NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value

Research Protocol

November 5, 2019

Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Table of Contents

Background, Objectives, and Research Questions

Background

Sickle cell disease (SCD) is a broad term referring to a group of inherited disorders carried by the beta (β) allele of the hemoglobin gene (Hb). It is characterized by abnormal hemoglobin polymerization during deoxygenation resulting in sickle-shaped erythrocytes (red blood cells [RBCs]). SCD includes the genotypes HbSS, as well as the compound heterozygous genotypes HbSβ^0 thalassemia, HbSC, HbSD, HbSβ^+ thalassemia.[1] The genotypes HbSS and HbSβ^0 thalassemia have similar clinical characteristics and together are frequently referred to as sickle cell anemia. Conversely, the heterozygous state with one normal gene and one Hb S gene (HbAS) is the carrier state and is referred to as "sickle cell trait". Sickle cell trait usually does not have clinical manifestations and confers protection against plasmodium falciparum malaria.[2]

Clinical manifestations of SCD derive from at least three different pathophysiologic mechanisms: the loss of deformability of the RBC leading to vascular obstruction and ischemia; a shortened lifespan of the RBC leading to both intravascular and extravascular hemolysis; a sticky RBC surface increasing adherence to the vascular endothelium which can result in vascular obstruction and can contribute to vascular proliferative lesions.[3]

Rates of SCD and sickle cell trait vary considerably by geography with the highest rates found in populations arising from areas where, historically, resistance to plasmodium falciparum malaria conferred a survival advantage.[2] These include equatorial Africa, Brazil, Saudi Arabia and central India. The incidence of SCD is estimated at 300,000 to 400,000 live births globally per year. In the United States (US), the current best prevalence estimate is approximately 100,000 individuals with SCD, although comprehensive surveillance and reporting is lacking and the true number of cases in the US is unknown.[4]

A marked decrease in mortality in infancy occurred in the US from 1979-2006, presumably due to the implementation of universal newborn screening, penicillin prophylaxis, and the use of conjugated pneumococcal vaccine.[4] During that same time, peak mortality shifted from the middle third decade of life to the late fourth decade of life with the mean age of death being 39 years.[5] Despite improved survival, life expectancy continues to be 20-30 years less than the US general population.[4]

Recurrent acute pain crises, or vaso-occlusive crises (VOCs), are considered among the most common manifestation of SCD. An understanding of the pathophysiology of VOCs continues to evolve with recent models focused on the complex cascade of inflammation, adherence of leukocytes, and blood flow obstruction. The management of acute pain crises is extremely important in patients with SCD yet is often misunderstood or inadequately addressed across all healthcare settings.[1]

In addition to VOCs, patients over time experience significant acute and chronic morbidity. Acute complications include serious infections such as meningitis, osteomyelitis, and sepsis, and non-infectious complications such as stroke, renal necrosis, and priapism.[6] Acute chest syndrome is a potentially life-threatening complication that can involve chest pain and shortness of breath among other symptoms; some episodes of acute chest syndrome are triggered by infection.[7] Chronic complications can emerge across multiple organs and include neurocognitive impairment, chronic kidney injury, delayed puberty, avascular necrosis, retinopathy, pulmonary hypertension, skin ulcers, and chronic pain.[6] Individuals with SCD face ongoing and evolving lifelong difficulties as a result of their disease. As their bodies grow, develop, and age, new problems can emerge while intermittent and persistent vaso-occlusion/ischemia produce an accumulation of injuries over time.[2] Resultant health care costs are high, with the total health system economic burden of SCD estimated at $2.98 billion per year in the US with 57% due to inpatient costs, 38% due to outpatient costs, and 5% due to out-of-pocket costs.[8]

At this time, only two interventions are proven to be disease modifying (i.e., therapies shown to affect the long-term course of disease): chronic transfusion with packed RBCs and hydroxyurea.[1] Chronic transfusion is generally used for primary or secondary stroke prevention; hydroxyurea is used to reduce the number of VOCs in those with frequent or severe crises, and in those with a history of acute chest syndrome or severe anemia.[1] Treatment with L-glutamine can also decrease the frequency of VOCs.[9] Acute VOCs may be managed with pain medications including opioids, and may require additional inpatient or outpatient treatments including hydration, transfusion, supplemental oxygen, and a variety of other treatments.[1]

There is clearly a large unmet need for additional treatments for SCD. Crizanlizumab (Novartis AG), is a humanized monoclonal antibody that binds to P-selectin. It is currently being evaluated by the US Food and Drug Administration (FDA) as prophylactic treatment for VOCs, with an approval decision expected by January 2020.[10] It is administered intravenously every four weeks. Voxelotor (Global Blood Therapeutics, Inc.) is an HbS polymerization inhibitor that reversibly binds to hemoglobin to stabilize the oxygenated hemoglobin state, thus shifting the oxyhemoglobin dissocation curve.[11] Voxelotor is currently being evaluated by the FDA as a treatment to increase Hb levels. It is administered orally and is dosed daily. A rolling New Drug Application requesting accelerated approval for voxelotor has been accepted by the FDA with an anticipated decision by February 26, 2020.

Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and cost effectiveness of crizanlizumab, voxelotor and L-glutamine, for the treatment of sickle cell disease. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the

assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). See the model analysis plan (expected publication: November 21, 2019) for details on the proposed methodology and model structure that will be used for the economic evaluation.

Research Questions

To inform our review of the clinical evidence, we have developed the following research questions with input from clinical experts, patients and patient groups:

- In patients with sickle cell disease, what is the comparative efficacy/effectiveness and safety of crizanlizumab in addition to usual care versus usual care alone in terms of acute complications (e.g., incidence of vaso-occlusive crises), chronic complications (e.g. chronic pain, organ damage), mortality, and quality of life?

- In patients with sickle cell disease, what is the comparative efficacy/effectiveness and safety of voxelotor in addition to usual care versus usual care alone in terms of acute complications (e.g., incidence of vaso-occlusive crises), chronic complications (e.g. chronic pain, organ damage), mortality, and quality of life?

- In patients with sickle cell disease, what is the comparative efficacy/effectiveness and safety of prescription-grade formulations of L-glutamine in addition to usual care versus usual care alone in terms of acute complications (e.g., incidence of vaso-occlusive crises), chronic complications (e.g. chronic pain, organ damage), mortality, and quality of life?

PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Population

The population of focus for this review is children and adults two years of age and older diagnosed with SCD.

We will look for information on subgroups that may experience smaller or larger net benefits than the population as a whole. These include but are not limited to subgroups defined by:

- Age
- Hydroxyurea use
- Use of chronic transfusions
- Sickle cell genotype
- Frequency of VOCs

Interventions

- Crizanlizumab (investigational; Novartis AG) in addition to usual care (e.g., hydroxyurea, acute transfusions)
- Voxelotor (investigational; Global Blood Therapeutics, Inc.) in addition to usual care (e.g., hydroxyurea, acute transfusions)
- Prescription-grade formulations of L-Glutamine (e.g., Endari™; Emmaus Medical, Inc.) in addition to usual care (e.g., hydroxyurea, acute transfusions)

Comparators

We intend to compare each intervention to usual care alone. We do not expect to compare the interventions to each other.

Outcomes

This review will examine key measures of benefit and safety associated with sickle cell disease, including, but not limited to, the outcomes listed below. Additional outcomes of interest, including intermediate and surrogate endpoints, are listed in Appendix C and will be captured when evidence on such outcomes is identified.

Acute Outcomes, including:

- Acute pain crisis
- Hospitalization
- Cardiovascular events (e.g., stroke)
- Acute chest syndrome
- Splenic sequestration
- Priapism
- Need for blood transfusion

Chronic Outcomes, including:

- Mortality
- Chronic pain
- Quality of life
- Fatigue
- Organ damage
- Opioid tolerance/dependence
- Neurocognitive dysfunction
- Mental health effects (e.g., depression, anxiety)

Safety

- Serious adverse events
- Adverse events leading to discontinuation
- Treatment-emergent adverse events

Timing

Evidence on intervention efficacy/effectiveness and safety will be collected from studies of any duration.

Setting

Evidence from all relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

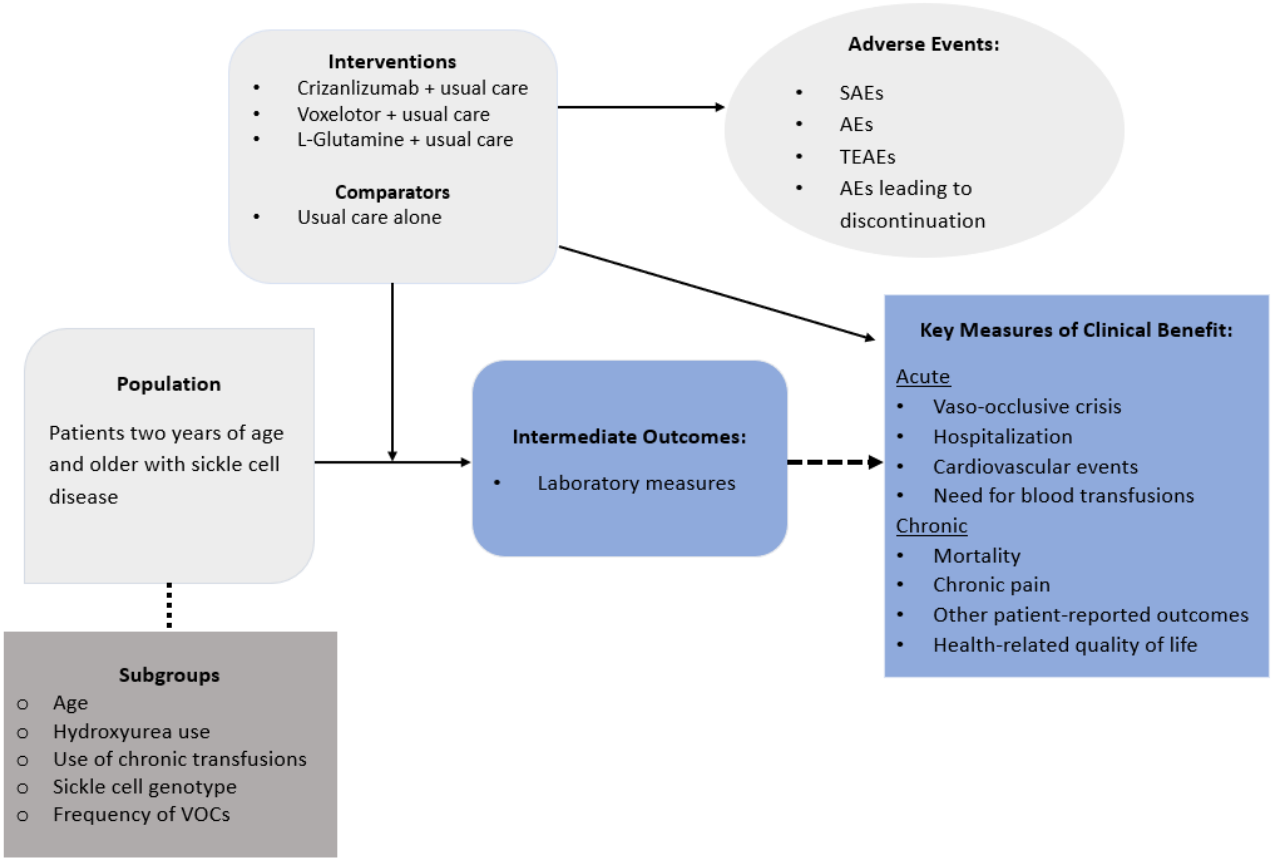
Study Design

Randomized controlled trials, non-randomized clinical trials, and observational studies with any sample size will be included.

Analytic Framework

The proposed analytic framework for this project is depicted below:

Figure 1. Analytic Framework: Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the dark blue boxes; those within the rounded box are intermediate outcomes (e.g., laboratory measures), and those within the dark blue squared-off box are key measures of benefit (e.g., vaso-occlusive crisis). A solid line also links the interventions to key measures of clinical benefit. The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. An arrow from interventions lead to the AEs of treatment which are listed within the light gray ellipse.

Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on crizanlizumab, voxelotor, and prescription-grade L-glutamine for sickle cell disease will follow established best methods.[12,13] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE and EMBASE for relevant studies. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 below.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 1: Search Strategy of Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

1	exp anemia, sickle cell/
2	((sickle adj3 (disease or an?emia)) or 'sickle cell' or meniscocyt* or drepanocyte* or sickl* or (SC adj3 (disease or an?emia))).ti,ab.
3	hemoglobin, sickle/ or (h?emoglobin adj5 sickl*).ti,ab.
4	((h?emoglobin or hb or hb- or hgb) adj3 (SS or S-S or SC or S-C or SB* or b0 or S-beta or thalassemia or beta-zero or beta plus)).ti,ab.
5	(glutamine or l-glutamine).ti,ab
6	(endari or xyndari).ti,ab
7	(crizanlizumab or seg101 or selg1).ti,ab
8	(voxelotor or gbt440).ti,ab
9	Or/6-8
10	Or/1-4
11	10 and 5
12	9 or 11
13	(addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
14	12 not 13
15	Animals.sh
16	Humans.sh
17	15 or (15 and 16)
18	14 not 17

19	Limit 18 to English Language
20	Remove duplicates from 19

Table 2. Search strategy of EMBASE

#1	'sickle cell anemia'/exp
#2	((sickle NEAR/3 (disease OR an*emia)):ti,ab) OR 'sickle cell':ti,ab OR meniscocyt*:ti,ab OR drepanocyte*:ti,ab OR sickl*:ti,ab OR ((sc NEAR/3 (disease OR an*emia)):ti,ab)
#3	'hemoglobin s'/exp OR ((h?emoglobin NEAR/5 sickl*):ti,ab)
#4	(h?emoglobin OR hb OR 'hb-' OR hgb) NEAR/3 (ss OR 's-s' OR sc OR 's-c' OR 'sb' OR b0 OR 's-beta' OR thalassemia OR 'beta-zero' OR 'beta plus')
#5	'glutamine'/mj OR glutamine:ti,ab OR 'l-glutamine':ti,ab
#6	endari:ti,ab OR xyndari:ti,ab
#7	'crizanlizumab' OR seg101:ti,ab OR selg1:ti,ab
#8	'voxelotor' OR gbt440:ti,ab
#9	#1 OR #2 OR #3 OR #4
#10	#6 OR #7 OR #8
#11	#5 AND #9
#12	#10 OR #11
#13	‘animal’/exp or ‘nonhuman’/exp or ‘animal experiment’/exp NOT ‘human’/exp
#14	#12 NOT #13
#15	#14 NOT (‘case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey’/it)
#16	#15 AND [english]/lim
#17	#16 AND [medline]/lim
#18	#16 NOT #17

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all identified publications using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during full-text review.

Data Extraction Strategy

Data will be extracted into evidence tables. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used, outcome assessments, results, and quality assessment for each study.

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.
2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[15]

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include

sickle cell, crizanlizumab, voxelotor and L-glutamine. We will select studies which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: (1) a summary of the evidence base and (2) a synthesis of outcome results.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. Evidence table shells are presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

The results of the studies will be synthesized for each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base.

Analyses are expected to be descriptive in nature only, as we do not intend to compare crizanlizumab, voxelotor, and L-glutamine to each other. Nevertheless, if studies are sufficiently similar in terms of patient populations, outcomes assessed, interventions, and comparators, we may conduct random effects pairwise meta-analyses where feasible. A pairwise meta-analysis quantitatively synthesizes results from multiple studies that assessed the same intervention and comparator.[16] The specific approach for any meta-analysis will depend on the available evidence and will be detailed in the report.

References

1. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of Sickle Cell Disease: Summary of the 2014 Evidence-Based Report by Expert Panel MembersManagement of Sickle Cell DiseaseManagement of Sickle Cell Disease. *JAMA.* 2014;312(10):1033-1048.
2. Serjeant GR. The natural history of sickle cell disease. *Cold Spring Harb Perspect Med.* 2013;3(10):a011783-a011783.
3. Telen MJ. Beyond hydroxyurea: new and old drugs in the pipeline for sickle cell disease. *Blood.* 2016;127(7):810-819.
4. Hassell KL. Population Estimates of Sickle Cell Disease in the U.S. *American Journal of Preventive Medicine.* 2010;38(4, Supplement):S512-S521.
5. CDC NCfHS. Compressed mortality file 1999-2006. 2009; Wonder.cdc.gov/cmf-icd10html.
6. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. *Nature Reviews Disease Primers.* 2018;4:18010.
7. Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *The New England journal of medicine.* 2000;342(25):1855-1865.
8. Huo J, Xiao H, Garg M, Shah C, Wilkie DJ, Mainous Iii A. The Economic Burden of Sickle Cell Disease in the United States. *Value in Health.* 2018;21:S108.
9. Niihara Y, Miller ST, Kanter J, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. *New England Journal of Medicine.* 2018;379(3):226-235.
10. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. *The New England journal of medicine.* 2017;376(5):429-439.
11. Vichinsky E, Hoppe CC, Ataga KI, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. *The New England journal of medicine.* 2019;381(6):509-519.
12. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
13. Higgins JP, Green S. *Cochrane Collaboration Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011].* The Cochrane Collaboration and John Wiley & Sons Ltd; 2008.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8(5):336-341.
15. Agency for Healthcare Research and Quality. *U.S. Preventive Services Task Force Procedure Manual.* 2008.
16. Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res.* 2001;10(4):277-303.
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339:b2700.

Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[14] Additional explanation of each item can be found in Liberati et al. 2009.[17]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
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 criteria for eligibility, giving rationale.	
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.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
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).	
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.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in 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.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
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).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
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.	
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.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
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., health care providers, users, and policy makers).	
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).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
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.	

doi:10.1371/journal.pmed.1000097.t001

Appendix B. Data Extraction Summary Table Shells

Table B1. Study Quality

Study	Comparable Groups	Adequate Randomization	Patient Blinding	Physician Blinding	Outcome Adjudication Blinding	Non-Differential Follow-Up	ITT Analysis	Appropriate Handling of Missing Data	Overall Quality

ITT: intent-to-treat

Table B2. Study Design

Study	Crizanlizumab	Voxelotor	L-Glutamine
Design			
Inclusion Criteria			
Exclusion Criteria			
N			
Interventions			
Follow-up			
Outcomes			

Table B3. Baseline Characteristics

Study	Interventions (n)	Age, Median (Range)	Female, n (%)	Black, n (%)	Concomitant Hydroxyurea, n (%)	SCD-related Pain Crises in Previous Year, Mean (SD)	HbSS Genotype, n (%)

Table B4. Efficacy Outcomes I

Study	Interventions (n)	Deaths		Acute Pain Crisis		Acute Chest Syndrome		Splenic Sequestration	
		N (%)	HR (95% CI) P-Value	Median Rate/year (IQR)	% Difference P-Value	Median Rate/year (IQR)	% Difference P-Value	Median Rate/year (IQR)	% Difference P-Value

Table B5. Efficacy Outcomes II

Study	Interventions (n)	Hepatic Sequestration		Priapism		Hospitalization		Stroke	
		Median Rate/year (IQR)	% Difference P-Value	Median Rate/year (IQR)	% Difference P-Value	Median Rate/year (IQR)	% Difference P-Value	N (%)	HR (95% CI) P-Value

Table B6. Efficacy Outcomes III

Study	Interventions (n)	Brief Pain Inventory		Quality of life		Mental Health Effects		Cognitive Effects	
		Mean Score Change	Difference p-value	Mean Score change	Difference P-Value				

Table B7. Change from Baseline in Laboratory Parameters

Study	Interventions (n)	Hemoglobin (g/dL)	Indirect Bilirubin (%)	Percentage of Reticulocytes (%)	Absolute Reticulocyte Count (%)	Lactate Dehydrogenase (%)	Haptoglobin (g/L)

Table B8. Safety

Study	Interventions (n)	Serious Adverse Events, n (%)	Treatment -Emergent Adverse Events, n (%)	Adverse Events Leading to Discontinuation, n (%)	Deaths, n (%)

Appendix C. Outcomes of Interest

Clinical Outcomes	
Acute	**Chronic**
Acute Pain Episode	Chronic Pain
Stroke/Cerebrovascular Event	Fatigue
Retinal Infarct	Anxiety
Septicemia	Depression
Acute Chest Syndrome	Neurocognitive Dysfunction
Pneumonia	Retinopathy
Splenic Sequestration	Opioid Dependence/Tolerance
Splenic Infarct	Cardiomyopathy
Sickle Cell Nephropathy	Diastolic Heart Failure
Acute Kidney Injury	Pulmonary Hypertension
Pregnancy Complications	Anemia
Priapism	Erectile Dysfunction
Gallstones	Chronic Kidney Disease
Osteomyelitis	Skin Ulcer
Bone Marrow Infarction	Avascular Necrosis
	Hearing Loss

Biomarkers/Surrogate Endpoints
Hemoglobin (Hb) Level
Fetal Hb Level
Hematocrit
Oxygen percent saturation

Mortality
Cause-specific mortality
All-cause mortality
Survival

Functional Outcomes/Health Related Quality of Life
Cognitive Function
Physical Function
Health-related quality of life
Missed days at school/work
Ability to return to usual activities
Patient satisfaction with treatment

Health Resource Utilization
Emergency department visits
Acute/ urgent care visits
Hospitalization
ICU Admission
Length of hospital stay
Need for blood transfusion