ClinicalTrial.gov

Search strategy

Search strategies have been developed individually for CENTRAL, MEDLINE, Embase and ClinicalTrial.gov and their results are listed in Appendix 1-4. The concept of a search strategy is elaborated using MEDLINE as an example (Table 2). The search strategy was constructed according to the criteria (e.g. outcomes, population, intervention and study design) using MeSH or Emtree terms (thesaurus terms, headings and subheadings) and text words to retrieve potential references.

Table 2. Search strings and concepts

No	Searches	Results	
1	anemia, sickle cell/	19329	Population
2	hemoglobin, sickle/	3011	
3	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	27120	
4	1 or 2 or 3	27602	
5	Blood Transfusion/	48056	Intervention
6	Erythrocyte Transfusion/	8033	
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	90906	
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	47785	
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	35184	
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	26829	
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1217	
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	24060	
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	183648	
14	Blood Component Transfusion/	3477	
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	16726	

16	14 not 15	3229	
17	ERYTHROCYTES/	128578	
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	216650	
19	17 or 18	258199	
20	16 and 19	834	
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	13177	
22	(((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	3326	
23	13 or 20 or 21 or 22	188025	
24	exp pain/	362648	
25	(pain or painfull).tw.	547392	
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	66169	Outcome
27	exp length of stay/	77857	
28	(hospital adj3 (admission or stay)).tw.	104873	
29	(patient adj3 (admission or stay)).tw.	6507	
30	or/24-29	901074	
31	4 and 23 and 30	848	
32	clinical trial/	512148	
33	(clinic adj5 trial*).ti,ab,sh.	1010	
34	single blind method/	25632	
35	double blind method/	147368	
36	random allocation/	95709	
37	placebos/	34063	RCT filter
38	(placebo or random*).ti,ab,sh.	1263924	
39	randomized controlled trial/	467730	
40	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	786522	
41	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	145215	
42	randomi?ed control trial*.tw.	6481	
43	or/32-42	1565168	

44	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	2187051	Single-arm studies filter
45	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	1071161	
46	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	615678	
47	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	340559	
48	Clinical Trial, Phase I.pt.	18409	
49	Clinical Trial, Phase II.pt.	29604	
50	Clinical Trial, Phase III.pt.	14110	
51	(registry or registries).ti,ab,kf,hw.	139501	
52	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	53439	
53	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	114108	
54	(nonrandom* or non-random*).ti,ab,kf.	34084	
55	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	2644	
56	(all adj3 received).ab.	41192	
57	or/44-56	3114626	
58	31 and 43	120	
59	31 and 57	278	

Search results

The numbers of references retrieved by search strategies from three databases are listed below. The search date was from the earliest date to 29th Aug 2018 in all databases. In total, there were 1,631references retrieved.

CENTRAL

- Number of references related to controlled trials: 332

MEDLINE

- Number of references related to randomised controlled trials: 120
- Number of references related to single-arm studies: 279

Embase

- Number of references related to randomised controlled trials: 245
- Number of references related to single-arm studies: 599

ClinicalTrial.gov

- Number of references: 56

Deduplication

Duplicates were identified firstly by 'find duplicates' function in Endnote X8 and then double-checked manually by sorting author, title, volume and issue. After that, all references were de-duplicate against references retrieved from previous systematic review. This left 825 references from the electronic databases to be screened.

In terms of references from ClinicalTrial.gov, there were only 16 references left to be screened after deduplication.

In total, there are 841 references to go through during the title and abstract screening stage.

Appendix 1. Search strategy and results for CENTRAL database

Search Strategy:

#	Searches	Results
#1	MeSH descriptor: [Anemia, Sickle Cell] this term only	583
#2	MeSH descriptor: [Hemoglobin, Sickle] this term only	19
#3	(sickle cell or sickle h*emoglobin or drepanocyt* or drepanotic or drepanocytemia or h*emoglobin-s or Hb-S or sickle an*emia or meniscocytosis):ti,ab,kw	4790
#4	#1 or #2 or #3	4790
#5	MeSH descriptor: [Blood Transfusion] this term only	1766
#6	MeSH descriptor: [Erythrocyte Transfusion] explode all trees	564
#7	((blood or erythrocyte* or "red cell*" or "red blood cell*" or RBC*) near/5 (transfus* or infus* or unit*))	14775
#8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) near/5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program* or therapy)):ab	30189
#9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)):ti	3612
#10	("allogeneic blood" or (unit* near/2 blood) or "allogenic blood" or (blood near/2 exposure) or "donor blood" or "blood product*" or "blood component*" or "blood support")	3365
#11	hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*	107
#12	(red cell* or erythrocyte* or blood or RBC*) and transfus*:ti	2434
#13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	41927
#14	MeSH descriptor: [Blood Component Transfusion] this term only	115
#15	MeSH descriptor: [Erythrocytes] this term only	1478
#16	(red cell* or red blood cell* or erythrocyte* or RBC*)	12756
#17	#14 and (#15 or #16)	39
#18	#13 or #17	41927
#19	MeSH descriptor: [Pain] explode all trees	42323
#20	(pain or painfull):ti,ab,kw	124349

#21	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises):ti,ab,kw	4404
#22	MeSH descriptor: [Length of Stay] explode all trees	6488
#23	(hospital near/3 (admission or stay)):ti,ab,kw	20854
#24	(patient near/3 (admission or stay)):ti,ab,kw	1779
#25	#19 or #20 or #21 or #22 or #23 or #24	153780
#26	#4 and #18 and #25	332

Of 332 results:

- Cochrane reviews: 35
- Cochrane Protocol: 1
- Trials: 296
- Editorials: 0
- Special collections: 0
- Clinical Answers: 0

Appendix 2. Search strategy and results for MEDLINE

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to August 29, 2018
Search Strategy:

#	Searches	Results
1	anemia, sickle cell/	19329
2	hemoglobin, sickle/	3011
3	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	27120
4	1 or 2 or 3	27602
5	Blood Transfusion/	48056
6	Erythrocyte Transfusion/	8033
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	90906
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	47785
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	35184
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	26829
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1217
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	24060
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	183648
14	Blood Component Transfusion/	3477
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	16726
16	14 not 15	3229
17	ERYTHROCYTES/	128578
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	216650

19	17 or 18	258199
20	16 and 19	834
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	13177
22	(((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	3326
23	13 or 20 or 21 or 22	188025
24	exp pain/	362648
25	(pain or painfull).tw.	547392
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	66169
27	exp length of stay/	77857
28	(hospital adj3 (admission or stay)).tw.	104873
29	(patient adj3 (admission or stay)).tw.	6507
30	or/24-29	901074
31	4 and 23 and 30	848
32	clinical trial/	512148
33	(clinic adj5 trial*).ti,ab,sh.	1010
34	single blind method/	25632
35	double blind method/	147368
36	random allocation/	95709
37	placebos/	34063
38	(placebo or random*).ti,ab,sh.	1263924
39	randomized controlled trial/	467730
40	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	786522
41	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	145215
42	randomi?ed control trial*.tw.	6481
43	or/32-42	1565168
44	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	2187051
45	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	1071161

46	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	615678
47	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	340559
48	Clinical Trial, Phase I.pt.	18409
49	Clinical Trial, Phase II.pt.	29604
50	Clinical Trial, Phase III.pt.	14110
51	(registry or registries).ti,ab,kf,hw.	139501
52	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	53439
53	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	114108
54	(nonrandom* or non-random*).ti,ab,kf.	34084
55	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	2644
56	(all adj3 received).ab.	41192
57	or/44-56	3114626
58	31 and 43	120
59	31 and 57	278

Appendix 3. Search strategy and results for Embase database

Database(s): **Embase** 1974 to 2018 Week 35
Search Strategy:

#	Searches	Results
1	exp Anemia, Sickle Cell/	32009
2	(h?emoglobin s or h?emoglobin sc or h?emoglobin se or h?emoglobin ss or h?emoglobin c or h?emoglobin d or Hb s or Hb sc or Hb se or Hb ss or Hb c or Hb d or sc disease*).tw.	5794
3	(sickle cell or sicklemia or sickled or sickling or meniscocyt* or drepanocyt*).tw.	29569
4	1 or 2 or 3	38361
5	Blood Transfusion/	108332
6	Erythrocyte Transfusion/	23021
7	((blood or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (transfus* or infus* or unit* or therap*)).ti,ab.	135137
8	((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj5 (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ab.	77239
9	((red cell* or RBC* or erythrocyte* or blood or transfus*) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or replac* or support* or strateg* or management or practic* or indicat* or criteri* or standard* or program*)).ti.	38387
10	(allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).ti,ab.	43111
11	(hemotransfus* or haemotransfus* or hypertransfus* or hemotherap* or haemotherap*).tw.	1555
12	(red cell* or erythrocyte* or blood or RBC*).tw. and transfus*.ti.	28985
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	273982
14	Blood Component Transfusion/	2629
15	PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/	19765
16	14 not 15	2279
17	ERYTHROCYTES/	112741
18	(red cell* or red blood cell* or erythrocyte* or RBC*).tw.	256379

19	17 or 18	278120
20	16 and 19	523
21	((transfus* or red cell* or red blood cell* or RBC*) adj10 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practice* or standard*)).tw.	22304
22	(((transfus* or red cell* or red blood cell* or RBC* or h?ematocrit*) and (level* or critical* or intensive* or h?emorrhag* or bleed*)) or hypertransfus*).ti.	4095
23	13 or 20 or 21 or 22	279695
24	exp pain/	1146280
25	(pain or painfull).tw.	789805
26	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	82887
27	exp length of stay/	150699
28	(hospital adj3 (admission or stay)).tw.	169748
29	(patient adj3 (admission or stay)).tw.	12514
30	or/24-29	1690290
31	4 and 23 and 30	2325
32	randomized controlled trial/	508600
33	(RCT or randomi#ed or randomi#ation).ab,ti,kw,hw.	1062285
34	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or subsitut* or treat*)).ab,kw.	560662
35	trial.ti.	248694
36	crossover procedure/	56042
37	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dumm*)).ti,ab,kw,hw.	276112
38	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	99658
39	or/32-38	1386841
40	prospective study/ or retrospective study/ or longitudinal study/ or cohort analysis/ or cross-sectional study/ or case control study/ or population based case control study/	1771952
41	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 study).ti,ab,kw.	1282224
42	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	790240
43	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab,kw.	500633

44	(registry or registries).ti,ab,kw,hw.	183687
45	(nonrandom* or non-random*).ti,ab,kw.	42777
46	((control* adj2 before adj2 after) or CBA study).ti,ab,kw.	3333
47	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kw.	80316
48	(all adj3 received).ab.	75969
49	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 1 clinical trial/	126474
50	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kw.	205403
51	or/40-50	3180246
52	31 and 39	245
53	31 and 51	599

Appendix 4. Search strategy and results for ClinicalTrial.gov

#	Searches	Search column
#1	Anemia, Sickle Cell OR Sickle Beta Thalassemia OR Sickle Cell Anemia OR Sickle Cell trait	Condition or disease
#2	SCD OR SCA OR Sickle	Other terms
#3	Transfusion OR blood OR RBC OR hematocrit OR erythrocyte	Intervention/treatment
#4	pain OR hospitalisation OR hospitalization OR (hospital AND (admission OR stay)) OR crisis OR VOC OR ((vaso OR vein OR vena OR venous) AND (occlusive OR occlusive OR interruption OR obstruction)) OR survival OR quality of life	Outcome Measures
	#1 or #2 or #3 or #4	

*Advanced Search option without any restrictions except search strings listed.

Appendix E. Additional details of the network meta-analysis

E.1 Methods of the network meta-analysis

We first define the Bayesian network meta-analysis (NMA) statistical models used to synthesize transformed outcomes, on the log hazard scale, from each randomized controlled trial (RCT). The link functions to connect these models to the different data summaries are then presented. The same statistical models are used for crisis, hospitalization days, adverse events, and serious adverse events but the link functions vary depending on what data is reported by each RCT (see main text for outcomes analyzed). The NMA models are in line with the recommendations of the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) technical support documents (TSD), in particular NICE DSU TSD 2. OpenBUGS code is provided for each outcome in appendix **B.4.**

For all random parameters (i.e. $\mu_{..}$ and $d_{..}$) vague $Normal(0, 0.001)$ priors were used.

Fixed-effects network meta-analysis model

When the available evidence consists of a network of multiple pairwise comparisons (i.e. AB-trials, AC-trials, BC-trials, etc.) the standard fixed effects model for NMA can be specified as follows:

$$\theta_{jk} = \begin{cases} \mu_{jb} & \text{if } k = b \\ \mu_{jb} + d_{bk} = \mu_{jb} + d_{Ak} - d_{Ab} & \text{if } k \succ b \end{cases} \qquad (3)$$
$$d_{AA} = 0$$

There are *k* treatments labelled as A, B, C, etc., and treatment A is taken to be the reference treatment for the analysis. μ_{jb} is the (transformed) outcome in study *j* on 'baseline' treatment *b* which will vary across studies. d_{bk} is the fixed effect of treatment *k* relative to 'baseline treatment' *b*. d_{bk} are identified by expressing 0them in terms of the reference treatment A: $d_{bk} = d_{Ak} - d_{Ab}$ with $d_{AA} = 0$.

Random-effects network meta-analysis model

$$\theta_{jk} = \begin{cases} \mu_{jb} & \text{if } k = b \\ \mu_{jb} + \delta_{jbk} & \text{if } k \succ b \end{cases} \qquad (4)$$

$$\delta_{jbk} \sim Normal(d_{bk}, \sigma^2) = Normal(d_{Ak} - d_{Ab}, \sigma^2)$$
$$d_{AA} = 0$$

δ_{jbk} is the trial-specific treatment effect of *k* relative to treatment *b*. These trial-specific effects are drawn from a random-effects distribution: $\delta_{jbk} \sim N(d_{bk}, \sigma^2)$. Again, the pooled effects, d_{bk}, are identified by expressing them in terms of the reference treatment A. The heterogeneity σ^2 is assumed constant for all treatment comparisons. (A fixed effect model is obtained if σ^2 equals zero.)

This random-effects model treats multiple-arm trials (>2 treatments) without taking account of the correlations between the trial-specific δs that they estimate. Bayesian random-effects models with a heterogeneity parameter for d_{Ak} can be easily extended to fit trials with 3 or more treatment arms by decomposing a multivariate normal distribution as a series of conditional univariate distributions.[1]

$$\begin{pmatrix} \delta_{jbk_1} \\ \vdots \\ \delta_{jbk_p} \end{pmatrix} \sim Normal\left(\begin{pmatrix} d_{bk_1} \\ \vdots \\ d_{bk_p} \end{pmatrix}, \begin{pmatrix} \sigma^2 & \cdots & \frac{\sigma^2}{2} \\ \vdots & \ddots & \vdots \\ \frac{\sigma^2}{2} & \cdots & \sigma^2 \end{pmatrix} \right) \quad (5)$$

Then the conditional univariate distributions for arm *i* given the previous *1,….(i-1)* arms are:

$$\delta_{jbk_i} | \begin{pmatrix} \delta_{jbk_1} \\ \vdots \\ \delta_{jbk_{i-1}} \end{pmatrix} \sim Normal\left(d_{bk_i} + \frac{1}{i}\sum_{j=1}^{i-1}\left(\delta_{jbk_j} - d_{bk_j}\right), \frac{(i-1)}{2i}\sigma^2 \right) \quad (6)$$

Random-effects network meta-analysis model with constant covariate interaction term

$$\theta_{jk} = \begin{cases} \mu_{jb} & \text{if } k = b \\ \mu_{jb} + \delta_{jbk} & \text{if } k \succ b \end{cases}$$

$$\delta_{jbk} = \begin{cases} Normal\left(d_{Ak} - d_{Ab} + \beta X_j, \sigma^2\right) & \text{if } b = A \\ Normal\left(d_{Ak} - d_{Ab}, \sigma^2\right) & \text{if } b \neq A \end{cases}$$

$$d_{AA} = 0$$

X_j is the trial-specific covariate value. β is the corresponding treatment-by-covariate interaction term, which is the same for all interventions.

Link functions for shared parameter models

As described above, the available data is connected to the model via the likelihood and the link function $\theta_{jk} = g(\gamma_{jk})$. If different data summaries are used by different studies, it is necessary to use a shared parameter model, where different link functions and likelihoods are used for each study[2]. Our underlying model will be on the log hazard ratios $d_{..}$, which can be fixed or random and include meta-regression effects as discussed. In SCD it will be necessary to connect the following data summaries.

1) Estimated annualized event log rate $\log(\lambda_{jk})$ (mean or median) with standard error se_{jk} are modelled with identity link and Normal likelihood

$$\log(\lambda_{jk}) \sim Normal(\theta_{jk}, se_{jk}^2)$$

2) Total number of events r_{jk} over exposure E_{jk} are modelled with log link and Poisson likelihood

$$r_{jk} \sim Pois(\lambda_{jk} E_{jk})$$

$$\theta_{jk} = \log(\lambda_{jk})$$

3) Mean number of events per patient $\bar{r}_{jk}$ over n_{jk} patients is transformed to total number of events r_{jk} and modelled as type 2 data.

4) Number of patients w_{ij} with ≥1 event over mean follow-up time t_{ij} are modelled with a binomial likelihood and complementary log log (cloglog) link with log time as offset

$$r_{jk} \sim Binomial(P_{jk}, n_{jk})$$

$$cloglog(P_{jk}) = \log(-\log(P_{jk})) = \log(t_{jk}) + \theta_{jk}$$

5) Log hazard ratio or log rate ratio $\log(hr_{jk})$ with standard error se_{jk} between active arm k and control arm b. This is slightly different as we no longer have data on both arms, only on the contrasts.

$$\log(hr_{jk}) \sim Normal(\theta_{jk}, se_{jk}^2), \text{ for } k \succ b$$

and

$$\theta_{jk} = d_{bk} \text{ if fixed effects}$$

$$\theta_{jk} = \delta_{jbk}, \text{ if random effects or meta-regressions}$$

An adjusted standard error is needed for log hazard ratios if trials have more than 2 arms, as there is induced correlation between arms due to the common control.

Table 1 Summary of analyses planned for different outcome measures on each of the outcomes

Outcome	Outcome measure	Analysis planned	Why this analysis
Crisis	Total pain crises	Poisson likelihood, log link (Type 2 data)	Multiple events per patient so modelling underlying log hazard with a Poison likelihood.

	Mean or rate pain crises	Scale to total pain crises	Mean per patient gives total when scaled by patient number.
	Patients with ≥1 pain crisis	Binomial likelihood with cloglog link (type 4 data)	At most one such 'event' per patient, giving a binomial. Convert to log hazard scale modelled via Poisson using a cloglog function and a log follow-up time offset.
	Risk ratio/hazard ratio of crisis	Normal likelihood with identity link (type 5 data)	Direct observation of difference in log rates/hazards.
Hospitalization	Total hospitalization days	Poisson likelihood, log link (Type 2)	Multiple events per patient so modelling underlying log hazard with a Poison likelihood.
	Mean, median, or rate hospitalization days	Scale to total hospitalization days	Mean per patient gives total when scaled by patient number.
Adverse events or serious adverse events	Total events	Poisson likelihood, log link (Type 2)	Multiple events per patient so modelling underlying log hazard with a Poison likelihood.
	No. of patients with ≥ 1 event	Binomial likelihood with cloglog link (type 4 data)	At most one such 'event' per patient, giving a binomial. Convert to log hazard scale modelled via Poisson using a cloglog function and a log follow-up time offset.
	% patients with ≥ 1 event	Scale to number of patients with ≥ 1 event	Percentage gives total when multiplied by patient numbers

E.2 Outcome definitions used in the analyzed trials

Table 2: Definitions of VOC used in 5 RCTs included in base case crisis network

Study	Treatments	Crisis
Ataga 2017	Placebo, High-dose Crizanlizumab, Low-dose Crizanlizumab	Sickle cell–related pain crises were defined as acute episodes of pain, with no medically determined 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 nonsteroidal anti-inflammatory drug. The acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism were also considered to be crisis events.
Ataga 2011	Placebo, senicapoc	A painful crisis was defined as an episode of acute pain with no cause other than a vaso-occlusive event that required a medical facility visit and treatment with oral or parenteral narcotics, or parenteral non-steroidal anti-inflammatory drugs. Included in the definition of painful crisis were acute chest syndrome, hepatic sequestration, splenic sequestration, priapism, stroke and death (with the exception of homicide, suicide, or accidental death). To ensure consistency across sites, all protocol-defined sickle-related painful crises identified by the Investigators that resulted in a visit to a medical facility were adjudicated by an independent, blinded, Crisis Review Committee (CRC).
Ataga 2008	Placebo, senicapoc (low-dose), senicapoc (high-dose)	An independent, blinded crisis review committee adjudicated all sickle cell painful crises and related adverse event data (Document S1). A painful crisis was defined as a period of severe pain (with no explanation other than SCD) lasting 4 or more hours in duration, requiring a visit to a health care facility, and requiring parenteral opiate or other narcotic for relief
Pace 2003	Placebo, NAC (low-dose) 600 mg/day, NAC (mid-dose) 1200mg/day, NAC (high-dose) 2400mg/day	Defined as a visit to a medical facility that lasted more than 4 hr for acute pain related to vaso-occlusion requiring parenteral narcotics. The occurrence of acute chest syndrome, priapism, splenic, or hepatic sequestration was also counted as a VOC episode. Acute chest syndrome included those subjects with chest wall pain and a new infiltrate on chest X ray.
Niihara 2018	Placebo, L-glutamine	A pain crisis was defined as pain leading to treatment with a parenterally administered narcotic or ketorolac in an emergency department (ED) (or outpatient treatment center) or during hospitalization.

Table 3: Adverse events reported in the 8 RCTs in the base case adverse events network

Study	Treatments	Outcome name	Adverse events included
Ataga 2017	Placebo, High-dose Crizanlizumab,	Adverse events	"Headache, Back pain, Nausea, Arthralgia, Pain in extremity, Urinary tract infection, Upper respiratory tract infection, Pyrexia, Diarrhea,

	Low-dose Crizanlizumab		Musculoskeletal pain, Pruritus, Vomiting, Chest pain
		Serious adverse events	Pyrexia, Influenza, Pneumonia
Ataga 2011	Placebo, senicapoc	Adverse events	Nausea, Urinary tract Infection, Headache, Arthralgia, Upper respiratory tract Infection, Vomiting, Pyrexia, Pneumonia, Back pain, Pain in extremity, Nasopharyngitis, Cough, Constipation, Fatigue, Hypokalaaemia, Haematuria, Diarrhoea, Abdominal pain, Pharyngolaryngeal pain, Pruritus, Drug hypersensitivity
Ataga 2008	Placebo, senicapoc (low-dose), senicapoc (high-dose)	Adverse events	Diarrhea, Nausea, Constipation, Gastroenteritis, Upper respiratory tract infection, Chest pain, Increased SGOT, Arthralgia, Back pain
Niihara 2018	Placebo, L-glutamine	Adverse events	Tachycardia, Constipation, Nausea, Vomiting, Abdominal pain upper, Diarrhea, Chest pain (noncardiac), Fatigue, Urinary tract infection, Pain in extremity, Back pain, Headache, Dizziness, Nasal congestion
		Serious adverse events	A serious adverse event was defined as any adverse event, occurring while the patient was receiving the trial medication or placebo at any dose, that resulted in death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or clinically significant disability or incapacity, or a congenital anomaly or birth defect. Notable medical events that might not have resulted in death, been life-threatening, or required hospitalization could be considered serious adverse events if it was determined, on the basis of appropriate medical judgment, that they could place the patient's health in jeopardy and might require medical or surgical intervention to prevent one of the outcomes listed in the definition of serious adverse events.

Glassberg 2017	mometasome placebo		Hoarseness of voice, thrush, sore throat
Sins 2017	NAC placebo	Adverse events	Gastro-intestinal complaints, Pruritus / Rash, plus Discontinuation of study drug or placebo because of adverse event and serious adverse events
		Serious adverse events	Acute Chest Syndrome, Liver/spleen sequestration, Pyelonefritis with admission, Cholelithiasis with admission, Gastrointestinal perforation, Pulmonary embolism, Pneumonia with admission
Wun 2013	Prasugrel, placebo	Any serious adverse event	No detail given but they were non-hemorrhagic events
NCT02482298	Placebo TICAGRELOR 10MG, TICAGRELOR 45MG	Adverse events	Sickle cell anaemia with crisis, Abdominal pain, nausea, toothache, vomiting, fatigue, non-cardiac chest pain, pain, pneumonia, Upper respiratory tract infection, Urinary tract infection, Arthralgia, Back pain, Musculoskeletal chest pain, Musculoskeletal pain, pain in extremity, Headache, Dysmenorrhoea, Cough, Epistaxis, Oropharyngeal pain
		Serious adverse events	Reticulocytopenia, Sickle cell anemia with crisis, Local swelling, Hepatic ischemia, Cellulitis, Gastroenteritis, Lower respiratory tract infection, Face injury, Arthralgia, Back pain, Musculoskeletal chest pain, headache, Acute chest syndrome, Vascular occlusion
Glassberg 2017	mometasome placebo		Hoarseness of voice, thrush, sore thr`oat

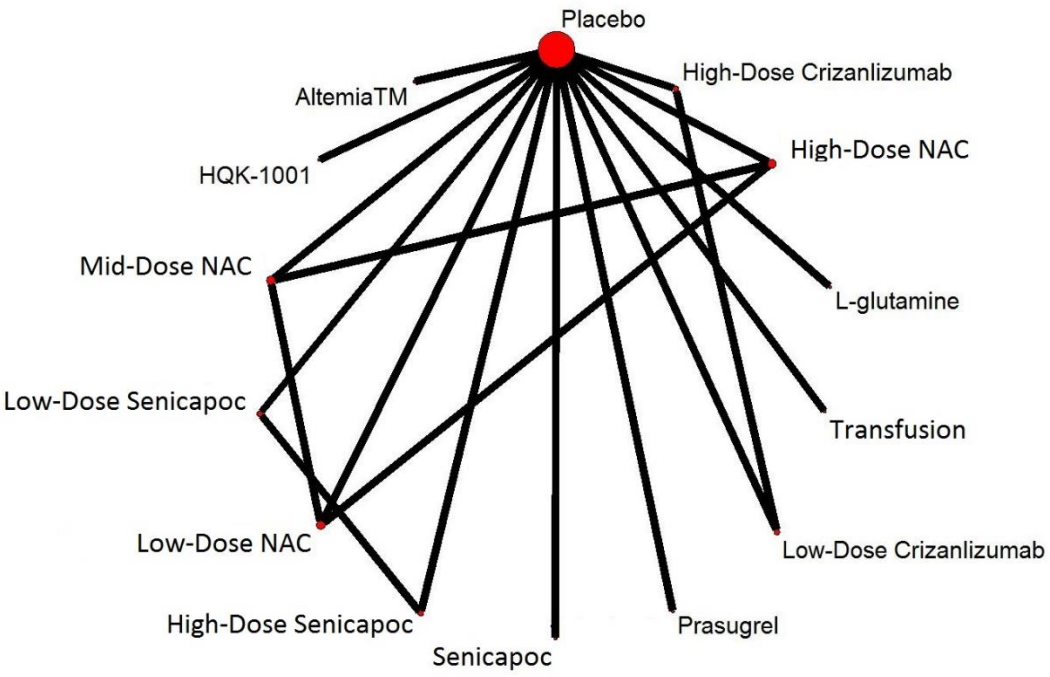
E.3 Additional results of the network meta-analysis

Extended network for potential indirect evidence

We wished to assess whether additional direct or indirect evidence would be provided on comparators studied in the 9 RCTs of the adult only NMA by including the 25 excluded non-adult RCTs as well as Vichinsky 2010 on transfusions under the assumption that their standard of care was a placebo. To do this we plotted the evidence networks including non-adult RCTs reporting on crisis, hospitalization days, adverse events, and serious adverse events and connected to high-dose crizanlizumab. However, there were only additional RCTs connected to high-dose crizanlizumab reporting on the crisis outcome. No additional RCTs connected to high-dose crizanlizumab reported on hospitalization days, adverse events, and serious adverse events.

The extended evidence network for crisis is presented in Figure 1. This network consists of 9 RCTs, including 4 RCTs not in the adult only network: Daak 2018 (AltemiaTM vs placebo)[3], Heeney 2016 (prasugrel vs placebo)[4], Reid 2014 (HQK-1001 vs placebo)[5], Vichinsky 2010 (transfusions vs standard of care)[6]. The extended network included 3 treatments not in the base case (AltemiaTM, HQK-1001, and Prasugrel). However, these additional RCTs did not provide direct or indirect evidence on any comparisons in the base case network.

Figure 1. Network of evidence for crisis in the extended population. Consists of 9 RCTs and 14 treatments.*

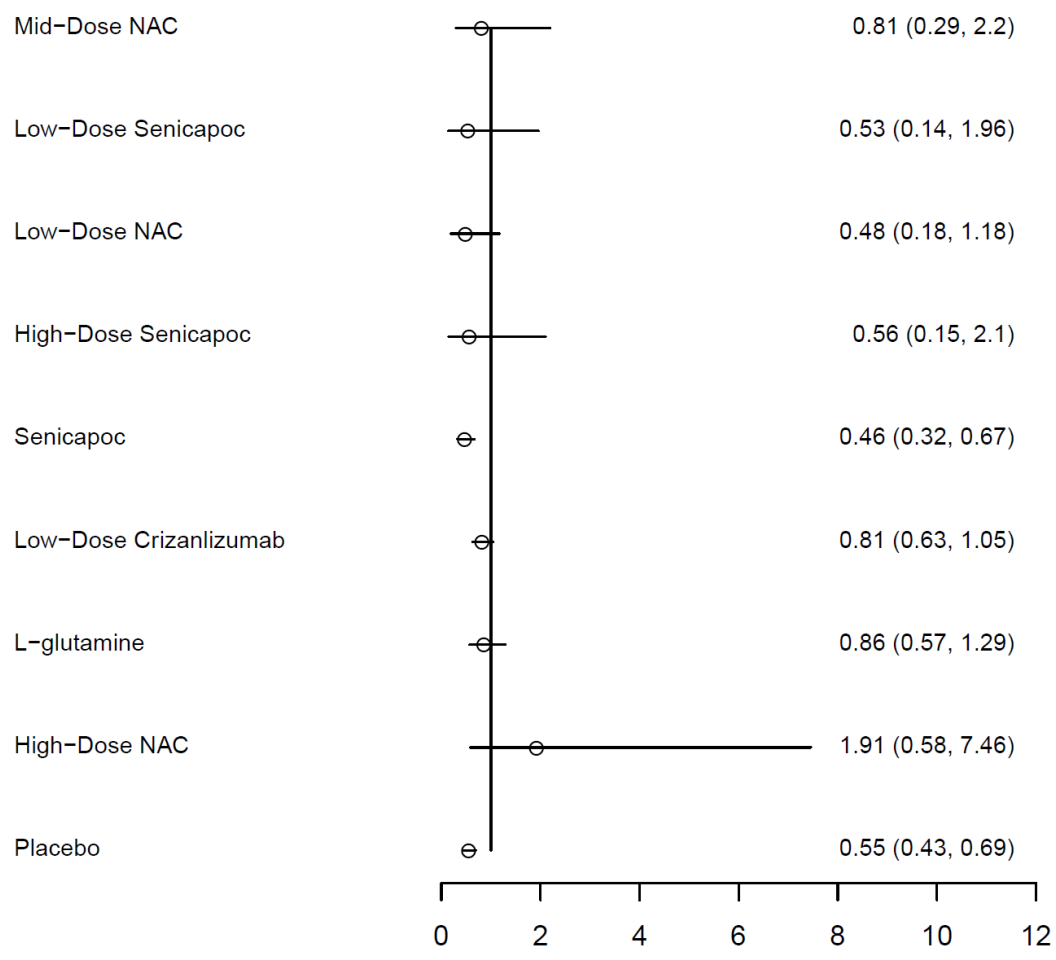


* Network included adult (base case) and non-adult studies. Adult studies: Ataga 2017 (crizanlizumab vs placebo), Ataga 2011 (senicapoc vs placebo), Ataga 2008 (senicapoc low-dose, senicapoc high-dose vs placebo), Pace 2003 (NAC vs placebo), Niihara 2017 (L-glutamine vs placebo), Vichinsky 2010 (transfusion vs placebo). Non-adult studies: Daak 2018 (AltemiaTM vs placebo), Heeney 2016 (prasugrel vs placebo), Reid 2014 (HQK-1001 vs placebo)

Sensitivity analysis using >18 years old subgroup results from Niihara 2018 on L-glutamine

As our target population was patients ≥16 years old the Niihara 2018 study with 51 patients aged 5-12, 67 aged 13-18, and 112 aged >18 potentially differed in important effect modifiers. We used the reported rate ratio of 0.64 with 95% confidence interval (0.45, 0.89) in a subgroup of patients aged >18 years old to repeat our NMA. The results are presented as forest plots in Figure 2 with p-value table in Table 4 and pairwise results in Table 13. Notably, the hazard ratio for crises on crizanlizumab vs L-glutamine is 0.86 (0.57, 1.29) with p-value 0.77; this is higher and more uncertain that the hazard ratio of 0.67 (0.51, 0.88) and p-value >0.99 estimated using the full results of Niihara 2018.

Figure 2. Forest plot using >18 years old subgroup results from Niihara 2018 on L-glutamine



Sd

Table 4. Bayesian probabilities that crizanlizumab is superior or inferior on each outcome analyzed using >18 year old subgroup results from Niihara 2018.

Treatment	Probability superior
Placebo	>0.9999
NAC (high-dose 2400mg)	0.1495
L-glutamine	0.7707
Low-Dose Crizanlizumab	0.9454
Senicapoc	>0.9999
High-Dose Senicapoc	0.8066
Low-Dose NAC	0.9429
Low-Dose Senicapoc	0.8354
Mid-Dose NAC	0.6649

Model assessment of the crisis network meta-analysis

Model fit and meta-regressions were explored. The base case fixed effects model fit well (total residual deviance close to number of data points[7]) but the meta-regressions did not converge (Gelman-Rubin Rhat statistic far from 1.000, very wide credible intervals for the regression coefficient). This was because there was only one RCT on each treatment contrast. Deviance and DIC do not in any case suggest evidence of effect modification as they are similar to the fixed effects analysis.

Table 5. Crisis among the adult population: Model comparison

Model	Number data points	Total residual deviance	DIC	Regression coefficient	Gelman-Rubin Rhat for regression
Base FE	14	15.44 (6.11, 25.85)	102.8	NA	NA
Proportion female FE	14	15.59 (6.14, 26.23)	102.9	45.66 (-83.88, 188.64)	1.681

Mean age FE	14	16.07 (6.23, 27.08)	103.8	-3.89 (-4.95, -2.85)	9.652
Proportion HbSS FE	14	15.4 (6.15, 25.73)	102.7	44.14 (8.16, 72.78)	2.018
Proportion HU use FE	14	15.29 (6.18, 25.44)	102.5	76.07 (47.4, 106.76)	7.392
Trial duration FE	14	15.18 (6, 25.34)	102.5	-7.35 (-50.24, 37.51)	7.528
Proportion black FE	14	15.77 (6.37, 26.29)	103.3	-2.93 (-78.26, 72.71)	21.211

Model assessment of the hospitalization days network meta-analysis

Model assessment and exploration of meta-regressions are presented in Table 6. The base case fixed effects model fits well (total residual deviance close to number of data points). Meta-regressions did not converge (Rhat statistic far from 1.000 and very wide credible intervals on the regression coefficient) as there was only one study on each treatment contrast. The deviance and DIC do not in any case suggest evidence of effect modification.

Table 6. Hospitalization days among the adult population: Model comparison

Model	Number data points	Total residual deviance	DIC	Regression coefficient	Gelman-Rubin Rhat for regression
Base FE	9	10.32 (3.02, 18.67)	72.69	NA	NA
Proportion female FE	9	10.46 (2.93, 19.2)	72.6	37.75 (-98.37, 172.76)	24.655
Mean age FE	9	10.52 (3.09, 19.2)	72.57	-5.85 (-7.09, -4.67)	6.029
Proportion HbSS FE	9	10.28 (2.91, 18.68)	72.71	39.4 (-33.02, 108.38)	21.868

Proprotion HU use FE	9	10.22 (2.99, 18.53)	72.44	78.51 (15.98, 139.67)	7.582
Trial duration FE	9	10.03 (2.9, 18.16)	72.33	16.54 (-3.57, 36.27)	34.345
Proportion black FE	9	9.99 (3.05, 17.91)	72.25	29.18 (-26.53, 86)	27.376

Model assessment for the adverse events network meta-anlaysis

Model assessment and exploration of meta-regressions are presented in Table 7. The base case fixed effects model fits well (total residual deviance close to number of data points). Meta-regressions did not converge (Rhat statistic far from 1.000 and very wide credible intervals on the regression coefficient) as there was only one study on each treatment contrast. The deviance and DIC do not in any case suggest evidence of effect modification.

Table 7. Adverse events among the adult population: Model comparison

Model	Number data points	Total residual deviance	DIC	Regression coefficient	Gelman-Rubin Rhat for regression
Base FE	11	12.38 (4.25, 21.55)	71.72	NA	NA
Proportion female FE	11	12.51 (4.27, 21.81)	71.96	57.94 (2, 114.04)	1.838
Mean age FE	11	12.35 (4.11, 21.73)	71.46	0.27 (-4.32, 4.95)	38.731
Proportion HbSS FE	11	12.65 (4.22, 22.29)	71.84	-45.33 (-137.28, 42.08)	10.813
Proprotion HU use FE	11	12.15 (4.25, 21.02)	71.4	-25.25 (-81.24, 28)	5.985

Trial duration FE	11	12.02 (4.18, 20.87)	71.11	21.33 (-1.45, 43.98)	20.575
Proportion black FE	11	12.31 (4.33, 21.3)	71.61	-20.3 (-48.26, 3.68)	4.349

Model assessment for the serious adverse events network meta-anlaysis

Model assessment and exploration of meta-regressions are presented in Table 8. The base case fixed effects model fits well (total residual deviance close to number of data points). Meta-regressions did not converge (Rhat statistic far from 1.000 and very wide credible intervals on the regression coefficient) as there was only one study on each treatment contrast. The deviance and DIC do not in any case suggest evidence of effect modification.

Table 8. Serious adverse events among the adult population: model comparison

Model	Number data points	Total residual deviance	DIC	Regression coefficient	Gelman-Rubin Rhat for regression
Base FE	12	13.49 (4.86, 23.2)	70.89	NA	NA
Proportion female FE	12	13.87 (4.96, 23.98)	71.27	-57.35 (-183.99, 65.33)	1.204
Mean age FE	12	13.98 (5.08, 24.06)	71.49	-2.06 (-4.45, 0.36)	40.773
Proportion HbSS FE	12	14.08 (5.04, 24.24)	71.96	51.6 (35.74, 65.75)	1.652
Proportion HU use FE	12	13.49 (4.92, 23.1)	70.99	-140.71 (-210.66, -68.54)	13.326
Trial duration FE	12	13.62 (4.92, 23.54)	70.87	-19.04 (-34.58, -3.28)	15.267

Proportion black FE	12	13.37 (4.75, 23.13)	70.66	-5.77 (-118.35, 104.8)	36.318

B.3 OpenBUGS code for the network meta-analysis

The code for the four shared parameter models used to analyze crisis, hospitalization days, adverse events, and serious adverse events are presented below. This code was run in OpenBUGS version 3.2.3 [8] with two MCMC chains of 400,000 iterations for burn-in and 30,000 iterations for posterior sampling.

Fixed effects model used for analyzing crisis.

```
model{
        # Data type 2; r2 events in exposure E2
        # Poisson likelihood, log link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns2){                    # LOOP THROUGH STUDIES
                mu2[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
                for (k in 1:na2[i]) {            # LOOP THROUGH ARMS
                        r2[i,k] ~ dpois(theta2[i,k])   # Poisson likelihood
                        theta2[i,k] <- lambda[i,k]*E2[i,k] # failure rate * exposure
                        # model for linear predictor
                        log(lambda[i,k]) <- mu2[i] + d[t2[i,k]] - d[t2[i,1]]
                        #Deviance contribution
                        dev2[i,k] <- 2*((theta2[i,k]-r2[i,k]) + r2[i,k]*log(r2[i,k]/theta2[i,k]))
                        }
                        #  summed residual deviance contribution for this trial
                        resdev2[i] <- sum(dev2[i,1:na2[i]])
                }
        totresdev2 <- sum(resdev2[])          #Total Residual Deviance
totresdev<-totresdev2+0
        # Treatment effect model is shared between the three likelihoods
        d[1]<-0       # treatment effect is zero for control arm
        # vague priors for treatment effects
        for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
        for(k in 1:nt)
        {
                # Bayesian one-sided p-values
                # Probability that treatment j has higher hazard than treatment k
                # step(x) is 1 if x>=0
                for (j in 1:nt){ pval[j,k] <- step(d[j]-d[k]) }
        }
}

# Data in BUGS format (some data is redundant)
list(E2= structure(.Data= c(6.50000E+01, 6.70000E+01, 6.60000E+01, NA, 1.44000E+02,
1.45000E+02, NA, NA, 6.92308E+00, 7.15385E+00, 6.69231E+00, NA, 1.75000E+00,
2.91667E+00, 2.33333E+00, 2.91667E+00, 7.20000E+01, 1.40308E+02, NA, NA), .Dim=c(5, 4)),
t2= structure(.Data= c(1.00000E+00, 2.00000E+00, 5.00000E+00, NA, 1.00000E+00, 6.00000E+00,
NA, NA, 1.00000E+00, 7.00000E+00, 9.00000E+00, NA, 1.00000E+00, 3.00000E+00,
8.00000E+00, 1.00000E+01, 1.00000E+00, 4.00000E+00, NA, NA), .Dim=c(5, 4)), r2=
structure(.Data= c(1.93700E+02, 1.09210E+02, 1.32660E+02, NA, 8.90000E+01, 1.06000E+02,
```

NA, NA, 5.00000E+00, 5.00000E+00, 5.00000E+00, NA, 8.00000E+00, 4.00000E+00, 1.20000E+01, 9.00000E+00, 3.04200E+02, 4.86400E+02, NA, NA), .Dim=c(5, 4)), n4= structure(.Data= c(3.80000E+01, 3.80000E+01), .Dim=c(1, 2)), ns1=0.00000E+00, ns2=5.00000E+00, ns4=0.00000E+00, ns5=0.00000E+00, na1=0.00000E+00, na2=c(3.00000E+00, 2.00000E+00, 3.00000E+00, 4.00000E+00, 2.00000E+00), na4=c(0.00000E+00, 0.00000E+00), na5=c(0.00000E+00, 0.00000E+00), nt=1.00000E+01, x= structure(.Data= c(NA, NA, NA, NA, NA, NA, 5.50505E-01, 2.80152E+01, 7.12121E-01, 6.21212E-01, 1.00000E+00, 9.19192E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 5.53633E-01, 2.89983E+01, 8.47751E-01, 5.64014E-01, 1.00000E+00, 9.51557E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 5.00000E-01, 3.54833E+01, 1.00000E+00, 5.37603E-01, 2.30769E-01, 8.14103E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 4.76190E-01, 2.05286E+01, 8.49869E-01, 5.37603E-01, 5.83333E-01, 8.14103E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 5.39130E-01, 2.20609E+01, 9.00000E-01, 6.65217E-01, 9.23077E-01, 9.43478E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA), .Dim=c(5, 4, 6)), mx=c(5.38790E-01, 2.52754E+01, 8.49869E-01, 5.37603E-01, 9.51465E-01, 8.14103E-01), r2.base=c(1.93700E+02, 1.22000E+02, 8.90000E+01, 5.00000E+00, 8.00000E+00, 3.04200E+02), E2.base=c(6.50000E+01, 1.27500E+02, 1.44000E+02, 6.92308E+00, 1.75000E+00, 7.20000E+01), r4.base=1.90000E+01, *time4.base=4.61538E-01, n4.base=3.80000E+01, ns2.base=6.00000E+00, ns4.base=1.00000E+00)*

 # Initial values (includes initial values for meta-regressions, which are redundant)
 # Inits 1
list(B=5.00000E-01, d=c(NA, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00), sd=1.00000E+00, mu.base=1.00000E+00, mu2=c(1.40000E+00, 1.40000E+00, 1.40000E+00, 1.40000E+00, 1.40000E+00))

 # Inits 2
list(B=1.00000E-01, d=c(NA, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01), sd=5.00000E-01, mu.base=5.00000E-01, mu2=c(7.00000E-01, 7.00000E-01, 7.00000E-01, 7.00000E-01, 7.00000E-01))

Fixed effects model used for analyzing hospitalization days.

```
model{
        # Data type 2; r2 events in exposure E2
        # Poisson likelihood, log link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns2){                    # LOOP THROUGH STUDIES
                mu2[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines
                for (k in 1:na2[i]) {             # LOOP THROUGH ARMS
                        r2[i,k] ~ dpois(theta2[i,k])   # Poisson likelihood
                        theta2[i,k] <- lambda[i,k]*E2[i,k] # failure rate * exposure
                        # model for linear predictor
                        log(lambda[i,k]) <- mu2[i] + d[t2[i,k]] - d[t2[i,1]]
                        #Deviance contribution
                        dev2[i,k] <- 2*((theta2[i,k]-r2[i,k]) + r2[i,k]*log(r2[i,k]/theta2[i,k]))
                        }
                        #  summed residual deviance contribution for this trial
                        resdev2[i] <- sum(dev2[i,1:na2[i]])
                }
        totresdev2 <- sum(resdev2[])           #Total Residual Deviance
totresdev<-totresdev2+0
        # Treatment effect model is shared between the three likelihoods
        d[1]<-0       # treatment effect is zero for control arm
        # vague priors for treatment effects
        for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
        for(k in 1:nt)
        {
```

```
                # Bayesian one-sided p-values
                # Probability that treatment j has higher hazard than treatment k
                # step(x) is 1 if x>=0
                for (j in 1:nt){ pval[j,k] <- step(d[j]-d[k]) }
        }
}

# Data in BUGS format (some data is redundant)
list(ns5=0.00000E+00, ns4=0.00000E+00, E2= structure(.Data= c(6.53846E+00, 1.34615E+01,    NA,
6.50000E+01,  6.70000E+01,  6.60000E+01,  8.50000E+00,  5.00000E+00,        NA,  7.20000E+01,
1.40308E+02,       NA), .Dim=c(4, 3)), t2= structure(.Data= c(1.00000E+00, 5.00000E+00,       NA,
1.00000E+00,  2.00000E+00,  6.00000E+00,  1.00000E+00,  3.00000E+00,        NA,  1.00000E+00,
4.00000E+00,       NA), .Dim=c(4, 3)), r2= structure(.Data= c(6.95300E+01, 9.34500E+01,       NA,
4.46550E+02,  2.68000E+02,  4.53420E+02,  5.30000E+01,  9.00000E+00,        NA,  1.81000E+01,
1.21000E+01,       NA), .Dim=c(4, 3)), ns1=0.00000E+00, ns2=4.00000E+00, na1=0.00000E+00,
na2=c(2.00000E+00,  3.00000E+00,  2.00000E+00,  2.00000E+00), nt=6.00000E+00,  x=
structure(.Data= c(  NA,  NA,  NA,  NA,  NA,  NA, 4.42308E-01, 3.19615E+01, 9.61538E-01,
5.23307E-01, 3.07692E-01, 8.09945E-01,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,
NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA, 5.50505E-01, 2.80152E+01, 7.12121E-01,
6.21212E-01, 1.00000E+00, 9.19192E-01,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,
NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA, 5.97015E-01, 2.88836E+01,
6.86567E-01, 4.17910E-01, 5.00000E-01, 5.67164E-01,  NA,  NA,  NA,  NA,  NA,  NA,  NA,
NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA, 5.39130E-01, 2.20609E+01,
9.00000E-01, 6.65217E-01, 9.23077E-01, 9.43478E-01,  NA,  NA,  NA,  NA,  NA,  NA,  NA,
NA,  NA,  NA,  NA,  NA), .Dim=c(4, 4, 6)), mx=c(5.32240E-01, 2.81176E+01, 8.15057E-01,
5.23307E-01, 6.82692E-01, 8.09945E-01))


# Initial values (includes initial values for meta-regressions, which are redundant)
# Inits 1
list(B=5.00000E-01,  d=c(        NA,  1.00000E+00,  1.00000E+00,  1.00000E+00,  1.00000E+00,
1.00000E+00), sd=1.00000E+00,  mu.base=1.00000E+00,  mu2=c(1.40000E+00,  1.40000E+00,
1.40000E+00, 1.40000E+00))

# Inits 2
list(B=1.00000E-01, d=c(   NA, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01),
sd=5.00000E-01, mu.base=5.00000E-01, mu2=c(7.00000E-01, 7.00000E-01, 7.00000E-01, 7.00000E-
01))
```

Fixed effects model used for analyzing adverse events.

```
model{
        # Data type 2; r2 events in exposure E2
        # Poisson likelihood, log link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns2){                # LOOP THROUGH STUDIES
                mu2[i] ~ dnorm(0,.0001)         # vague priors for all trial baselines
                for (k in 1:na2[i]) {           # LOOP THROUGH ARMS
                        r2[i,k] ~ dpois(theta2[i,k])   # Poisson likelihood
                        theta2[i,k] <- lambda[i,k]*E2[i,k] # failure rate * exposure
                        # model for linear predictor
                        log(lambda[i,k]) <- mu2[i] + d[t2[i,k]] - d[t2[i,1]]
                        #Deviance contribution
                        dev2[i,k] <- 2*((theta2[i,k]-r2[i,k]) + r2[i,k]*log(r2[i,k]/theta2[i,k]))
                        }
                        #  summed residual deviance contribution for this trial
                        resdev2[i] <- sum(dev2[i,1:na2[i]])
                }
        totresdev2 <- sum(resdev2[])          #Total Residual Deviance
```

```
        # Data type 4; number of patients r4 out of n4 with >=1 event in time4
        # Binomial likelihood, cloglog link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns4){                    # LOOP THROUGH STUDIES
            mu4[i] ~ dnorm(0,.0001)         # vague priors for all trial baselines
            for (k in 1:na4[i]) {           # LOOP THROUGH ARMS
                r4[i,k] ~ dbin(p[i,k],n4[i,k]) # Binomial likelihood
                # model for linear predictor
                cloglog(p[i,k]) <- log(time4[i,k]) + mu4[i] + d[t4[i,k]] - d[t4[i,1]]
                rhat[i,k] <- p[i,k] * n4[i,k]       # expected value of the numerators
                #Deviance contribution
                dev4[i,k] <- 2 * (r4[i,k] * (log(r4[i,k])-log(rhat[i,k]))
            +  (n4[i,k]-r4[i,k]) * (log(n4[i,k]-r4[i,k]) - log(n4[i,k]-rhat[i,k])))       }
                #  summed residual deviance contribution for this trial
                resdev4[i] <- sum(dev4[i,1:na4[i]])
            }
        totresdev4 <- sum(resdev4[])          #Total Residual Deviance
totresdev<-totresdev2+totresdev4+0
        # Treatment effect model is shared between the three likelihoods
        d[1]<-0      # treatment effect is zero for control arm
        # vague priors for treatment effects
        for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
        for(k in 1:nt)
        {
            # Bayesian one-sided p-values
            # Probability that treatment j has higher hazard than treatment k
            # step(x) is 1 if x>=0
            for (j in 1:nt){ pval[j,k] <- step(d[j]-d[k]) }
        }
}

# Data in BUGS format (some data is redundant)
list(ns5=0.00000E+00, ns1=0.00000E+00, E2= structure(.Data= c(3.92308E+00, 8.07692E+00,
2.40000E+01, 2.40000E+01, 1.44000E+02, 1.45000E+02), .Dim=c(3, 2)), t2= structure(.Data=
c(1.00000E+00, 3.00000E+00, 1.00000E+00, 2.00000E+00, 1.00000E+00, 4.00000E+00), .Dim=c(3,
2)), r2= structure(.Data= c(9.00000E+00, 3.20000E+01, 3.60000E+01, 3.90000E+01, 1.19000E+02,
1.27000E+02), .Dim=c(3, 2)), time4= structure(.Data= c(1.00000E+00, 1.00000E+00, 1.00000E+00,
9.23077E-01, 9.23077E-01,    NA), .Dim=c(2, 3)), n4= structure(.Data= c(6.20000E+01, 6.60000E+01,
6.40000E+01, 7.80000E+01, 1.52000E+02,    NA), .Dim=c(2, 3)), t4= structure(.Data= c(1.00000E+00,
5.00000E+00, 7.00000E+00, 1.00000E+00, 6.00000E+00,    NA), .Dim=c(2, 3)), r4= structure(.Data=
c(5.50000E+01, 5.70000E+01, 5.60000E+01, 7.75000E+01, 1.48460E+02,    NA), .Dim=c(2, 3)),
ns2=3.00000E+00,    ns4=2.00000E+00,    na2=c(2.00000E+00,    2.00000E+00,    2.00000E+00),
na4=c(3.00000E+00, 2.00000E+00), nt=7.00000E+00, x= structure(.Data= c(    NA,    NA,    NA,    NA,
NA,    NA, 4.42308E-01, 3.19615E+01, 9.61538E-01, 5.31449E-01, 3.07692E-01, 8.45348E-01,
5.50505E-01, 2.80152E+01, 7.12121E-01, 6.21212E-01, 1.00000E+00, 9.19192E-01,    NA,    NA,
NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA, 5.97015E-01, 2.88836E+01,
6.86567E-01, 4.17910E-01, 5.00000E-01, 5.67164E-01, 5.39130E-01, 2.20609E+01, 9.00000E-01,
6.65217E-01, 9.23077E-01, 9.43478E-01,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,
NA,    NA,    NA, 5.53633E-01, 2.89983E+01, 8.47751E-01, 5.64014E-01, 1.00000E+00, 9.51557E-
01,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA), .Dim=c(3, 4,
6)), mx=c(5.36518E-01, 2.82643E+01, 8.21596E-01, 5.31449E-01, 7.46154E-01, 8.45348E-01),
r2.base=c(9.00000E+00, 3.60000E+01, 1.19000E+02), E2.base=c(3.92308E+00, 2.40000E+01,
1.44000E+02), r4.base=c(5.50000E+01, 7.75000E+01), time4.base=c(1.00000E+00, 9.23077E-01),
n4.base=c(6.20000E+01, 7.80000E+01), ns2.base=3.00000E+00, ns4.base=2.00000E+00)


# Initial values (includes initial values for meta-regressions, which are redundant)
# Inits 1
```

```
list(B=5.00000E-01, d=c(          NA, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00,
1.00000E+00, 1.00000E+00), sd=1.00000E+00, mu.base=1.00000E+00, mu2=c(1.40000E+00,
1.40000E+00, 1.40000E+00), mu4=c(5.00000E-01, 5.00000E-01))

# Inits 2
list(B=1.00000E-01, d=c(    NA, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01,
5.00000E-01), sd=5.00000E-01, mu.base=5.00000E-01, mu2=c(7.00000E-01, 7.00000E-01,
7.00000E-01), mu4=c(2.50000E-01, 2.50000E-01))
```

Fixed effects model used for analyzing serious adverse events.

```
model{
        # Data type 2; r2 events in exposure E2
        # Poisson likelihood, log link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns2){                # LOOP THROUGH STUDIES
                mu2[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
                for (k in 1:na2[i]) {           # LOOP THROUGH ARMS
                        r2[i,k] ~ dpois(theta2[i,k])   # Poisson likelihood
                        theta2[i,k] <- lambda[i,k]*E2[i,k] # failure rate * exposure
                        # model for linear predictor
                        log(lambda[i,k]) <- mu2[i] + d[t2[i,k]] - d[t2[i,1]]
                        #Deviance contribution
                        dev2[i,k] <- 2*((theta2[i,k]-r2[i,k]) + r2[i,k]*log(r2[i,k]/theta2[i,k]))
                        }
                        #  summed residual deviance contribution for this trial
                        resdev2[i] <- sum(dev2[i,1:na2[i]])
                }
        totresdev2 <- sum(resdev2[])          #Total Residual Deviance

        # Data type 4; number of patients r4 out of n4 with >=1 event in time4
        # Binomial likelihood, cloglog link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns4){                # LOOP THROUGH STUDIES
                mu4[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
                for (k in 1:na4[i]) {           # LOOP THROUGH ARMS
                        r4[i,k] ~ dbin(p[i,k],n4[i,k]) # Binomial likelihood
                        # model for linear predictor
                        cloglog(p[i,k]) <- log(time4[i,k]) + mu4[i] + d[t4[i,k]] - d[t4[i,1]]
                        rhat[i,k] <- p[i,k] * n4[i,k]        # expected value of the numerators
                        #Deviance contribution
                        dev4[i,k] <- 2 * (r4[i,k] * (log(r4[i,k])-log(rhat[i,k]))
                +  (n4[i,k]-r4[i,k]) * (log(n4[i,k]-r4[i,k]) - log(n4[i,k]-rhat[i,k])))     }
                        #  summed residual deviance contribution for this trial
                        resdev4[i] <- sum(dev4[i,1:na4[i]])
                }
        totresdev4 <- sum(resdev4[])          #Total Residual Deviance
totresdev<-totresdev2+totresdev4+0
        # Treatment effect model is shared between the three likelihoods
        d[1]<-0      # treatment effect is zero for control arm
        # vague priors for treatment effects
        for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
        for(k in 1:nt)
        {
                # Bayesian one-sided p-values
                # Probability that treatment j has higher hazard than treatment k
                # step(x) is 1 if x>=0
                for (j in 1:nt){ pval[j,k] <- step(d[j]-d[k]) }
        }
}
```

 # Data in BUGS format (some data is redundant)
list(ns5=0.00000E+00, ns1=0.00000E+00, E2= structure(.Data= c(2.40000E+01, 2.40000E+01, NA, 1.56164E+00, 3.36986E+00, NA, 6.92308E+00, 6.92308E+00, 6.00000E+00), .Dim=c(3, 3)), t2= structure(.Data= c(1.00000E+00, 2.00000E+00, NA, 1.00000E+00, 3.00000E+00, NA, 1.00000E+00, 4.00000E+00, 5.00000E+00), .Dim=c(3, 3)), r2= structure(.Data= c(2.00000E+00, 8.00000E+00, NA, 4.00000E+00, 8.00000E+00, NA, 6.00000E+00, 5.00000E+00, 6.00000E+00), .Dim=c(3, 3)), time4= structure(.Data= c(1.00000E+00, 1.00000E+00, 1.00000E+00, 9.23077E-01, 9.23077E-01, NA), .Dim=c(2, 3)), n4= structure(.Data= c(6.20000E+01, 6.60000E+01, 6.40000E+01, 7.80000E+01, 1.52000E+02, NA), .Dim=c(2, 3)), t4= structure(.Data= c(1.00000E+00, 6.00000E+00, 8.00000E+00, 1.00000E+00, 7.00000E+00, NA), .Dim=c(2, 3)), r4= structure(.Data= c(1.70000E+01, 1.70000E+01, 2.10000E+01, 6.79380E+01, 1.18864E+02, NA), .Dim=c(2, 3)), ns2=3.00000E+00, ns4=2.00000E+00, na2=c(2.00000E+00, 2.00000E+00, 3.00000E+00), na4=c(3.00000E+00, 2.00000E+00), nt=8.00000E+00, x= structure(.Data= c(NA, NA, NA, NA, NA, NA, 5.97015E-01, 2.88836E+01, 6.86567E-01, 4.17910E-01, 5.00000E-01, 5.67164E-01, 5.50505E-01, 2.80152E+01, 7.12121E-01, 6.21212E-01, 1.00000E+00, 9.19192E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 4.83871E-01, 3.24258E+01, 5.96774E-01, 5.23307E-01, 6.45161E-02, 7.39642E-01, 5.39130E-01, 2.20609E+01, 9.00000E-01, 6.65217E-01, 9.23077E-01, 9.43478E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 5.40230E-01, 2.22448E+01, 7.23866E-01, 5.23307E-01, 2.30769E-01, 5.28736E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA), .Dim=c(3, 4, 6)), mx=c(5.42150E-01, 2.72162E+01, 7.23866E-01, 5.23307E-01, 5.43672E-01, 7.39642E-01), r2.base=c(2.00000E+00, 4.00000E+00, 6.00000E+00), E2.base=c(2.40000E+01, 1.56164E+00, 6.92308E+00), r4.base=c(1.70000E+01, 6.79380E+01), time4.base=c(1.00000E+00, 9.23077E-01), n4.base=c(6.20000E+01, 7.80000E+01), ns2.base=3.00000E+00, ns4.base=2.00000E+00)

 # Initial values (includes initial values for meta-regressions, which are redundant)
 # Inits 1
list(B=5.00000E-01, d=c(NA, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00), sd=1.00000E+00, mu.base=1.00000E+00, mu2=c(1.40000E+00, 1.40000E+00, 1.40000E+00), mu4=c(5.00000E-01, 5.00000E-01))

 # Inits 2
list(B=1.00000E-01, d=c(NA, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01), sd=5.00000E-01, mu.base=5.00000E-01, mu2=c(7.00000E-01, 7.00000E-01, 7.00000E-01), mu4=c(2.50000E-01, 2.50000E-01))

E.4 Pairwise results of the NMA

Table 9 Hazard ratios comparing all treatments on crisis*

Placebo	1.83 (1.45, 2.31)	3.48 (1.06, 13.60)	1.22 (1.06, 1.40)	1.49 (1.19, 1.85)	0.84 (0.64, 1.12)	1.03 (0.28, 3.88)	0.88 (0.33, 2.15)	0.97 (0.26, 3.49)	1.48 (0.55, 3.90)
0.55 (0.43, 0.69)	High-Dose Crizanlizumab	1.91 (0.57, 7.58)	0.67 (0.51, 0.88)	0.81 (0.63, 1.05)	0.46 (0.32, 0.67)	0.57 (0.15, 2.17)	0.48 (0.18, 1.21)	0.53 (0.14, 1.95)	0.81 (0.29, 2.18)
0.29 (0.07, 0.95)	0.52 (0.13, 1.76)	High-Dose NAC	0.35 (0.09, 1.16)	0.43 (0.11, 1.42)	0.24 (0.06, 0.82)	0.30 (0.04, 1.77)	0.25 (0.07, 0.74)	0.27 (0.04, 1.65)	0.42 (0.11, 1.32)
0.82 (0.71, 0.95)	1.50 (1.14, 1.97)	2.85 (0.86, 11.31)	L-glutamine	1.22 (0.94, 1.59)	0.69 (0.50, 0.95)	0.85 (0.23, 3.22)	0.72 (0.27, 1.79)	0.80 (0.21, 2.90)	1.21 (0.44, 3.22)
0.67 (0.54, 0.84)	1.23 (0.96, 1.59)	2.34 (0.70, 9.28)	0.82 (0.63, 1.07)	Low-Dose Crizanlizumab	0.57 (0.40, 0.81)	0.70 (0.18, 2.65)	0.59 (0.22, 1.48)	0.65 (0.17, 2.39)	1.00 (0.36, 2.65)
1.18 (0.89, 1.57)	2.17 (1.50, 3.13)	4.12 (1.22, 16.55)	1.45 (1.05, 1.99)	1.76 (1.23, 2.53)	senicapoc	1.23 (0.32, 4.75)	1.04 (0.38, 2.63)	1.15 (0.30, 4.29)	1.75 (0.62, 4.75)
0.97 (0.26, 3.63)	1.77 (0.46, 6.74)	3.39 (0.57, 22.44)	1.18 (0.31, 4.43)	1.44 (0.38, 5.47)	0.82 (0.21, 3.15)	High-Dose Senicapoc	0.84 (0.17, 4.19)	0.93 (0.25, 3.47)	1.42 (0.27, 7.25)

1.14 (0.46, 3.00)	2.09 (0.82, 5.65)	3.97 (1.36, 15.03)	1.39 (0.56, 3.68)	1.70 (0.68, 4.58)	0.97 (0.38, 2.62)	1.19 (0.24, 6.02)	Low-Dose NAC	1.11 (0.22, 5.61)	1.70 (0.71, 4.16)
1.03 (0.29, 3.88)	1.89 (0.51, 7.20)	3.65 (0.61, 23.66)	1.26 (0.34, 4.76)	1.54 (0.42, 5.86)	0.87 (0.23, 3.38)	1.08 (0.29, 3.97)	0.90 (0.18, 4.46)	Low-Dose Senicapoc	1.53 (0.30, 7.79)
0.68 (0.26, 1.83)	1.23 (0.46, 3.46)	2.36 (0.76, 8.95)	0.82 (0.31, 2.26)	1.00 (0.38, 2.80)	0.57 (0.21, 1.61)	0.70 (0.14, 3.67)	0.59 (0.24, 1.41)	0.65 (0.13, 3.35)	Mid-Dose NAC

***** Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Table 10 Hazard ratios comparing all treatments on all-cause hospitalization days*

Placebo	1.72 (1.48, 2.00)	3.57 (1.85, 7.95)	2.97 (1.44, 6.35)	1.53 (1.12, 2.09)	1.00 (0.88, 1.14)
0.58 (0.50, 0.68)	High-Dose Crizanlizumab	2.08 (1.06, 4.66)	1.73 (0.82, 3.76)	0.89 (0.63, 1.26)	0.58 (0.50, 0.68)
0.28 (0.13, 0.54)	0.48 (0.21, 0.95)	Low-Dose NAC	0.83 (0.28, 2.28)	0.43 (0.18, 0.89)	0.28 (0.12, 0.55)
0.34 (0.16, 0.70)	0.58 (0.27, 1.22)	1.21 (0.44, 3.52)	L-glutamine	0.51 (0.23, 1.13)	0.34 (0.16, 0.71)

0.66 (0.48, 0.90)	1.13 (0.80, 1.58)	2.35 (1.13, 5.47)	1.95 (0.89, 4.41)	Mometasome	0.66 (0.47, 0.92)
1.00 (0.88, 1.14)	1.72 (1.48, 2.00)	3.57 (1.82, 8.03)	2.97 (1.42, 6.45)	1.52 (1.09, 2.14)	Low-Dose Crizanlizumab

***** Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Table 11 Hazard ratios comparing all treatments on adverse events*

Placebo	0.92 (0.59, 1.46)	0.57 (0.25, 1.13)	0.94 (0.74, 1.21)	1.09 (0.70, 1.70)	1.42 (0.79, 2.97)	1.05 (0.67, 1.64)
1.08 (0.69, 1.71)	Low-Dose NAC	0.61 (0.25, 1.42)	1.02 (0.61, 1.72)	1.19 (0.62, 2.24)	1.56 (0.74, 3.66)	1.14 (0.60, 2.17)
1.77 (0.88, 4.01)	1.64 (0.70, 4.08)	Mometasome	1.67 (0.80, 3.86)	1.95 (0.84, 4.83)	2.55 (1.02, 7.58)	1.86 (0.80, 4.59)
1.06 (0.82, 1.36)	0.98 (0.58, 1.65)	0.60 (0.26, 1.25)	Senicapoc	1.16 (0.69, 1.91)	1.51 (0.80, 3.30)	1.11 (0.67, 1.86)
0.91 (0.59, 1.43)	0.84 (0.45, 1.60)	0.51 (0.21, 1.19)	0.86 (0.52, 1.44)	High-Dose Crizanlizumab	1.31 (0.62, 3.08)	0.96 (0.61, 1.48)
0.70 (0.34, 1.26)	0.64 (0.27, 1.36)	0.39 (0.13, 0.98)	0.66 (0.30, 1.25)	0.76 (0.32, 1.60)	L-glutamine	0.73 (0.31, 1.53)
0.95 (0.61, 1.50)	0.88 (0.46, 1.68)	0.54 (0.22, 1.25)	0.90 (0.54, 1.50)	1.04 (0.67, 1.63)	1.37 (0.65, 3.21)	Low-Dose Crizanlizumab

***** *Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.*

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Table 12 Hazard ratios comparing all treatments on serious adverse events*

Placebo	0.22 (0.03, 0.92)	1.04 (0.27, 3.36)	1.22 (0.35, 4.39)	0.88 (0.27, 2.85)	1.08 (0.54, 2.14)	1.34 (0.95, 1.89)	0.80 (0.42, 1.53)
4.50 (1.08, 37.94)	Low-Dose NAC	4.67 (0.68, 50.13)	5.70 (0.81, 63.02)	4.05 (0.59, 43.70)	4.92 (1.00, 42.52)	6.05 (1.40, 50.86)	3.66 (0.75, 31.45)
0.96 (0.30, 3.64)	0.21 (0.02, 1.48)	Prasugrel	1.19 (0.22, 7.18)	0.85 (0.16, 4.95)	1.04 (0.27, 4.55)	1.30 (0.38, 5.12)	0.78 (0.20, 3.32)
0.82 (0.23, 2.82)	0.18 (0.02, 1.24)	0.84 (0.14, 4.63)	High-Dose Ticagrelor	0.72 (0.20, 2.42)	0.87 (0.21, 3.69)	1.10 (0.29, 3.97)	0.65 (0.16, 2.66)
1.14 (0.35, 3.75)	0.25 (0.02, 1.69)	1.18 (0.20, 6.24)	1.40 (0.41, 5.00)	Low-Dose Ticagrelor	1.23 (0.32, 4.86)	1.53 (0.45, 5.28)	0.92 (0.24, 3.52)
0.93 (0.47, 1.87)	0.20 (0.02, 1.00)	0.96 (0.22, 3.74)	1.14 (0.27, 4.81)	0.81 (0.21, 3.17)	High-Dose Crizanlizumab	1.24 (0.58, 2.70)	0.75 (0.39, 1.43)

0.74 (0.53, 1.05)	0.17 (0.02, 0.71)	0.77 (0.20, 2.64)	0.91 (0.25, 3.41)	0.65 (0.19, 2.22)	0.80 (0.37, 1.72)	L-glutamine	0.60 (0.29, 1.24)
1.24 (0.65, 2.40)	0.27 (0.03, 1.33)	1.29 (0.30, 4.95)	1.54 (0.38, 6.35)	1.09 (0.28, 4.20)	1.34 (0.70, 2.58)	1.67 (0.81, 3.47)	Low-Dose Crizanlizumab

* Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Table 13 Hazard ratios comparing all treatments on crisis using >18 year old subgroup results from Niihara 2018*

Placebo	1.83 (1.44, 2.32)	3.49 (1.09, 13.48)	1.56 (1.11, 2.19)	1.48 (1.19, 1.86)	0.85 (0.64, 1.12)	1.02 (0.28, 3.75)	0.88 (0.34, 2.10)	0.97 (0.26, 3.52)	1.47 (0.55, 3.90)
0.55 (0.43, 0.69)	High-Dose Crizanlizumab	1.91 (0.58, 7.46)	0.86 (0.57, 1.29)	0.81 (0.63, 1.05)	0.46 (0.32, 0.67)	0.56 (0.15, 2.10)	0.48 (0.18, 1.18)	0.53 (0.14, 1.96)	0.81 (0.29, 2.20)
0.29 (0.07, 0.92)	0.52 (0.13, 1.72)	High-Dose NAC	0.45 (0.11, 1.52)	0.43 (0.11, 1.40)	0.24 (0.06, 0.81)	0.29 (0.04, 1.66)	0.25 (0.07, 0.74)	0.27 (0.04, 1.60)	0.42 (0.11, 1.32)
0.64 (0.46, 0.90)	1.17 (0.77, 1.77)	2.24 (0.66, 8.93)	L-glutamine	0.95 (0.63, 1.43)	0.54 (0.35, 0.84)	0.65 (0.17, 2.51)	0.56 (0.20, 1.43)	0.62 (0.16, 2.35)	0.94 (0.33, 2.66)

0.67 (0.54, 0.84)	1.23 (0.96, 1.59)	2.35 (0.71, 9.19)	1.05 (0.70, 1.58)	Low-Dose Crizanlizumab	0.57 (0.40, 0.81)	0.69 (0.18, 2.57)	0.59 (0.22, 1.45)	0.65 (0.17, 2.43)	0.99 (0.37, 2.69)
1.18 (0.89, 1.57)	2.16 (1.50, 3.12)	4.14 (1.23, 16.30)	1.85 (1.19, 2.88)	1.76 (1.23, 2.51)	Senicapoc	1.21 (0.32, 4.58)	1.04 (0.38, 2.60)	1.14 (0.30, 4.29)	1.75 (0.62, 4.79)
0.98 (0.27, 3.61)	1.79 (0.48, 6.83)	3.45 (0.60, 22.24)	1.53 (0.40, 5.91)	1.45 (0.39, 5.48)	0.82 (0.22, 3.14)	High-Dose Senicapoc	0.86 (0.18, 4.13)	0.94 (0.25, 3.47)	1.43 (0.28, 7.35)
1.13 (0.48, 2.94)	2.08 (0.85, 5.48)	3.98 (1.35, 14.62)	1.77 (0.70, 4.89)	1.68 (0.69, 4.45)	0.96 (0.38, 2.61)	1.17 (0.24, 5.71)	Low-Dose NAC	1.10 (0.23, 5.49)	1.68 (0.72, 4.17)
1.04 (0.28, 3.84)	1.89 (0.51, 7.17)	3.66 (0.63, 23.10)	1.63 (0.43, 6.32)	1.54 (0.41, 5.82)	0.88 (0.23, 3.39)	1.07 (0.29, 3.93)	0.91 (0.18, 4.36)	Low-Dose Senicapoc	1.53 (0.30, 7.76)
0.68 (0.26, 1.81)	1.24 (0.46, 3.41)	2.36 (0.76, 9.08)	1.06 (0.38, 3.00)	1.01 (0.37, 2.73)	0.57 (0.21, 1.60)	0.70 (0.14, 3.53)	0.60 (0.24, 1.39)	0.65 (0.13, 3.31)	Mid-Dose NAC

***** Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

E.5 Cumulative ranking plots - Rankograms

In this appendix we provide the cumulative ranking plots, which are called 'rankograms'. These are the cumulative probability that each treatment is in the top 1, 2, 3, … treatments on the basis of each outcome.

Figure 3 Cumulative ranking plot for Crisis

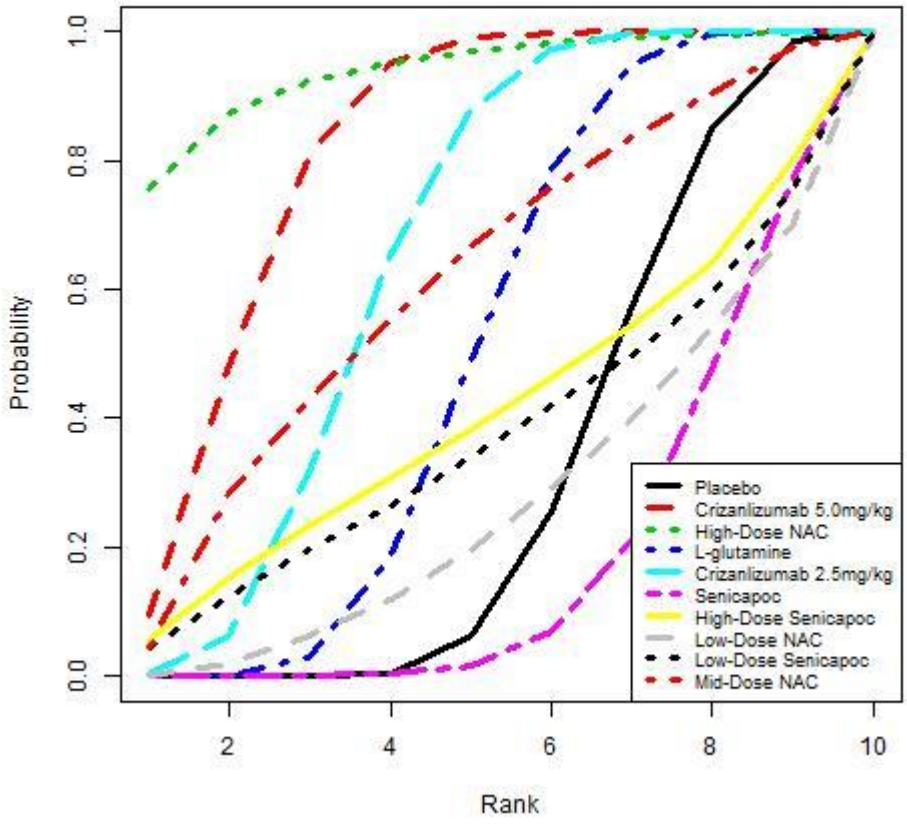


Figure 4 Cumulative ranking plot for adverse events

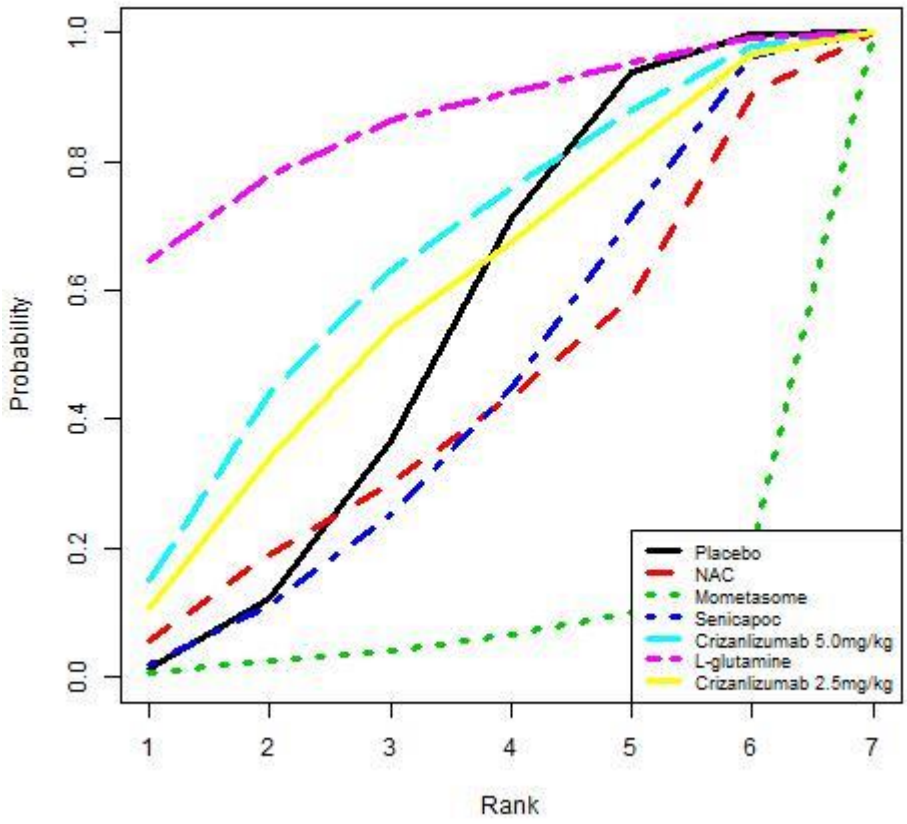

Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
2
3
4
5
6
7
Rank
Placebo
NAC
Mometasome
Senicapoc
Crizanlizumab 5.0mg/kg
L-glutamine
Crizanlizumab 2.5mg/kg

Figure 5 Cumulative ranking plot for serious adverse events

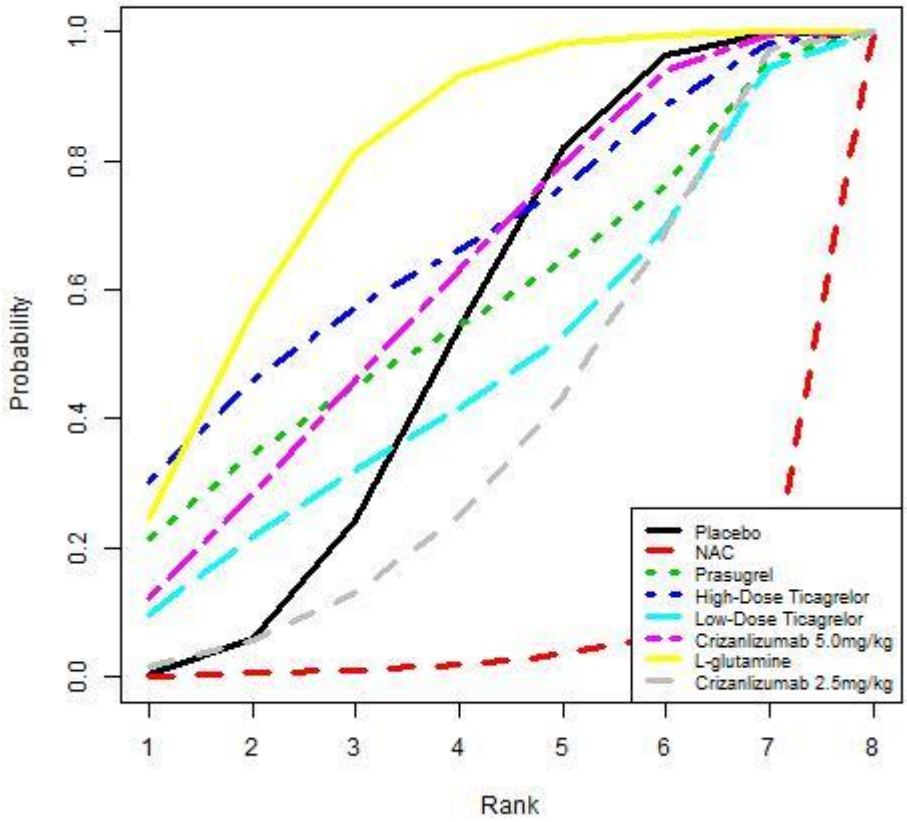
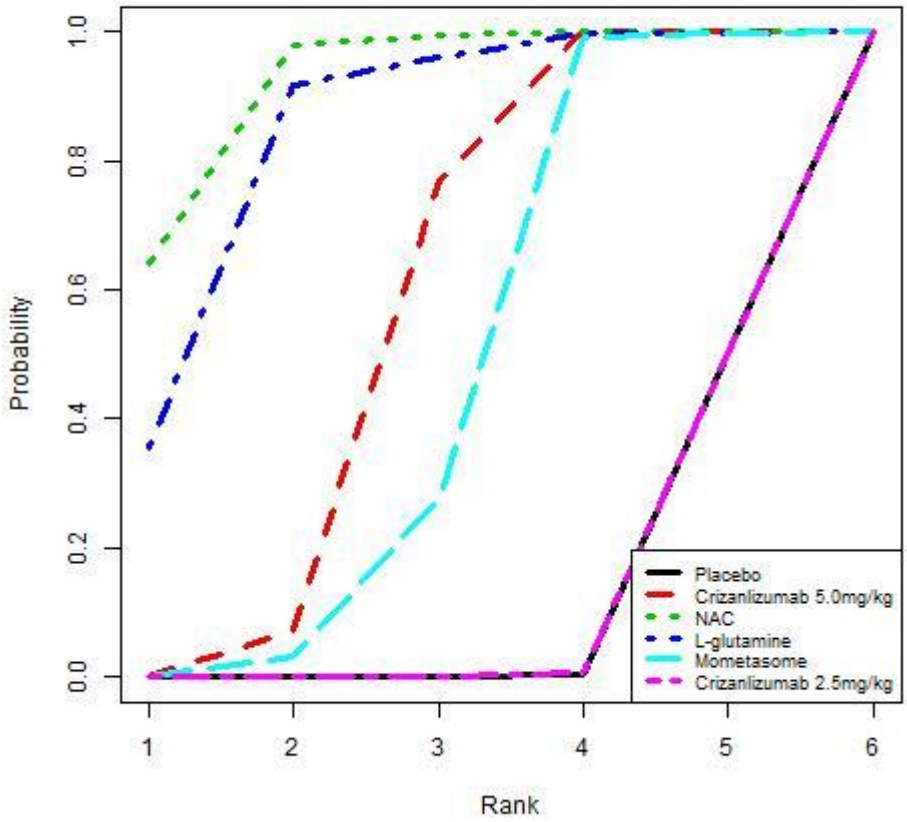


Figure 6 Cumulative ranking plot for all-cause hospitalization days



E.6 Sensitivity analysis using precise priors on treatment and baseline effects

A sensitivity analysis was conducted using a more precise prior on the baseline and treatment effects (i.e. $\mu_{..}$ and $d_{..}$, respectively). Instead of the base case priors of $Normal(0, 0.0001)$ we used $Normal(0, 0.1)$. The forest plot of results is in Figure 7 and the Bayesian probabilities of superiority (along with a comparison with base case results) are presented in Table 14. There is very limited impact on the results so our results are likely robust to prior assumptions.

Figure 7. Forest plot of all outcomes using more precise prior distributions

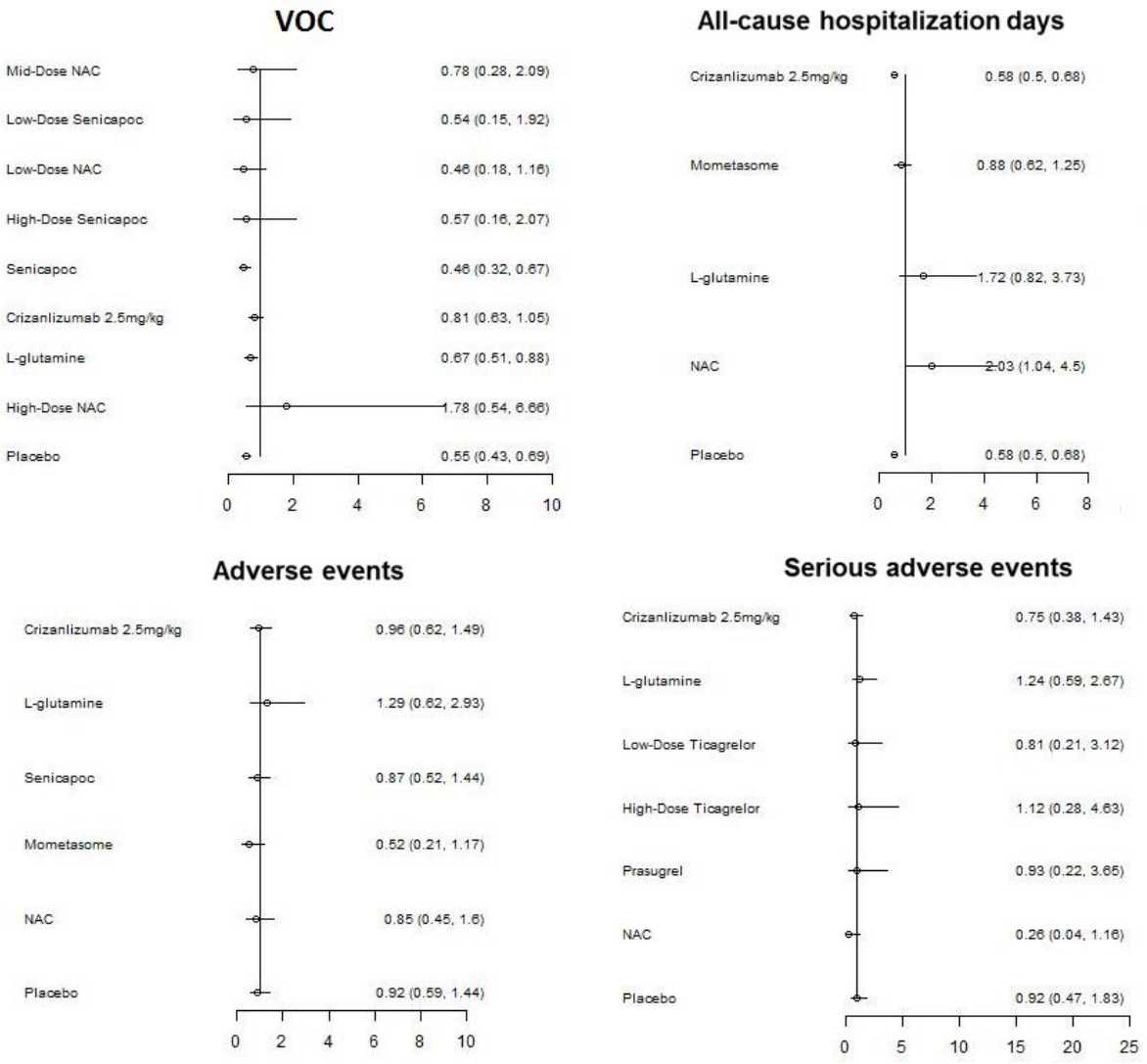


Table 14 Bayesian probabilities that crizanlizumab is superior on each outcome analyzed using both the precise prior sensitivity analysis and the vague priors of the base case*

	VOC	All-cause hospitalization	Adverse events	Serious adverse events	VOC	All-cause hospitalization	Adverse events	Serious adverse events
Placebo	>0.9999	>0.9999	0.6384	0.5895	>0.9999	>0.9999	0.6558	0.5857
L-glutamine	0.9982	0.0747	0.2563	0.2847	0.9982	0.0731	0.2480	0.2854
Crizanlizumab 2.5mg/kg	0.9425	>0.9999	0.5772	0.8136	0.9452	>0.9999	0.5743	0.8134
Mometasome	-	0.7548	0.9408	-	-	0.7496	0.9399	-
Low-Dose NAC	0.9486	0.0193	0.6978	0.9601	0.9396	0.0166	0.6996	0.9744
Mid-Dose NAC	0.6919	-	-	-	0.6619	-	-	-
High-Dose NAC	0.1720	-	-	-	0.1507	-	-	-
Prasugrel	-	-	-	0.5398	-	-	-	0.5242
Senicapoc	>0.9999	-	0.7038	-	>0.9999	-	0.7176	-

High-Dose Senicapoc	0.8077	-	-	-	0.8010	-	-	-
Low-Dose Senicapoc	0.8328	-	-	-	0.8334	-	-	-
High-dose Ticagrelor	-	-	-	0.4380	-	-	-	0.4247
Low-dose Ticagrelor	-	-	-	0.6267	-	-	-	0.6181

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Appendix F: Characteristics and outcomes of studies included in the network meta-analysis*

Author/Year/Country Ref/Enrolment/NCT registry	Design Total N of PT (N of female); N of arm Follow-ups	Interventions	Crisis	All-cause Hospitalization days	Adverse events (AE)	Serious adverse events (SAE)
Glassberg 2017[47] USA	RCT, triple-blind Adults and adolescents	1. Mometasone furoate 220mcg OD inhale (n=35) In addition to standard SCD care		Rate hospitalization days: 2.67	Total number of AE: 32	
Feb 2014 to Oct 2016 NCT02061202	Single centre 54 (23); 2 16 weeks	2. Placebo (n=17) In addition to standard SCD care		Rate of hospitalization days: 4.09	Total number of AE: 9	
Ataga 2017[15] Brazil, Jamaica, USA	RCT, double-blind Adults and adolescents	1. Crizanlizumab 5 mg/kg IV (n=67) Two doses 2 weeks apart (loading dose) and then every 4 weeks. A total of 14 doses for 50 weeks	Median annual rate of crisis 1.63	Annual rate of days hospitalized 4.00	Number of patients with ≥1 AE: 57	Number of patients with ≥1 SAE: 17
Aug 2013 to Jan 2015 NCT01895361	Multicentre 198 (109); 3 52 weeks	2. Crizanlizumab 2.5 mg/kg IV (n=66) Two doses 2 weeks apart (loading dose) and then every 4 weeks. A total of 14 doses for 50 weeks	Median annual rate of crisis 2.01	Annual rate of days hospitalized 6.87	Number of patients with ≥1 AE: 56	Number of patients with ≥1 SAE: 21
		3. Placebo (n=65)	Median annual rate of crisis 2.98	Annual rate of days hospitalized 6.87	Number of patients with ≥1 AE: 55	Number of patients with ≥1 SAE: 17
Sins 2017[48] Netherlands, Belgium, UK	RCT, double-blind Adults	1. NAC 600mg BID oral (n=27)		Total hospital admission days: 9	Total number of AE: 39	Total number of SAE: 8
Apr 2013 to Nov 2015 NCT01849016	Multicentre 96 (40); 2 6 months	2. Placebo (n=40)		Total hospital admission days: 53	Total number of AE: 36	Total number of SAE: 2
Niihara 2018[12] US	RCT, double-blind (phase 3)	1. L-glutamine 0.3 g/kg BID oral (n=152) Maximum dose: 30mg	Mean number pain crises: 3.2	Total hospitalization days: 12.1	Percentage with ≥1 AE: 0.98	Percentage with ≥1 SAE: 0.782

Jun 2010 to Dec 2013 NCT01179217	Adults and children Multicentre 230 (124); 2 48 weeks	2. placebo (n=78)	Mean number pain crises: 3.9	Total hospitalization days: 18.1	Percentage with ≥1 AE: 1.00	Percentage with ≥1 SAE: 0.871
Ataga 2011[56] United States, Jamaica, Brazil, France, Trinidad and the United Kingdom.	RCT, double-blind (phase 3, terminated early) Adults and adolescents	1. Senicapoc 20mg/d BID (loading) and then 10mg/dOD oral (n=145)		Total number of crises: 89		Total number of AE: 127
	Multicentre 297 (160); 2 52 weeks	2. Placebo (n=144)		Total number of crises: 106		Total number of AE: 119
Feb 2005 to Apr 2007 NCT00102791						
Ataga 2008[52] US	RCT, double-blind (phase 2) Adults	1. Senicapoc (high-dose): 150 mg (loading dose); 10 mg/d (maintenance) oral OD (n=31)		Total number of crises: 5		
		2. Senicapoc (low-dose): 100 mg (loading dose); 6 mg/d(maintenance) oral OD (n=29)		Total number of crises: 5		
Feb 2002 and Jan 2004 NCT00040677	Multicentre 90 (45); 3 12 weeks	3. Placebo (n=30)		Total number of crises: 5		
Pace 2003[51] USA	RCT, double-blind Adults and Adolescents	1. NAC (high-dose) 2400mg/day (n=6) All doses were divided by 3 to be taken		Total number of crises: 5		
	Single centre 21 (10); 4 7 months	2. NAC (mid-dose) 1200mg/day (n=5) All doses were divided by 3 to be taken		Total number of crises: 5		
		3. NAC (low-dose) 600 mg/day (n=5) All doses were divided by 3 to be taken		Total number of crises: 4		
		4. Placebo (n=5)		Total number of crises: 3		
NCT02482298[55] USA, Egypt, France, Italy, Kenya, Lebanon, UK, Turkey	RCT, double-blind Adults	1. Ticagrelor 45mg BID oral (n=30)				Total number of SAE: 5
		2. Ticagrelor 10MG BID oral (n=27)				Total number of SAE: 6

	Multicentre	3. Placebo (n =30)	Total number of SAE: 6
Jul 2015 to Nov 2016	87 (47); 3		
	12 weeks		
Wun 2013[46]	RCT, double-blind (phase 2)	1. Prasugrel 5 mg/day oral (n=41)	Total number of SAE: 8
United States and Canada	Adults		
		2. placebo (n=19)	Total number of SAE: 4
	Multicentre		
26 Aug 2010 to 13 Jun 2011 NCT01167023	62 (30); 2		

*ACS: Acute chest syndrome; ALT: Alanine transaminase; CA: Conference abstract; Cr: creatinine; CSRPM: Center for Scientific Research into Plant Medicine; CT: Clinical trial registry; DDCF: Doris Duke Charitable Foundation; ED: emergency department; HbSS: Homozygous sickle haemoglobin (HbS); HbSC: sickle haemoglobin S and haemoglobin C; HbSβ: sickle beta thalassemia, type '0' or '+'; HU: hydroxyurea; JA: Journal article; MTX: Methotrexate; NAD: N-acetylcysteine ;NCATS: National Center for Advancing Translational Sciences; NCRR: National Center for Research Resources; NHLBI: National Heart Lung and Blood Institute; NSAID: Nonsteroidal anti-inflammatory drugs; NR: Not reported; OOPD: FDA's Office of Orphan Products Development; PT: patient; SCD: sickle cell disease; TCD: transcranial Doppler; ZonMw: The Netherlands Organisation for Health Research and Development

** Entry is blank if no data provided for crisis, all-cause hospitalization days, adverse events, or serious adverse events. See appendix for relevant link function to connect different outcome summaries to network meta-analysis.