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

Draft Evidence Report

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NEW ENGLAND CEPAC

COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

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About ICER

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit:
https://icer-review.org/material/sickle-cell-disease-stakeholder-list/

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Table of Contents

List of Acronyms Used in this Report

AE	Adverse event
ACS	Acute chest syndrome
AKI	Acute kidney injury
BPI	Brief Pain Inventory
CI	Confidence interval
CKD	Chronic kidney disease
CMS	Centers for Medicare and Medicaid Services
ED	Emergency department
FDA	Food and Drug Administration
GDP	Gross domestic product
HB	Hemoglobin
HR	Hazard ratio
IQR	Interquartile range
ITT	Intent-to-Treat
LS	least squares
LY	Life year
MCC	Major complications and comorbidities
MI	Myocardial Infarction
NICE	National Institute for Health and Care Excellence
No.	Number
NS	Not significant
NR	Not reported
PICOTS	Population, Interventions, Comparisons, Outcomes, Timing, Setting, and Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
QOL	Quality of life
RCT	Randomized controlled trial
SAE	Serious adverse event
SCD	Sickle cell disease
SF-36	36-Item Short Form Survey
TEAE	Treatment-emergent adverse event
US	United States
USPSTF	United States Preventive Services Task Force
VOC	Vaso-Occlusive Crisis
WAC	Wholesale acquisition cost

1. Introduction

1.1 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 (Hb) gene. 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, and HbSβ^+ thalassemia.[2] 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.[3]

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.[4]

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.[3] 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 exact number of cases in the US is unknown.[5]

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.[5] 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.[6] Despite improved survival, life expectancy continues to be 20-30 years less than the US general population.[5]

Recurrent acute pain crisis, or vaso-occlusive crisis (VOC), is the most prevalent manifestation of SCD. An understanding of the pathophysiology of acute pain crises 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 health care settings.[2]

In addition to acute pain crises, patients experience significant acute and chronic morbidity over time. Acute complications include serious infections such as meningitis, osteomyelitis, and sepsis, and non-infectious complications such as stroke, renal necrosis, and priapism.[7] Acute chest syndrome (ACS) is a potentially life-threatening complication that can involve chest pain and shortness of breath among other symptoms; some episodes of ACS are triggered by infection.[8] Chronic complications can emerge across multiple organs and include delayed puberty, avascular necrosis, skin ulcers, chronic pain, neurocognitive impairment, chronic kidney injury, pulmonary hypertension, cardiovascular disease, and can result in early mortality.[7] 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.[3] 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.[9]

Our understanding of the relationship of hemoglobin levels and ongoing hemolysis, to acute and chronic morbidity and survival continues to evolve. Low hemoglobin levels have been associated with fatigue, silent cerebral infarct, pulmonary hypertension, kidney disease, and mortality.[10-13]. More recently, the clinical manifestations and risk of mortality have been linked to the degree of intravascular hemolysis and the release of lysed erythrocyte byproducts.[14,15] In fact some of the heterogeneity in the phenotypic expression of SCD is now being attributed to subphenotypes with some patients expressing more hemolytic anemia related manifestations of the disease and others more vaso-occlusive morbidities. The interrelationship of anemia related morbidity and VOC related morbidity remains unclear. Nonetheless, future individualized care plans will undoubtedly incorporate this level of specificity as new information continues to emerge.

The impact of SCD on quality of life (QOL) is complex and affects both patients and their caregivers in many ways. In addition to the health-related burden of disease many other factors further diminish QOL. The lack of treatment options, discrimination, stigma around the need for chronic pain management, disruption of family and social activities, missed school and/or work all combine to make living with SCD extraordinarily difficult. Children worry about dying early from the disease. Pain and fatigue limit their ability to perform well in school and maintain relationships with friends. They feel the impact of chronic pain, daily fatigue, and emotional distress, and often recognize that they are not able to live a normal life like their friends. As children mature, they often carry the same concerns as in childhood with the addition of mobility issues, difficulty managing work and careers, difficulty caring for themselves and their families, and ongoing concerns about the progression of their disease. SCD is a lifelong, all-encompassing, biopsychosocial condition, that constitutes one of the most difficult of all chronic illnesses for patients and their families.

Treatment for SCD

Despite many dedicated caregivers and clinicians across the US, the picture of "baseline" or "usual" care for patients with SCD is highly variable and represents a failure of the US health care system. Deep dysfunction in care is driven by poor coordination within provider systems and by barriers to access that arise from a broad range of factors including systemic racism, uninformed clinicians, poverty, and insurance systems poorly designed to coordinate coverage for patients with multi-system chronic conditions. Upon that background of poor performance in service of patients with SCD, innovation in specific disease-modifying treatments has also been lacking for several decades. Until recently only three specific interventions were considered helpful for SCD: stem cell transplantation, chronic transfusion with packed RBCs, and hydroxyurea. While stem cell transplant engraftment rate is dependent upon the degree of myeloablation, it can result in the complete replacement of abnormal hemoglobin with completely normalized hemoglobin and resolve hemolysis. Unfortunately, the degree of myeloablation required and the availability of matched donors limit its use. Chronic transfusion is generally used for primary or secondary stroke prevention; hydroxyurea is used to reduce the number of acute pain crises in those with frequent or severe crises, and in those with a history of ACS or severe anemia.[2] Acute pain crisis 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.[2]

Within the past several years several new options have gained regulatory approval in the US Table 1.1). L-glutamine supplementation is used to decrease the frequency of acute pain crises.[16] It was approved by the US Food and Drug Administration (FDA) on July 7, 2017 to reduce the acute complications of SCD in adult and pediatric patients 5 years of age and older. Crizanlizumab (Novartis AG), is a humanized monoclonal antibody that binds to P-selectin.[17] It was approved by the FDA on November 15, 2019 to reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with SCD. It is administered intravenously in two loading doses two weeks apart and then every four weeks thereafter. 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 dissociation curve.[18] Voxelotor was approved by the FDA on November 25, 2019 for the treatment of SCD in adults and pediatric patients 12 years of age and older.

Table 1.1. Recently Approved Therapies for SCD

	Date of FDA Approval	FDA Indication	FDA Dosage	WAC	Cost per Year*
Crizanlizumab (Adakveo®)	11/15/2019	Indicated to reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with SCD	Administer 5 mg/kg (IV) over a period of 30 minutes on week 0, week 2, and every 4 weeks thereafter	$2,357.14 per 10ml package	$107,700
Voxelotor (Oxbryta™)	11/25/2019	Indicated for the treatment of SCD in adults and pediatric patients 12 years of age and older.	1,500 mg orally once daily with or without food	$10,417.00 per 90 packages 115.74 per one 500mg package)	$104,357
Pharmaceutical grade L-Glutamine (Endari®)	7/7/2017	Indicated to reduce the acute complications of SCD in adult and pediatric patients 5 years of age and older	5 – 15 grams orally, twice daily based on body weight	$18.50 per 5gm package	$26,082

IV: intravenous, SCD: sickle cell disease, WAC: wholesale acquisition cost
WAC per Redbook® accessed on December 17, 2019
*Based on a 26-27% discount off WAC

1.2 Scope of the Assessment

Two new therapies and one relatively new therapy have become available for patients with SCD. Questions on the impact of these therapies on both acute and chronic complications of SCD along with long term safety remain. Further, the alignment of costs with potential patient benefits for these new therapies is unclear. This assessment evaluates the clinical effectiveness and cost effectiveness of crizanlizumab, voxelotor, and pharmaceutical-grade L-glutamine for patients with SCD.

The scope for this assessment is described on the following pages using the Population, Intervention, Comparators, Outcomes, Timing, and Settings (PICOTS) framework. Evidence was abstracted from randomized controlled trials (RCTs) and nonrandomized studies as well as high quality systematic reviews; high-quality comparative cohort studies were considered, particularly for long-term outcomes and uncommon AEs. Our evidence review includes input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more

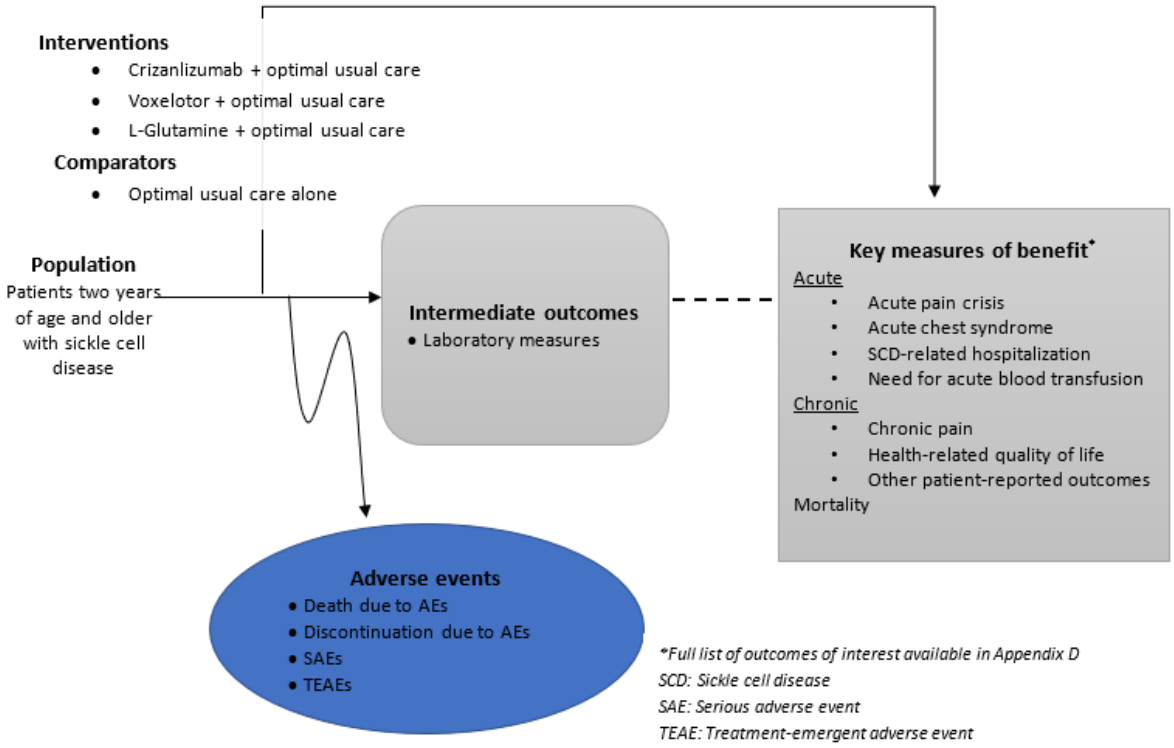
information, see https://icer-review.org/methodology/icers-methods/icer-value-assessmentframework/grey-literature-policy/).

All relevant evidence was summarized qualitatively. We sought head-to-head studies of the interventions and comparators of interest. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis were provided in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of therapies for SCD is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Crizanlizumab, L-Glutamine, and Voxelotor for SCD



AEs: adverse events, SAE: serious adverse event, SCD: sickle cell disease , TEAE: treatment emergent adverse event

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 shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., laboratory measures), and those within

the square boxes are key measures of benefit (e.g., acute pain crisis). 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. Curved arrows lead to the AEs of an action (typically treatment), which are listed within the blue ellipse.

Populations

The population of focus for this review is children and adults, two years of age and older, who have been diagnosed with SCD. Where data were available, we examined evidence for key subgroups suggested by clinical experts, including the following:

- Age
- Hydroxyurea use
- Use of chronic transfusions
- Sickle cell genotype
- Frequency of acute pain crises

Interventions

The interventions of interest for this review are listed below:

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

Comparators

Evidence will be sought to compare each intervention to optimal "usual" care as provided in clinical trials. For context, we will seek evidence on how the usual care provided in the trials differs from the real-world usual care experienced by many/most patients with SCD. We are not seeking to compare the clinical effectiveness of the three new interventions directly to each other given differences in patient populations and outcome measures, but we will create a common population for economic modeling in order to provide all stakeholders with the ability to compare long-term cost-effectiveness.

Outcomes

This review examines key measures of benefit and safety associated with SCD, including, but not limited to, the outcomes listed below. Additional outcomes of interest, including intermediate and

surrogate endpoints, are listed in Appendix D and were captured when evidence on such outcomes was identified.

Acute Outcomes

- Acute pain crisis
- Acute chest syndrome
- Acute myocardial infarction (MI)
- Stroke
- Acute kidney injury/Renal infarction
- Iron overload
- Splenic sequestration
- Priapism
- Change in hemoglobin
- Need for blood transfusion
- Quality of Life
- Hospitalization
- Mortality
- Change in hemolysis markers

Chronic Outcomes

- Pulmonary hypertension
- Heart failure
- Opioid tolerance/dependence
- Nephropathy/CKD
- Chronic chelation therapy
- Chronic pain
- Fatigue
- Other organ damage
- Neurocognitive dysfunction
- Mental health effects (e.g., depression, anxiety)
- Mortality

Safety

- Serious adverse events (SAE)
- AEs leading to discontinuation
- Treatment-emergent adverse events (TEAE)

Timing

Evidence on intervention effectiveness and evidence on harms was derived from studies of any duration.

Settings

All relevant settings were considered, with a focus on outpatient settings in the US.

1.3 Definitions

Acute Chest Syndrome (ACS)[19]: defined as a new radiodensity on chest radiography accompanied by fever and/or respiratory symptoms. ACS in adults with SCD requires prompt management to prevent clinical deterioration.

Acute Hepatic Sequestration[20]: patients with hepatic sequestration usually present with right upper quadrant pain, rapidly increasing hepatomegaly, and a falling hematocrit. Treatment of hepatic sequestration crisis involves prompt, aggressive restoration of blood volume. Typically, simple transfusion therapy is sufficient because the goal is to increase the hemoglobin to a level where the patient no longer has evidence of symptomatic anemia.

Acute Kidney Injury/Renal Infarction[21]: a condition resulting from a sudden disruption of blood flow to the renal artery. This may cause irreversible damage to kidney tissues.

Chronic Kidney Disease (Nephropathy): defined in trials as either having a glomerular filtration rate (GFR) of less than 60ml/min/1.73 $m^2$for greater than or equal to 3 months with or without kidney damage or having evidence of kidney damage for greater than or equal to 3 months, with or without decreased GFR, manifested by either pathologic abnormalities or markers of kidney damage independent of cause.

Chronic Sickle Cell Pain: pain that does not resolve and lasts for more than 3 months.

HbSβ^0 thalassemia[22]: occurs in patients who inherit one sickle cell gene and one beta thalassemia gene that results in no production of HbA**.**

HbSβ^+ thalassemia[22]: occurs in patients who inherit one sickle cell gene and one beta thalassemia gene resulting in reduced production of HbA.

HbSC: sickle cell hemoglobin C disease

HbSD, HbSE and HbSO[22]: one inherited sickle cell gene ("S") and one gene from an abnormal type of hemoglobin ("D","E" or "O").

HbSS: homozygous sickle cell disease.

Opioid Tolerance[23]: occurs when a person using opioids begins to experience a reduced response to medication, requiring more opioids to experience the same effect.

Opioid Dependence[23]: occurs when the body adjusts its normal functioning around regular opioid use. Unpleasant physical symptoms occur when medication is stopped.

Pulmonary Arterial Hypertension (PAH)[24]: an elevation of pulmonary arterial systolic pressure (PASP) (greater than 20 mmHg at rest or greater than 30 mmHg with exercise) determined by right heart catheterization.

Vaso-occlusive Crisis (VOC): pain as a result of decreased blood flow in the microcapillaries (can include blood vessel blockage) resulting in tissue ischemia, occurring most commonly in bone or bone marrow. VOC's are also known as vaso-occlusive episodes or acute pain crises.

1.4 Potential Cost-Saving Measures in SCD

ICER now includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by therapies for SCD (e.g., reduction in acute pain crises), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of SCD beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with SCD that could be reduced, eliminated, or made more efficient. To date, no suggestions have been received.

2. Patient Perspectives

An All-Encompassing Condition

"SCD is long overdue for a treatment and cure. It is buried in years of racial discrimination and to this day health care professionals treat based on assumptions not science. We need new drugs and treatments. [It's] about time we matter."

Patients, family members, clinicians, and other members of the sickle cell community conveyed that it is hard to imagine a condition that ravages people's lives more than SCD. It is a danger to minimize the impact of the condition by reducing it to pain crises, or even to the better known acute and chronic organ effects. Pain crises are, of course, horrible to experience, and their accumulated impact over many years has effects on mental health as well as the potential risks associated with opioid treatment. In addition, the range of acute adverse effects of the condition includes almost every organ system, with strokes, ACS, and other life-threatening events a constant threat. These acute effects contribute to long-term risks for additional major organ dysfunction such as congestive heart failure and liver failure.

But while these acute and long-term clinical harms are legion, patients and others emphasize that there is truly an all-encompassing biopsychosocial impact of SCD that is hard to capture, even by adding up one by one the multitude of organ system effects. There is fatigue, there is anxiety and depression, there is a hopelessness that has haunted patients with SCD. The condition presents challenges at home, school, work, and social relationships. People with SCD often end up on formal disability programs, which unfortunately carries its own stigma. The cumulative effect of all these effects can be staggering.

"SCD is extremely unpredictable, even for the most aware patient. There is such a stigma that I feel from having this disease, wanting to do so much and contributing to society and yet I am limited from achieving many of my hopes and dreams."

This is not to say that people with SCD are unable to function at a high level in society, but that the challenges and the barriers are extraordinary. One of the most important perspectives we learned from the SCD patient community and clinicians was that SCD remains a misunderstood, marginalized, condition. To fully appreciate the potential benefits of new treatments, a broad

appreciation for the impact of SCD on the lives of patients and their families must be achieved and must be kept front and center when making judgments about the value of these treatments.

Stigma and Limitations on Daily Life

Patients with SCD may appear healthy. An outward appearance of wellbeing can present additional barriers to appropriate care and contribute to social stigmas surrounding the disease. A general lack of awareness about the disease among nurses, hospitalists, and society at large means that healthy-looking patients suffering from an acute pain crisis, ACS, or other SCD-related complication may not be taken seriously. Patients presenting at the ER may be made to wait longer before receiving attention. One particularly jarring anecdote that was recorded in the FDA's *Voice of the Patient* report described a child who was sent back to class by the school nurse after suffering a silent infarct because he was "deemed unruly."[25] We also heard patient testimony of young men being called perverts because they were experiencing priapism.

> *"Day to day is hard. [We] are in pain a lot and our energy levels are low. We just want to be treated like the next. We are not lazy, we want fairness."*

The appearance of health, coupled with a lack of SCD awareness in patients' broader communities, can lead to ignorant judgments of character. Patients who are unable to participate in their daily commitments at work or school due to unsurmountable fatigue, pain, or other complications, may be accused of laziness or be subject to bullying. Both children and their caregivers felt SCD challenged their ability to perform well in school and work. Chronic daily pain, fatigue, and the sudden onset of acute pain crises increase absenteeism, make it difficult to concentrate, disrupt school and social interactions and create a lot of stress and anxiety. Patients reported difficulty in remembering tasks, retaining what they learn in school, and difficulty staying engaged and focused on school activities. Some children reported frustration and social isolation from limitations on their ability to participate in physical activities, travel on long flights, play outside in cold weather, or swim in unheated water. Although SCD is an inherited condition, a lack of societal awareness about the disease leads some patients to hide their diagnoses so that their peers will not misperceive them as contagious.

> *"My son feels very isolated by sickle cell, and I know he thinks he prevents our family from doing many things because so much of the year we have to stay indoors. He loves to visit places where the temperature is nice and he can easily be outside."*

Family members described the tremendous responsibility of caregiving, including the need to leave the work force to provide care for their loved one while facing the impact of lost wages and significant out-of-pocket expenses. Adult patients reported difficulty in maintaining employment

because of frequent, unexpected, or prolonged absences due to acute SCD-related events. Some patients and family members described making decisions to avoid marriage to maintain health insurance or forego having children to avoid passing on the gene to the next generation. A number of patients reported serious problems with mental health issues such as depression, anxiety, and suicidal thoughts.

Racial Bias

> *"To improve health care access, the sickle cell community is faced with the awesome task of trying to rewrite the dominant narratives about their patients whose genetic disease marks them in the United States as quintessentially black. This narrative presumes that sickle cell patients are socially dysfunctional, dependent on narcotics, and poorly educated or, worse, uneducable. Knowing only a patient's race or ethnicity, even a well-meaning doctor may make presumptions that influence how he or she communicates with and medically treats a patient."*[1] *-Rouse, 2009*

We heard consistently, from patients, family members, clinicians, and other members of the sickle cell community, that the experience of living with SCD and all aspects of its treatment are mired in racism. Although SCD affects individuals of different races and ethnicities, it has historically been viewed in the US as a "black disease."[1,26] Racism, implicit or otherwise, presents devastating obstacles to care in what is already a debilitating and frequently lethal condition.[1]

We heard frustration from the sickle cell community about the lack of investment in research or comprehensive treatment centers that might increase access to better treatment, improve health outcomes, and reduce other disparities faced by SCD patients and their families. Historically, SCD has been underfunded, with no breakthroughs or developments in two decades. Although the populations of patients living with other severe hereditary conditions such as cystic fibrosis are significantly less than that of SCD, these conditions often enjoy greater funding in research and treatment. Cystic fibrosis, for example, affects approximately 30,000 people in the US (versus about 100,000 with SCD) and receives 7-11 times the amount of funding per patient.[27-29]

> *"Consider the fact that we get stigmatized at regular ER hospitals, consider that our bodies work 3 times more than a regular human being, consider that this nation doesn't make sickle cell as a top priority as cancer, leukemia, or AIDS/HIV."*

Pain relief

Racial bias and treatment disparities are glaringly obvious in the dispensing of analgesics for

patients with SCD. Patients who present at emergency rooms in crisis are treated with suspicion. Efforts to avoid categorization as drug seeking lead patients during excruciating pain to get dressed up in professional attire before going to the ER. Patients expressed a hesitancy to reveal any familiarity with pain regimens they know to be effective out of fear they would be denied relief or labeled as an addict. Many hospitals follow "one size fits all" pain management protocols that limit dosing or cease dispensing after a predetermined period of time, irrespective of whether an individual's pain is adequately managed.

Racial bias in the prescription of pain medications has been well documented. A survey of more than 100 physicians who care for patients with SCD suggested that provider attitudes toward opioid addiction can have negative implications for patients, including undertreatment of pain and discrediting a patient's report of pain severity.[27,30] Furthermore, a 2014 study of attitudes toward patients with SCD among 215 emergency department providers (nurses and physicians) found that relative to physicians, who have less frequent and shorter interactions with patients, nurses had greater levels of negative attitudes toward SCD patients; nurses expressed more frustration in caring for patients, estimated a higher prevalence of opioid addiction among patients with SCD, and reported less unease with the ways in which their colleagues treated patients.[27,31]

"Most of us aren't coming into the hospitals until the pain is at ridiculous levels because we HATE feeling judged all the time. I don't know what these docs are being taught, but it seems compassion ain't part of the curriculum! […] Most times when describing my pain I don't look at them at all, because if I do and I see that apathetic or judge-y, doubtful look on they face it makes me instantly regret coming in. It's hard because they want you to give eye contact, speak clearly and be so detailed, all of which are incredibly hard when you in pain […]. I've felt like I had to put on a show when I was younger because if I said I'm a 8, 9, or 10 without crying or writhing in pain, they'd never believe me. It was obvious they didn't believe it by how long it would take me to get my medication, or all the tests I'd be forced to take before getting anything for pain."

The ongoing opioid crisis has further complicated patients' ability to access pain medicine, as doctors have grown increasingly wary of over-prescribing addictive therapies. The Centers for Medicare & Medicaid Services recently issued a policy to recommend that Medicare beneficiaries with SCD be exempt from opioid safety restrictions; similar exemptions have been recommended in some state Medicaid programs, although such policies will not improve patient access if provider attitudes do not also change.[27,32,33]

Lack of Specialists & Competent Treatment

Patients lamented that SCD education and awareness among clinicians, even among hematologists, is severely lacking. Because there is a paucity of facilities and hematologists with expertise in SCD, patients commonly receive care from generalists, emergency nurses, and hospitalists who are not equipped to help them manage their disease. We heard repeated concerns that there were not enough doctors and other medical providers who are adequately trained in the management of SCD, particularly for adults. A national survey of over 3,000 family physicians revealed that only 20% respondents felt comfortable treating SCD.[34,35]

Clinical experts and patients alike commented that incompetent care can be catastrophic; we heard several anecdotes about deaths that might have been prevented had the patient received care from a more knowledgeable provider. Patients are conscious of the deaths and irreversible damage that results from long wait times in the ER, as well as the increased mortality from events that occur in the hospital; they reported feeling intense anxiety and stress about going to the hospital, sometimes delaying or avoiding seeking necessary care.

> *"Too often Sickle Cell Patients are marginalized, treated with stereotypical idealism and inherent bias that ultimately leads to them avoiding going for help or simply not receiving it in their greatest time of need, during the Vaso-Occlusive Crisis. This leads to many damaging side effects including death but more so the damage taking place in their bodies while they are lingering in an untreated state of ongoing necrosis taking place throughout their bodies!"*

Among non-specialist providers, there is often the misperception that SCD is a pain condition. This over-simplification can lead to inappropriate care of the disease's many complications. In the ER, treatment with fluids, oxygen, and other medicines may be lacking and patients may be not be appropriately triaged. One caregiver, who was not a trained clinician, told us about needing to adjust a patient's oxygen level while in the hospital out of fear that inadequate attention from the attending providers would prove fatal to the patient.

While the management of pediatric patients with SCD has improved dramatically in recent years, the transition from pediatric to adult care presents a major risk for many patients. There is a significant shortage of adult care providers with the requisite knowledge and skill set. Patients described the difficulty they faced trying to navigate a very different system of care, and

> *"Finding a great doctor that knows information about sickle cell is finding a needle in a hay stack"*

recounted a worsening of health as result of limited access to multi-dimensional care. Indeed, there is a sharp increase in mortality during the transition from pediatric to adult care.[36,37]

This problem is magnified in smaller cities, towns, and rural areas, where patients report needing to travel several hours to see a specialist, participate in a clinical trial, or access treatment through a compassionate use programs. Patients were anxious that the retirement of a community's only specialist would lead to a spike in SCD mortality. A retired specialist from California, Dr. Keith Quirolo, provided some sobering statistics about the severe shortage of sickle cell hematologists; in the state of California, where Dr. Quirolo used to practice, there are only about five physicians who specialize in the treatment of SCD for an estimated 7,000 residents living with the condition.[34]

Attitude toward New Therapies

There is consensus in the SCD community about the dire need for disease-modifying drugs. Over the past several years, few treatment options aside from analgesia were available. Barriers to accessing and utilizing the few available options, such as pharmaceutical-grade L-glutamine and hydroxyurea are many; these include insufficient payer coverage, a lack of pharmacies that stock these drugs, a lack of awareness among providers about L-glutamine (and reluctance to prescribe it), patient fears and/or intolerance of undesirable side effects (e.g., running to the bathroom from gastrointestinal side effects of L-glutamine; hair loss or infertility from hydroxyurea). In addition, patients pay out of pocket for supplements commonly recommended for SCD, such as zinc, vitamin B12, chlorophyll, iron, and folic acid.

There is cautious optimism about the promising pipeline of therapies, particularly gene therapies, that may soon become available. Nevertheless, patients and families worry about being able to afford expensive new drugs and are concerned that high drug prices may cause insurance policies to implement barriers to access. Patients are concerned that doctors will not know enough about the new therapies to be willing to write prescriptions for them. Patients also wonder whether they will be eligible for treatment with these new treatments. We heard from some patients that they fear they will be too old or have too much organ damage to be candidates for gene therapy.

"The quality of life for most Sickle Cell Patients is a life of extreme suffering from pain and rejection of medical care. We are stigmatized as drug seekers because there is hardly any tools a care provider can offer us but pain killers. Life is painful and frustrating, and we have few choices in our options for care."

Finally, stakeholders emphasized the importance of multidisciplinary care. New therapies need to be integrated into treatment plans that care for the whole patient.

SCD Patient and Caregiver Survey

To date, ICER has received public comment submissions from 110 stakeholders (82 patients and/or family members of patients, 19 advocacy groups, 2 manufacturers, 1 provider group, 1 clinical society, and 4 clinical experts), participated in conversations with 19 key informants (3 patients and/or family members of patients, 2 advocacy groups, 3 manufacturers, 1 clinical society, and 9 clinical experts), and reviewed literature germane to the patient experience. In order to supplement what we have learned from the literature and stakeholder engagement, ICER is collaborating with Sick Cells and the Sickle Cell Disease Association of America (SCDAA) to conduct an online survey. The survey may provide valuable information needed to assess the comparative effectiveness of the interventions and help us to better quantify important information on quality of life and productivity. Data points from the survey results will be incorporated into the cost-effectiveness model where appropriate.

The goal of the survey is to collect information and perspectives from people living with and who care for people living with SCD. In particular, it will capture data not adequately addressed in the literature on the impact of SCD and its complications on their ability to work, go to school, or perform usual activities, as well as out of pocket costs for treatments and supportive care. The questions will be both qualitative and quantitative in nature. Survey questions will be included in the Appendix and responses will be summarized in the report.

The patient advocacy group Sick Cells has been working with ICER on all aspects of the survey, from planning to execution. The clinical, economic, and program teams at ICER have consulted with Sick Cells on a list of survey questions, and Sick Cells and SCDAA have distributed a web-based survey to its members. At the time this draft report was published, the results of this survey were not yet available, but we expect to integrate the results into our updated Evidence Report that will guide the public deliberation and voting at the meeting of the New England CEPAC.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

For our review of pharmaceutical grade L-glutamine (Endari)'s insurance coverage, we reviewed publicly-available coverage policies for US national and regional commercial payers (Aetna, Anthem, Blue Cross Blue Shield Massachusetts [BCBSMA], CareFirst, Cigna, Emblem, and UnitedHealth care) and public plans of MassHealth (Massachusetts Medicaid), Neighborhood Health Plan of Rhode Island (Rhode Island Medicaid), and New Hampshire Department of Health and Human Services (NH Medicaid). We also reviewed the Centers for Medicare and Medicaid Services (CMS)[38] and were unable to locate any National Coverage Determinations or Local Coverage Determinations for L-glutamine.

At the time this report was published, with the exception of Florida Medicaid's coverage policy for crizanlizumab (Adakveo), no other commercial or public payer policies had been updated to include crizanlizumab or voxelotor (Oxbryta) following their FDA approval in November 2019.

Pharmaceutical Grade L-Glutamine

Excluding Cigna, the remaining six of the seven surveyed commercial payers covered L-glutamine for SCD with varying prior authorization criteria (Table 3.1). We were only able to locate publicly-available coverage policies for three of these payers – Aetna, Emblem, and UnitedHealthcare[39-41] – all of whom specified a patient age restriction of 5 years or older for coverage. Emblem covered L-glutamine for all FDA approved indications[42] (i.e., SCD patients 5 years of age or older) while Aetna and UnitedHealthcare also required that the patient have experienced two or more painful sickle cell crises within the last year.[39-41] Emblem and UnitedHealthcare required a SCD specialist or hematologist, respectively, to prescribe L-glutamine.[40,41] Aetna restricted coverage to those who showed a documented contraindication or failure of hydroxyurea while UnitedHealthcare required both a history of failure to non-prescription L-glutamine supplementation and also concurrent use of or contraindication to hydroxyurea.[39,41] All payers offered initial coverage for 12 months duration, with Aetna and UnitedHealthcare specifying positive or improved clinical response for reauthorization.[39-41]

Of the three surveyed public payers, only MassHealth covered L-glutamine (Table 3.1).[43] Similar to the commercial payers, MassHealth covered L-glutamine for patients with a diagnosis of SCD, five years of age or older, having experienced two or more painful sickle cell crises in the last year.[43] Coverage was restricted to those having inadequate or contraindicated response to hydroxyurea,

and no prescriber criteria were specified.[43] Initial duration of coverage spanned 12 months and no criteria were specified for reauthorization.[43]

Table 3.1. Private and Public Coverage Restrictions and Specifications for L-Glutamine

Coverage Specifications						
	Age	**Diagnosis & Clinical Criteria**	**Prescriber Restriction**	**Required Medical Information**	**Initial Authorization Duration**	**Reauthorization Criteria**
Aetna[39]	≥5 years	Diagnosis of SCD **and** 2 or more painful sickle cell crises within past 12 months	NA	A documented contraindication, intolerance, allergy, or failure of hydroxyurea	12 months	Clinical documentation indicating disease stability or improvement from baseline
Emblem Health[40]	≥5 years	All FDA approved indications not otherwise excluded from Part D	Prescribed by, or in consultation with, a physician who specializes in SCD	NA	12 months	NA
UnitedHealthcare[41]	≥5 years	Diagnosis of SCD **and** 2 or more painful sickle cell crises within past 12 months	Prescriber is a hematologist	History of failure to non-prescription L-glutamine supplementation **and** Using concurrent hydroxyurea or unable to take hydroxyurea due to contraindication/intolerance	12 months	Documentation of positive clinical response to Endari therapy
MassHealth[43]	≥5 years	Diagnosis of SCD **and** 2 or more painful sickle cell crises within past 12 months	NA	Inadequate response, adverse reaction, or contraindication to hydroxyurea	12 months	NA

NA: not applicable, SCD: sickle cell disease

CareFirst[44], Anthem[45], and Blue Cross Blue Shield of Massachusetts (BCBSMA)[46] require prior authorization for L-glutamine but their policies were not publicly available. Anthem and BCBSMA specify coverage as a tier three option.[45,46]

Cigna, Rhode Island Medicaid, and New Hampshire Department of Health and Human Services do not cover L-glutamine.

Crizanlizumab

Florida Medicaid was the only publicly-available policy providing prior authorization criteria for crizanlizumab.[47] Coverage was specified for patients age 16 or older with a diagnosis of SCD (all genotypes included) and who have experienced two or more acute pain crises within the past year.[47] Administration of crizanlizumab should follow this dosing pattern: 5 mg/kg intravenously over 30 minutes at weeks 0 and 2, and then every four weeks thereafter, with a single dose vial measured at 100mg/10ml.[47]

3.2 Clinical Guidelines

American Society of Hematology (ASH)

2019 Guidelines for Sickle Cell Disease: Cardiopulmonary and Kidney Disease[48]

A multidisciplinary guideline panel formed by ASH agreed on 10 recommendations to support the screening, diagnosis, and management of SCD and its cardiopulmonary and renal complications. Due to a lack of direct, high-quality evidence on the SCD outcomes of interest, the majority of recommendations were conditional rather than strong. Although these recommendations advise on management of patients with pulmonary arterial hypertension, albuminuria, unprovoked venous thromboembolism, and sleep-disordered breathing, we have summarized only the two recommendations pertaining to outcomes relevant to our review: chronic kidney disease (CKD) and management with hydroxyurea.

The panel suggests referral for a renal transplant for those with advanced CKD or end-stage renal disease. For those with worsening anemia associated with CKD, the panel suggest combination therapy with hydroxyurea and erythropoiesis-stimulating agents.

National Heart, Lung, and Blood Institute (NHLBI)

Evidence-Based Management of Sickle Cell Disease: Expert Panel, 2014[49]

The NHLBI convened a multidisciplinary panel to develop guidelines for the management, recognition, and treatment of acute and chronic complications of SCD, for patients ranging from infancy through adulthood. These guidelines cover an extensive list of recommendations and for the purpose of this report, we have summarized only those which are most strongly recommended and focus on the outcomes and management options related to our review: acute pain crisis, acute chest syndrome (ACS), acute and chronic transfusion, hemoglobin, hydroxyurea, and stroke.

Health Maintenance (with focus on outcomes listed above)

- Only in children with sickle cell anemia (SCA; does not include those with HbSC, HbSD, $HbS\beta^0$ thalassemia, or $HbS\beta^+$ thalassemia), from age two through at least 16, the panel strongly recommends annual screening with transcranial doppler (TCD) imaging for the risk of stroke.

Management of Acute Complications of SCD (with focus on outcomes listed above)

- The panel strongly recommends treatment with parenteral opioids for adults and children experiencing an acute pain crisis with severe pain.
- For those hospitalized for an acute pain crisis, the panel recommends incentive spirometry while awake to reduce the risk of ACS.
- For patients who have ACS, the panel strongly recommends treatment with 1) intravenous cephalosporin, 2) an oral macrolide antibiotic, 3) supplemental oxygen, and 4) monitoring for hypoxemia, acute anemia, and bronchospasm.
- Among all patients, when there is rapid progression of ACS, the guidelines recommend urgent exchange transfusion and use of incentive spirometry while awake.

Hydroxyurea Therapy for Management of SCD (with focus on outcomes listed above)

- The panel strongly recommends treatment with hydroxyurea among adults with SCA for all of the following: those who have at least three moderate to severe pain crises within a year, those whose pain interferes with daily activities and quality of life, those who have a history of severe and/or recurrent ACS, and those who have severe symptomatic chronic anemia.
- For infants at least nine months of age, and children and adolescents with SCA , treatment with hydroxyurea to reduce SCD-related complications is recommended regardless of clinical severity.

Blood Transfusions for Management of SCD (with focus on outcomes listed above)

- Prior to undergoing a surgical procedure, the guidelines state that all adults and children with SCA are to be transfused with red blood cells to raise hemoglobin level to 10 g/dL.
- For both children and adults, the guidelines suggest consulting a blood bank for a workup of possible delayed hemolytic transfusion reaction (DHTR), for patients showing signs of acute anemia, jaundice, or pain within three weeks after a blood transfusion.
- For patients receiving chronic transfusion therapy, the guidelines recommend performing serial assessment of iron overload.
- In children with TCD results >170 cm/sec, the guidelines recommend referral to a specialist who may initiate chronic transfusion therapy for the prevention of stroke.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the clinical effectiveness of crizanlizumab, voxelotor, and L-glutamine in the treatment of SCD, we sought evidence related to each of these therapies in comparison with optimal usual care. We did not attempt to compare the interventions to each other, as these therapies may have a complementary role in the management of SCD. Our review focused on clinical benefits (i.e., mortality, acute pain crisis, organ damage, and quality of life), as well as potential harms (drug-related AEs). Methods and findings of our review of the clinical evidence are described in the sections that follow.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on crizanlizumab, voxelotor, and L-glutamine for SCD followed established best research methods.[50,51] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[52] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE and EMBASE for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, and Comparator elements described in Section 1.2. The search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms (see Appendix Tables A2 and A3).

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

Study Selection

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection was accomplished through two levels of screening at the abstract and full-text level. Two reviewers independently screened the titles and abstracts of all identified publications using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. Citations accepted during abstract-level screening were retrieved in full text for review. Reasons for exclusion were categorized according to the PICOTS elements during full-text review.

Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted studies (See Appendix D). Elements included a description of patient populations, sample size, duration of follow-up, study design features, interventions (agent, dosage, dosing frequency, method of administration), results, and quality assessment for each study. Extracted data were reviewed for logic and were validated by a third investigator for additional quality assurance.

We used 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."[53]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms included sickle cell, crizanlizumab, voxelotor and L-glutamine. We searched for studies which would have met our inclusion criteria, and for which no findings have been published.

Data Synthesis and Statistical Analyses

The results of included studies are described narratively in the sections that follow. Analyses are descriptive in nature only, as we did not intend to compare crizanlizumab, voxelotor, and L-glutamine to each other through indirect quantitative analysis. Insufficient data were identified to allow for pairwise meta-analyses of individual agents.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among crizanlizumab, voxelotor, and L-glutamine relative to optimal supportive care (see Appendix D).[54]

4.3 Results

Study Selection

Our literature search identified 103 potentially relevant references (see Appendix Figure A1), of which 14 references (5 publications, 6 conference presentations, and 3 FDA Multidisciplinary Review packets) relating to 4 individual studies met our inclusion criteria. The primary reasons for study exclusion included interventions or dosing protocols not of focus and evaluation of outcomes not of interest (e.g., red cell nicotinamide adenine dinucleotide redox potential).

Of the 11 included references, 5 references related to a single Phase II RCT of crizanlizumab.[17,55-58] We identified a single publication of a Phase III RCT of voxelotor and 3 conference abstracts related to the same trial; earlier phase studies of voxelotor were excluded due to the use of lower doses of the drug.[59] We included 4 references of L-glutamine, which corresponded to a Phase II and a Phase III RCT.[16,60-62] Details of all included studies are summarized in Appendix D and in the sections that follow.

Although we defined several chronic SCD complications (e.g., chronic pain, organ damage, mortality) in our scope as outcomes of interest, we did not identify any data related to the effect of crizanlizumab, voxelotor, or L-glutamine on these outcomes. Consequently, the results described below summarize the short-term treatment effects of these therapies, including acute complications (e.g., incidence of acute pain crises, ACS), health care utilization (e.g. hospitalizations and emergency department visits), quality of life, and changes in hemolysis markers).

Quality of Individual Studies

We rated the key studies of crizanlizumab and voxelotor to be of good quality using criteria from the USPSTF (Appendix D).[17,59] The trials had adequate blinding of patients, investigators, and outcome assessors. The groups were comparable at baseline and there was non-differential follow-up. We rated the Phase III trial of L-glutamine to be fair quality because there was a high and different loss to follow-up between groups; statistical imputation to account for these differences may have introduced further bias.[16] We considered the Phase II trial of L-glutamine to be poor quality because of differences in the groups assembled at baseline, a large and differential rate of drop-out, and inadequate control for potential confounders (e.g., hydroxyurea use).[60]

Key Studies of Crizanlizumab

Evidence on crizanlizumab was derived from the SUSTAIN trial.[17] This study was a Phase II, placebo-controlled trial that randomized 198 individuals with SCD to 5.0 mg/kg of crizanlizumab (n=67), 2.5 mg/kg of crizanlizumab (n=66), or placebo (n=65). The trial included a 30-day screening phase, a 52-week treatment phase, and a 6-week follow-up evaluation phase. Crizanlizumab was

administered intravenously in two loading doses, two weeks apart, and every 4 weeks thereafter through week 50 of the trial (14 total doses). As crizanlizumab was approved at the higher dose (5.0 mg/kg), efficacy evidence pertaining to the low-dose arm of SUSTAIN was not summarized in this review. Safety data were supplemented with evidence from the low-dose arm.

Patients 16-65 years of age were eligible to participate in SUSTAIN if they had any genotype of SCD and experienced 2-10 SCD-related acute pain crises in the 12 months prior to enrollment.[17] Patients who had been receiving treatment with hydroxyurea for at least 6 months and had maintained a stable dose during the 3 months immediately preceding enrollment, were permitted to continue therapy during the trial; receipt of chronic red-cell transfusions was an exclusion criterion.

At baseline, patient characteristics were balanced across intervention arms. Patients in the crizanlizumab group had a median age of 29 years, 52% were females, 90% were black, 70% had an HbSS SCD genotype, and 63% were receiving concomitant therapy with hydroxyurea.[17] The proportion of patients with 2-4 or 5-10 SCD-related crises in the previous year, was 63% and 37%, respectively (Table 4.1).

Table 4.1. Key Trial of Crizanlizumab: SUSTAIN[17]

Interventions	Inclusion Criteria	Treatment Duration	Baseline Characteristics*	Primary Endpoint
1. Crizanlizumab (5 mg/kg, N=67) **2. Crizanlizumab** (2.5 mg/kg, n=66)‡ **3. Placebo** (N=65)	16 – 65 years of age SCD diagnosis (any genotype) 2-10 acute pain crises in 12 months before enrollment	52-weeks of treatment + 6-week evaluation phase **Early discontinuation** **Crizanlizumab**: 36% Placebo: 37%	**Median age**: 29 years (range 16-63) **Black**: 90% **HbSS**: 70% **HbSC:** 13% **HbSβ0:** 4% **HbSβ+:** 10% **Other**: 1% **Hydroxyurea use:** 63% **Acute pain crises in prior 12 months:** 2-4: 63%, 5-10: 37%	Annual rate of acute pain crises 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 agents or with a parenteral nonsteroidal anti-inflammatory drug.

SCD: sickle cell disease

* Baseline Characteristics reported from crizanlizumab 5 mg/kg arm. Baseline characteristics were balanced across treatment arms; ‡ evidence pertaining to efficacy of low-dose crizanlizumab was not summarized in this report, however we supplemented our safety review with data from this dosage arm

The SUSTAIN trial's primary endpoint was the annual rate of sickle cell-related pain crises, 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.[17] Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) were also considered to be crisis events.

Clinical Benefits of Crizanlizumab

Compared to optimal usual care alone (i.e., placebo), patients treated with crizanlizumab experienced fewer acute pain crises per year and sustained a longer period of time before the first (and second) crises following initiation of the trial therapy. The annual rate of days hospitalized was numerically lower with crizanlizumab, although this outcome did not reach statistical significance. Crizanlizumab did not improve quality of life, as measured in the study.

Acute complications of SCD

As noted above, SUSTAIN evaluated the annual rate of sickle cell-related acute pain crises as its primary endpoint. The median annualized crisis rate was 1.63 in the crizanlizumab group and 2.98 in the placebo group (median difference -1.01, p=0.01).[17] Time to event analyses suggested that

crizanlizumab reduced the risk of a first and second acute pain crisis by approximately 50% (Table 4.2).

The FDA performed sensitivity analyses that excluded patients who discontinued the trial early and that only included patients who discontinued early. The results suggested that the reduction in the annual rate of crisis was slightly lower in the analysis that excluded the non-completers (median rate of 1.18 vs. 2.98 for crizanlizumab and placebo, respectively) and higher in the analysis of discontinued patients (1.75 vs. 2.59).[57] As patients were discontinued from the study if they missed doses of the study drug (due to hospitalization or otherwise) this may have accounted for the difference.

Uncomplicated crises, defined as crises other than ACS, hepatic sequestration, splenic sequestration, or priapism, occurred at a median rate per year of 1.08 (IQR 0.00-3.96) in patients treated with crizanlizumab, compared to a rate of 2.91 (IQR 1.00-5.00; p=0.02) in the placebo arm.[17]

The median rate of ACS did not statistically differ across treatment arms, as all groups had a rate of zero.[17] At the end of the treatment phase, 36% of the crizanlizumab group had a crisis rate of zero, compared to 18% of the placebo group.[17]

Table 4.2. Acute SCD Complications in the SUSTAIN Trial of Crizanlizumab[17,63]

	Crizanlizumab (n=67)	Placebo (n=65)	p-value
Annual rate of acute pain crises per year, Median (IQR)	1.63 (0.00-3.97)	2.98 (1.25-5.87)	Median difference:* -1.01 p=0.01
Patients with crisis rate of zero, n (%)	24 (35.82)	11 (16.92)	p=0.013
Time to first acute pain crisis, Median months (IQR)	4.07 (1.31-NR)	1.38 (0.39-4.90)	p=0.001
Time to first acute pain crisis, HR (95% CI)	0.50 (0.33 to 0.74)		
Time to second acute pain crisis, Median months (IQR)	10.32 (4.47-NR)	5.09 (2.96-11.01)	p=0.02
Time to second acute pain crisis, HR (95% CI)	HR 0.53 (0.33 to 0.87)		
Annual rate of uncomplicated acute pain crises, Median (IQR)	1.08 (0.00-3.96)	2.91 (1.00-5.00)	p=0.02
Annual rate of ACS, Median (IQR)	0 (0.00-0.00)	0 (0.00-0.00)	p=0.78

ACS: acute chest syndrome, CI: confidence interval, HR: hazard ratio, IQR: interquartile range, NR: not reported, SCD: sickle cell disease, *Median difference and CI estimated using Hodges-Lehmann method

Hospitalization

The median rate of days hospitalized per year was 4.0 (IQR 0.0-25.7) in the crizanlizumab group and 6.9 (IQR 0.0-28.3) in the placebo group; this difference did not reach statistical significance.[17] A post-hoc time to event analysis also did not reach statistical significance but suggested that crizanlizumab may have delayed time to first hospitalization (median 6.3 vs. 3.2 months for the crizanlizumab and placebo arms, respectively; HR 0.68 [95% CI 0.44 to 1.07]).[55]

Table 4.3. Hospitalizations in the SUSTAIN Trial of Crizanlizumab[17,55,57]

	Crizanlizumab (n=67)	Placebo (n=65)	Difference p-value
Annual rate per year of days hospitalized, Median (IQR)	4.0 (0.0-25.7)	6.9 (0.0-28.3)	Median: 0.0 (95% CI -4.4 to 0.0) p=0.45
Patients with ≥1 hospitalization, n (%)	36 (54)	42 (65)	NR
Median time to first hospitalization (months)	6.3	3.2	NR
Time to first hospitalization	HR: 0.68, 95% CI (0.44 to 1.07)		

CI: confidence interval, HR: hazard ratio, IQR: interquartile range, NR: not reported

Quality of Life

The SUSTAIN trial evaluated quality of life using the Brief Pain Inventory (BPI) Questionnaire and the 36-Item Short Form Survey (SF-36) as exploratory endpoints. The BPI is a patient-reported instrument to rate the severity of a patient's pain and its impact on daily function. Significant changes from baseline in BPI scores were not observed during the SUSTAIN trial.[17]

The SF-36 is a general patient-reported quality of life instrument that measures patients' perceptions of health and well-being along 8 scales: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to personal or emotional problems, and mental health. Significant differences in the LS mean change from baseline to Week 52 were not observed in any of the domains of the SF-36, including the bodily pain scale.[57]

Markers of Hemolysis

No significant differences were observed in changes in hemoglobin, lactate dehydrogenase, number of reticulocytes, haptoglobin, and indirect bilirubin between the crizanlizumab and placebo arms of the SUSTAIN trial.[17]

Subgroup Analyses

Treatment with crizanlizumab resulted in a lower rate of acute pain crises across a number of subgroups of interest, including groups characterized by concomitant hydroxyurea use, the number of pain crises in the prior year, and sickle cell genotype. Table 4.4 reports the median annual rate of pain crises in these groups; additional outcomes in these subgroups, including the proportion of patients who were crisis free, time to first and second crisis, and type of crisis are reported in Appendix table D4. Interaction tests to assess whether treatment efficacy differed between subgroups were not reported.

Table 4.4. Annual Rate of SCD-Related Pain Crises in Subgroups of the SUSTAIN Trial, Median (IQR)[17,58]

	Crizanlizumab	Placebo	Hazard ratio (95% CI)
Annual Rate of Acute Pain Crises, Median IQR			
Concomitant hydroxyurea	2.43 (0.00-4.01)	3.58 (1.13-6.23)	NR
No concomitant hydroxyurea	1.00 (0.00-2.00)	2.00 (1.63-3.90)	NR
2-4 SCD pain crises in previous 12 months	1.14 (0.00-2.00)	2.00 (1.00-3.90)	NR
5-10 SCD pain crises in previous 12 months	1.97 (0.00-3.98)	5.32 (2.01-11.05)	NR
HbSS genotype	1.97 (0.00-3.96)	3.01 (1.01-6.00)	NR
Other genotype	0.99 (0.00-4.01)	2.00 (1.86-5.00)	NR
Time to first on-Treatment Acute Pain Crisis, Median months (IQR)			
Concomitant hydroxyurea	2.43 (1.15-NR)	1.15 (0.33-4.90)	0.58 (0.35-0.96)
No concomitant hydroxyurea	5.68 (3.09-NR)	2.86 (0.79-4.53)	0.39 (0.20-0.76)
2-4 acute pain crises in previous 12 months	4.76 (1.81-NR)	1.61 (0.62-6.70)	0.53 (0.31-0.90)
5-10 acute pain crises in previous 12 months	2.43 (1.25-7.75)	1.03 (0.30-2.97)	0.47 (0.25-0.89)
HbSS genotype	4.07 (1.31-NR)	1.12 (0.33-4.17)	0.50 (0.31-0.80)
Other genotype	6.90 (1.41-NR)	3.09 (1.12-6.21)	0.47 (0.21-1.05)

CI: confidence interval, IQR: interquartile range, NR: not reported, SCD: sickle cell disease

Harms of Crizanlizumab

There were three deaths among patients treated with crizanlizumab, although none were considered by the investigator to be related to the study therapy. The rate of discontinuation due to an AE was low. The most commonly reported AEs included back pain, nausea, arthralgia, and pyrexia. The prescribing information for crizanlizumab includes warnings for infusion-related reactions and interference with automated platelet counts (i.e., platelet clumping).

There were three deaths among patients treated with crizanlizumab in the SUSTAIN trial.[17] These deaths included 2 patients in the high-dose crizanlizumab group (1 from ACS and 1 from endocarditis and sepsis) and 1 in the low-dose crizanlizumab group (from ACS, aspiration,

respiratory failure, and progressive vascular congestion). None of these deaths were considered related to crizanlizumab.

SAEs that occurred in at least 2 crizanlizumab-treated patients included pyrexia (3%) and influenza (5%). In addition, there was one life-threatening case of anemia and one intracranial hemorrhage reported in the low-dose crizanlizumab group. Fewer patients discontinued treatment due to an AE in the crizanlizumab groups (2%) than the placebo group (5%). AEs that occurred in at least 10% of patients treated with high-dose crizanlizumab are reported in Table 4.5.

Table 4.5. AEs in the SUSTAIN Trial of Crizanlizumab[17]

	High-Dose Crizanlizumab (n=66) n, (%)	Placebo (n=62) n, (%)
Headache	11 (17)	10 (16)
Back pain	10 (15)	7 (11)
Nausea	12 (18)	7 (11)
Arthralgia	12 (18)	5 (8)
Pain in extremity	11 (17)	10 (16)
Urinary tract infection	9 (14)	7 (11)
Upper respiratory tract infection	7 (11)	6 (10)
Pyrexia	7 (11)	4 (6)
Diarrhea	7 (11)	2 (3)
Musculoskeletal pain	8 (12)	6 (10)
Pruritus	5 (8)	3 (5)
Vomiting	5 (8)	3 (5)
Chest pain	1 (2)	1 (2)

The prescribing information for crizanlizumab includes warnings for infusion-related reactions and interference with automated platelet counts (i.e., platelet clumping). The FDA is requiring several postmarketing studies, including a clinical trial, to assess the risk of infusion-related reactions and immunogenicity, bleeding complications, and infections. Antibodies against crizanlizumab were not detected during the SUSTAIN trial.

Key Studies of Voxelotor

Evidence on voxelotor was derived from the HOPE trial.[59] This study was a Phase III, placebo-controlled trial that randomized 274 individuals with SCD to receive a once-daily oral dose of 1500 mg of voxelotor (n=90), 900 mg of voxelotor (n=92), or placebo (n=92).

The trial included a screening period of 28-35 days, a treatment period up to 72 weeks, and an end-of-trial visit 3-5 weeks subsequent to the last dose of the trial regimen.[59] As voxelotor was approved at the higher dose (1500 mg), evidence pertaining to the low-dose arm of HOPE was not

summarized in this review. We supplemented our safety review with evidence from the low-dose arm.

Patients 12-65 years of age were eligible to participate in the HOPE trial if they had any genotype of SCD, a hemoglobin level between 5.5 and 10.5 g per deciliter (g/dL) during screening, and experienced 1-10 SCD-related acute pain crises in the 12 months prior to enrollment.[59] Patients who had been receiving hydroxyurea at a stable dose for at least 3 months prior to enrollment were permitted to continue therapy during the trial. Patients were excluded if they were receiving chronic red-cell transfusions, had received a transfusion in the past 60 days, or had been hospitalized for an SCD-related acute pain crisis within 14 days of providing informed consent.

At baseline, patient characteristics were balanced across intervention arms. Patients in the voxelotor group had a median age of 24 years and were made up of 64% females; 66% of the trial population were black, 68% had an HbSS SCD genotype, and 64% were receiving concomitant therapy with hydroxyurea.[59] The proportions of patients with 1 versus 2-10 SCD-related crises in the previous year, was 39% and 61%, respectively (Table 4.6).

Table 4.6. Key Trial of Voxelotor: HOPE[59]

Interventions	Inclusion Criteria	Treatment Duration	Baseline Characteristics*	Primary Endpoint
1. Voxelotor (1500 mg QD, N=90) **2. Voxelotor** (900 mg QD, N=92)‡ **3. Placebo** (N=92)	12-65 years of age SCD diagnosis regardless of genotype 1-10 acute pain crises in past 12 months Hb level between 5.5 and 10.5 g/dL	52-weeks End-of-trial visit 4 weeks after last dose of trial drug or placebo **Early discontinuation** Voxelotor: 27% Placebo: 21%	**Median age:** 24 years (range 12-59) **Black**: 66% **HbSS**: 68% **HbSC**: 3% **HbSβ0:** 20% **HbSβ+:** 8% **Other:** 1% **Hydroxyurea use:** 64% **Acute pain crises in prior 12 months**: 1: 39%, 2-10: 61%	Percentage of participants with Hb response Hb response was defined as an increase from baseline of more than 1.0 g per deciliter at week 24

G: gram, g/dL: grams per deciliter, Hb: hemoglobin, SCD: sickle cell disease

*Baseline Characteristics reported from voxelotor 1500 mg Arm. baseline characteristics were balanced across treatment arms; ‡ evidence pertaining to efficacy of low-dose voxelotor was not summarized in this report. Safety data from low-dose voxelotor was included in our review of potential harms

The HOPE trial's primary endpoint was the proportion of patients who had a hemoglobin response, which was defined as an increase from baseline in hemoglobin of more than 1.0 g/dL at week 24.[59] The annualized rate of SCD-related acute pain crises was evaluated as a secondary endpoint. The trial's definition of SCD-related acute pain crises was a composite of ACS and/or moderate to severe pain lasting at least 2 hours with no explanation other than a vaso-occlusive event. The crises must have required oral or parenteral opioids, ketorolac, or other analgesics and have been documented in a medical record that the patient was seen or contacted a physician within 1 business day of the event.

Clinical Benefits of Voxelotor

Compared to optimal usual care alone (i.e., placebo), voxelotor increased hemoglobin levels and reduced markers of hemolysis. It did not significantly reduce the number of acute pain crises and did not improve quality of life as measured by the study. We did not identify any data related to health care utilization for voxelotor.

Effect on Hemoglobin

The HOPE trial's primary endpoint was hemoglobin response, defined as a 1 g/dL change in hemoglobin.[59] At week 24, 51% of the voxelotor group and 7% of the placebo group ($p<0.001$) had a response; sensitivity analyses accounting for missing data demonstrated consistent results.[64]

Improvements in hemoglobin were observed as early as 2 weeks of follow-up. At week 24, the adjusted mean change in hemoglobin from baseline was 1.1 g/dL (95% CI 0.9 to 1.4) in the voxelotor group and -0.1 g/dL (95% CI -0.3 to 0.2; p<0.001; Table 4.7).[59]

Markers of Hemolysis

Patients in the voxelotor group had significantly greater reductions from baseline in indirect bilirubin levels and percentage of reticulocytes (Table 4.7).[59] Other laboratory parameters, including absolute reticulocyte count and lactate dehydrogenase level, were not statistically different between groups at week 24. Red-cell transfusions during the trial period were administered to 33% of voxelotor patients and 25% of placebo patients (statistical testing not reported); the majority of these transfusions were due to acute pain crises.[59]

Table 4.7. Change in Hemoglobin and Markers of Hemolysis in the HOPE Trial[59]

	Voxelotor	Placebo	p-value
Primary Endpoint			
Hemoglobin response, n (%)*	46 (51)	6 (7)	p<0.001
LS Mean change from Baseline (95% CI) to Week 24 in Markers of Hemolysis			
Absolute change in hemoglobin level, g/dL	1.1 (0.9 to 1.4)	-0.1 (-0.3 to 0.2)	p<0.001
Relative change in indirect bilirubin level, %	-29.1 (-35.9 to -22.2)	-3.2 (-10.1 to 3.8)	p<0.001
Relative change in percentage of reticulocytes, %	-19.9 (-29.0 to -10.9)	4.5 (-4.5 to 13.6)	p<0.001
Relative change in absolute reticulocyte count, %	-8.0 (-18.1 to 2.1)	3.1 (-7.0 to 13.2)	NS
Relative change in lactate dehydrogenase level, %	-4.5 (-11.9 to 2.8)	-3.4 (-4.0 to 10.9)	NS

CI: confidence interval, g/dL: grams per deciliter, LS: least squares, NS: not significant, *hemoglobin response was defined as a 1 g/dL change in hemoglobin

Subgroup Analyses

A greater proportion of patients with a hemoglobin response was observed with voxelotor in subgroups defined by age, use of concurrent hydroxyurea, and baseline hemoglobin level (Table 4.8).[59] The mean change in hemoglobin from baseline to Week 24 in patients treated with voxelotor ranged from 1.0 g/dL to 1.5 across subgroups with and without hydroxyurea use and anemia severity subgroups; hemoglobin levels remained relatively stable in subgroups treated with placebo. Interaction tests to assess whether treatment efficacy differed between subgroups were not reported.

Table 4.8. Hemoglobin Response in Subgroups of the HOPE Trial[59]

	Mean Change in Hemoglobin from Baseline to Week 24, g/dL (95% CI)‡		Difference in Hemoglobin Response Rates at Week 24, % (95% CI)*
	Voxelotor	Placebo	
Age 12-17 years	NR	NR	51.3 (23.0 to 79.5)
Age ≥18 years	NR	NR	43.3 (30.7 to 56.0)
1 prior acute pain crisis in prior 12 months	NR	NR	55.2 (37.1 to 73.2)
2-10 acute pain crises in prior 12 months	NR	NR	37.9 (22.8 to 53.0)
No hydroxyurea use	1.2 (0.8 to 1.7)	0 (-0.3 to 0.3)	34.9 (15.3 to 54.6)
Baseline hydroxyurea use	1.0 (0.7 to 1.4)	-0.1 (-0.3 to 0.1)	50.0 (36.0 to 64.0)
Baseline hemoglobin <7 g/dL	1.5 (0.6 to 2.4)	0.2 (-0.2 to 0.6)	42.9 (-2.0 to 87.8)
Baseline hemoglobin ≥7 g/dL	1.1 (0.8 to 1.4)	-0.1 (-0.3 to 0.1)	44.7 (32.7 to 56.6)

‡Per protocol analysis with observed data, *ITT analysis: Difference in response rates: voxelotor 1500mg minus placebo, CI: confidence interval, g/dL: grams per deciliter, SCD: sickle cell disease

Acute complications of SCD

The annualized incidence rate of SCD-related acute pain crisis was evaluated as a secondary endpoint in the HOPE trial and did not differ among trial arms.[59] In the voxelotor group, there were 2.77 (95% CI 2.15 to 3.57) crises per person-year versus 3.19 (95% CI 2.50 to 4.07) in the placebo group (incidence rate ratio 0.87 [95% CI 0.61 to 1.23]); 67% and 69% of patients in the voxelotor and placebo arms, respectively, had at least 1 crisis. Investigators noted that a longer duration of follow-up is required to evaluate the effect of voxelotor on the incidence of acute pain crises. A final analysis will be performed when all subjects complete 72 weeks of treatment or their final study visit.

Sickle cell anemia with crisis, ACS, pneumonia, priapism, and osteonecrosis were recorded as SCD-related TEAEs in the HOPE trial.[59] Collectively, these events occurred in 76% of voxelotor-treated patients and 73% of placebo-treated patients.[59]

Hospitalization

Although the rate and duration of hospitalizations for SCD-related acute pain crisis were originally defined as outcomes of interest in the HOPE trial's protocol, a protocol amendment in January of 2019 removed it from consideration.[59]

Quality of Life

The HOPE trial assessed the Sickle Cell Disease Severity measure (SCDSM) total symptom score and EuroQOL 5-dimension 5-level (EQ-5D-5L) as exploratory endpoints; no differences were observed between the voxelotor and placebo groups for either outcome.[59,64] Investigators also collected data

related to rate of opioid use and school and work attendance, however no results were identified in the public domain.

Harms of Voxelotor

Rates of SAEs and treatment discontinuation due to an AE were relatively low in the HOPE trial of voxelotor. The most commonly reported AEs were diarrhea, nausea, abdominal pain, rash, and headache. The FDA prescribing information for voxelotor includes warnings for hypersensitivity reactions and interference with laboratory tests.

There were 4 fatal AEs in the HOPE trial, two of which occurred in patients treated with voxelotor (one from pulmonary sepsis, sickle cell anemia with crisis and acute sickle hepatic crisis; the second from sickle cell anemia with crisis); none of the deaths were determined to be related to the trial drug.[59]

Serious TEAEs that were deemed related to treatment were reported in 3% of patients treated with voxelotor and 1% of placebo-treated patients; 9% of patients in the voxelotor groups discontinued therapy due to a TEAE compared to 4% of patients in the placebo group. The most commonly reported AEs were diarrhea, nausea, abdominal pain, rash, and headache (Table 4.9).[59] The FDA prescribing information for voxelotor includes warnings for hypersensitivity reactions and interference with laboratory tests for quantification of hemoglobin species.

Table 4.9. Treatment-Emergent Adverse Events in the HOPE Trial of Voxelotor[59]

	Voxelotor, n (%)	Placebo, n (%)
TEAE leading to discontinuation	8 (9.1)	4 (4.4)
Treatment-related serious TEAE	3 (3.4)	1 (1.1)
Treatment-related TEAE	34 (38.6)	23 (25.3)
Diarrhea	11 (12.5)	3 (3.3)
Nausea	6 (6.8)	5 (5.5)
Abdominal pain	6 (6.8)	1 (1.1)
Rash	7 (8.0)	4 (4.4)
Headache	5 (5.7)	3 (3.3)
Abdominal pain upper	2 (2.3)	2 (2.2)
Fatigue	0 (0)	0 (0)

SCD: sickle cell disease, TEAE: treatment-emergent adverse event
Table excludes SCD-related adverse events, defined as sickle cell anemia with crisis, acute chest syndrome, pneumonia, priapism, and osteonecrosis

Key Studies of L-Glutamine

The primary source of evidence for our review of L-glutamine was the Phase III, placebo-controlled trial from Niihara et al. (2018);[16] a similarly designed Phase II study also informed our review, although due to a large rate of trial discontinuation and imbalance in baseline characteristics, evidence from this latter study was considered low quality.[65]

Both studies randomized patients with SCD to receive a twice-daily dose of L-glutamine (0.3 g per kilogram up to 30 g per day) or placebo.[16,65] The trials included a 48-week treatment phase, followed by a 3-week tapering period and 2-week observation period. Patients ≥5 years of age with a diagnosis of HbSS or Hbβ0-thalassemia were eligible to participate if they experienced at least two acute pain crises in the previous year (Table 4.10). Patients who had been receiving hydroxyurea at a stable dose for at least 3 months prior to enrollment were permitted to continue therapy during the trial. Patients were excluded if they had been hospitalized within 2 months of screening for something unrelated to SCD, had a prothrombin time international normalized ratio higher than 2, a serum albumin level less than 3.0 g/dL, had received any blood products 3 weeks prior to screening or L-glutamine within 30 days of screening, or had clinically significant renal or liver disease.

In the Phase III study, randomization was stratified by study site and baseline hydroxyurea use; characteristics were comparable across intervention arms at baseline.[16] Patients in the L-glutamine group had a median age of 19 years and were made up of 52% females; 95% of the trial population was black, 90% had a diagnosis of sickle cell anemia, two thirds were receiving concomitant hydroxyurea, and 84% had experienced 2-5 acute pain crises in the year prior to enrollment.

Conversely, the Phase II study did not stratify randomization by hydroxyurea use and there were several imbalances in patient characteristics present at baseline; most notably, the Phase II trial

differed at baseline with respect to the proportion of females in each group (67% in the L-glutamine group versus 35% in the placebo group), and hydroxyurea use (57% in the L-glutamine-treated group versus 39% in the placebo group.[65]

Table 4.10. Key Trials of L-Glutamine[16,61,65]

Trial	Interventions	Inclusion Criteria	Treatment Duration	Baseline Characteristics*	Primary Endpoint
Phase III[16]	**1. L-glutamine** (0.3 g/kg, N=152) **2. Placebo** (N=78)	• ≥ 5 years old age • SCD diagnosis (homozygous hemoglobin S [HbSS], or sickle cell thalassemia ($HbS\beta^0$-thalassemia) • ≥2 acute pain crises documented in previous year	52-weeks 3-week tapering period followed by 2-week observation after 48 weeks **Early discontinuation** L-glutamine: 36% Placebo: 24%	**Median age**: 19 years (range 5-57) **Black**: 95% **HbSS**: 90% **HbSC:** NR **$HbS\beta^0$:** 10% **$HbS\beta^+$:** 2% **Other:** NR **Hydroxyurea use**: 66% **Acute pain crises in prior 12 months**: 0-1: 0.7%, 2-5: 84%, 6-9: 10%, ≥ 10: 5%	**Number of acute pain crises through week 48:** Pain leading to treatment with a parenterally administered narcotic or ketorolac in an emergency department (ED) or outpatient treatment center or during hospitalization. Acute chest syndrome, priapism, and splenic sequestration were classified as sickle cell–related events regardless of the need for narcotics or ketorolac.
Phase II[65]	**1. L-glutamine** (0.3 g/kg N=37) **2. Placebo** (N=33)	• ≥ 5 years old age • SCD diagnosis (homozygous hemoglobin S [HbSS], or sickle cell thalassemia ($HbS\beta^0$-thalassemia) • ≥2 acute pain crises in previous year	52-weeks 3-week tapering period followed by 2-week observation after 48 weeks **Early discontinuation** L-glutamine: 51% Placebo: 64%	**Median age**: 29 (range 13-58) **Black**: 97% **HbSS**: 94% **HbSC:** NR **$HbS\beta^0$:** 7%** **$HbS\beta^+$:** 7%** **Other:** NR **Hydroxyurea use**: 57%	**Number of acute pain crises through week 48:** A visit to a medical facility lasting >4 hours for acute sickling-related pain that was treated with a parenterally administered narcotic (except for facilities in which only orally administered narcotics were used).

*Baseline Characteristics reported from L-Glutamine 0.3k/kg arm. Baseline characteristics were balanced across treatment arms,**: reported as beta thalassemia

The primary endpoint in both trials of L-glutamine was the number of acute pain crises through week 48 (Table 4.10). In the Phase III study, an acute pain crisis was defined as pain that led to treatment with a parenterally administered narcotic or ketorolac in a medical facility.[16] Acute chest syndrome, priapism, and splenic sequestration were considered acute pain crises, irrespective of the need for narcotics or ketorolac. The Phase II study's definition required that the visit to the medical facility last more than 4 hours and permitted treatment with oral narcotics in facilities where that was the only formulation in utilization; ACS, priapism, and hepatic or splenic sequestration were considered acute pain crises.[65]

There was a high and differential rate of dropout across treatment groups in both studies. More than half of the Phase II participants withdrew from the trial early (51% and 64% in the L-glutamine and placebo arms, respectively), and about a third of participants in the Phase III trial discontinued prior to completing 48 weeks (36% of the L-glutamine arm and 24% of the placebo arm).[16,65] The most commonly cited reasons for discontinuation included withdrawal of consent and nonadherence.

Two additional Phase II studies were identified in our review of the FDA clinical review packet for L-glutamine and the clinicaltrials.gov site that would have matched our PICOTS criteria for inclusion. Both trials seemed to have been completed more than two years ago, yet our literature search did not find any publications related to these trial. We have summarized the limited information we have for these two studies in Appendix Table D18, but note that there may be potential publication bias in the evidence supporting L-glutamine.

Clinical Benefits of L-Glutamine

Compared to optimal usual care alone (i.e., placebo), treatment with L-glutamine appeared to reduce the number of acute pain crises and hospitalizations, although the magnitude of benefit is uncertain. Due to a large and differential rate of withdrawal from the Phase II and Phase III studies of L-glutamine, investigators relied on imputation methods to calculate the rate of crises. These results were sensitive to the applied assumptions and were not statistically significant under certain approaches. We did not identify any data related to quality of life for L-glutamine.

Acute Complications of SCD

Both the Phase II and Phase III studies of L-glutamine evaluated the number of SCD-related acute pain crises through Week 48 as a primary endpoint, although each study defined a pain crisis slightly differently (see Table 4.10.). The Phase II study did not meet the prespecified significance level for this analysis.[65] Statistically significant differences in the number of SCD-related acute pain crises were reported in the Phase III trial, with a median count of 3.0 in the L-glutamine group and 4.0 in the placebo group (p=0.005).[16] Interim analyses at 24 weeks did not reach specified significance levels (0.005) in either study.[16]

Due to the high and differential rate of trial discontinuation prior to the completion of the 48-week treatment period, investigators in the Phase III study imputed the crisis results.[16,61] The investigators assigned a crisis count to patients who dropped out of the study that was derived from the rounded group average for patients who completed the 48-week treatment period. A count of 3 was assigned to patients in the L-glutamine arm who dropped out of the study early who experienced fewer than 3 crises and a count of 4 was assigned to placebo patients who dropped out early having experienced fewer than 4 crises. Patients who dropped out of the study early with more than these averages were included with the count at the time of dropout carried forward through 48 weeks.

This method may have introduced bias in the results because the high number of non-completers meant that the large proportion of imputed counts may have changed the distribution of data. Moreover, the FDA was concerned that the imputation method did not control for variables that could modify the outcome, such as time spent on study, or study stratification factors (i.e., region of participating site and hydroxyurea use).[61]

The FDA conducted several sensitivity analyses using different assumptions about the dropout data. Their analyses suggested that the reduction in crises from L-glutamine versus placebo ranged from 0.4 to 0.9.[61] Consequently, FDA concluded that the results show a "modest trend supporting a claim of benefit for [L-glutamine]", but noted that in some analyses, the upper limits of the confidence intervals for rate ratios comparing the treatment groups included 1.[61]

Table 4.11. Rates of Sickle Cell Crisis through Week 48 using Different Analysis Assumptions in the Phase III Trial of L-Glutamine[16,61]

Analysis set	L-Glutamine (n=132) Median (range)	Placebo (n=74) Median (range)	Rate Ratio (95% CI)
Investigator's imputation method	3 (0 to 15)	4 (0 to 15)	NR
Sensitivity analyses from FDA using Negative binomial Regression			
FDA sensitivity analysis: excludes non-completers with zero crises recorded (n=206)	3.3 (2.8 to 3.8)	4.1 (3.3 to 4.9)	0.80 (0.64 to 1.01)
ITT population assuming crisis count for non-completers with zero crises recorded was 0 (n=230)	3.3 (2.7 to 3.9)	4.2 (3.4 to 5.1)	0.77 (0.61 to 0.99)
Multiple imputation for crisis counts in non-completers with zero crises recorded, using information on treatment group, study stratification factors, time on study, baseline age, and baseline crisis count	3.9 (3.3 to 4.5)	4.3 (3.2 to 5.4)	0.91 (0.73 to 1.12)

All FDA analyses take time on study into account control for study stratification factors (region of study site and baseline hydroxyurea use)
CI: confidence interval, NR: not reported, ITT: intention to treat

The median number of days to first SCD-related acute pain crisis was an unplanned analysis in the Phase III study. The results suggested that L-glutamine delayed the time to first crisis (median 84 days [95% CI 62.0 to 109.0]) compared to placebo (median 54 days [95% CI 31.0 to 73.0]; p-value=0.0152).[16,61] The Phase II study reported a median of 64 days with L-glutamine versus 44 days with placebo (p=0.5861).[61,65]

An analysis of the incidence of ACS in the Phase III study was also unplanned but suggested a lower incidence among patients treated with L-glutamine (mean 0.1 [SD 0.37] versus 0.3 [SD 0.63] in the L-glutamine and placebo arms, respectively; 8.6% in the L-glutamine group vs. 23.1% in the placebo group experienced one or more episodes of ACS (p=0.003).[16,61] There were only two episodes of ACS in the Phase II study, so no analyses were performed.[61,65]

Hospitalization

At Week 48, the median number of SCD-related hospitalizations in the Phase III trial was lower in the L-glutamine group than the placebo group (p=0.005).[16] The trial also reported fewer days spent in the hospital, but not fewer emergency department visits (Table 4.12.). Statistically significant differences in the mean number of hospitalizations were observed at Week 24 of the Phase II study (mean [SD] 0.8 [1.2] with L-glutamine vs. 1.3 [1.4] with placebo; p=0.04] but not Week 48. The mean number of emergency room visits did not statistically differ in the Phase II trial.

Table 4.12. Health Care Utilization in Phase III Trial of L-Glutamine through Week 48[16]

	L-Glutamine (n=152)	Placebo (n=78)	p-value
No. of hospitalizations for SCD-related pain, median (range)	2 (0-14)	3 (0-13)	p=0.005
No. of ED visits for SCD-related pain, median (range)	1 (0-12)	1 (0-15)	p=0.09
Cumulative no. of days in hospital, median (range)	6.5 (0-94)	11 (0-187)	p=0.02

ED: emergency department, No.: number, SCD: sickle cell disease

Quality of Life

The Phase II trial of L-glutamine planned to evaluate pediatric quality of life as an exploratory endpoint but did not perform any analyses due to the small number of pediatric patients who were enrolled.[61,65] The Phase III trial did not assess quality of life.

Markers of Hemolysis

No significant differences were observed between groups in changes in hemoglobin, hematocrit level, or reticulocyte count in the Phase III trial of L-glutamine.[16]

Subgroup Analyses

The Phase III trial of L-glutamine performed subgroup analyses of the rate of SCD-related acute pain crises in patient groups defined by hydroxyurea use at baseline, sex, and age.[16] Due to the high level of early withdrawal from the study, and resulting uncertainties surrounding the imputation methods employed by study investigators, the FDA also analyzed the data from these subgroups by excluding the non-completers.[61] Results from both analyses are reported in Table 4.13. Overall, L-glutamine appeared to have a consistent treatment benefit across subgroups, although the rate of crises in pediatric patients (age ≤18) seemed to be similar in both treatment arms (estimated 3.3 vs 3.5 crises in the L-glutamine and placebo arms respectively).[61] A similar trend was observed in patients who received a lower dosage (analyzed by the FDA only) due to a lower body weight. Nevertheless, interaction tests to assess whether treatment efficacy differed between subgroups were not significant.

Table 4.13. Subgroup Analyses of Rate of Acute Pain Crises through 48 Weeks in the Phase III Trial of L-Glutamine

	Niihara 2018[16]		FDA[61]	
	Rate Ratio	95% CI	Rate Ratio	95% CI
Hydroxyurea Use at Baseline	0.77	NR	0.79	(0.59 to 1.06)
No Hydroxyurea Use at Baseline	0.78	NR	0.83	(0.58 to 1.21)
Male	0.73	NR	0.71	(0.50 to 1.02)
Female	0.81	NR	0.86	(0.63 to 1.17)
Age ≤18	0.93	NR	0.95	(0.69 to 1.29)
Age >18	0.64	NR	0.67	(0.48 to 0.94)
Dose <30 g/day	NR	NR	0.90	(0.66 to 1.22)
Dose 30 g/day	NR	NR	0.58	0.43 to 0.79)
2 acute pain crises in prior year	0.87	(0.58 to 1.33)	NR	NR
3-5 acute pain crises in prior year	0.74	(0.53 to 1.04)	NR	NR
≥6 acute pain crises in prior year	0.82	(0.50 to 1.34)	NR	NR

FDA: Food and Drug Administration, CI: confidence interval, NR: not reported

Harms of L-Glutamine

The majority of SAEs observed with L-glutamine were considered to be unrelated to study treatment. A greater proportion of patients treated with L-glutamine experienced gastrointestinal disorders (constipation, nausea, vomiting), headache, pain in extremities, back pain, and noncardiac chest pain. Treatment discontinuation resulting from AEs was low with L-glutamine.

A total of three treatment-emergent deaths occurred in patients treated with L-glutamine during the Phase II and Phase III trials from sudden cardiac death and/or multiorgan failure.[16,61,65] These patients had a history of organ failure and comorbidities and the investigator did not determine the deaths to be related to the study drug. The FDA concluded that the role of L-glutamine in these deaths was unlikely but in the absence of autopsy findings, there was insufficient data available to be able to categorically rule it out.[61] FDA reviewers noted that the mortality rate observed in other clinical studies of patients with SCD was like that observed in the L-glutamine trials. However, the safety data on L-glutamine from trials in other conditions provides less reassurance. The REDOXS trial of critically ill patients with multiorgan failure reported that patients treated with 0.35 g/kg/day of IV glutamine had significantly higher in-hospital mortality and mortality at 6 months than patients who did not receive L-glutamine.[66]

In the Phase III trial, SAEs occurred in 78% of patients treated with L-glutamine versus 87% of placebo-treated patients.[16] The most common SAEs in the L-glutamine arm were considered to be related to SCD rather than treatment; these included sickle cell anemia with crisis (66%), ACS (7%), and pneumonia (5%).[61] TEAEs that were considered by investigators to be related to study drug

occurred in 19% of patients treated with L-glutamine and 14% of patients treated with placebo.[61] SAEs that were deemed to be related to L-glutamine included hypersplenism (n=1), sickle cell anemia with crisis (n=1), abdominal pain (n=1), and chest pain (n=1).[61]

Discontinuation due to TEAEs was reported in 3% of the L-glutamine group and 1% of the placebo group. The most commonly reported AEs included gastrointestinal disorders (constipation, nausea, vomiting), headache, pain in extremity, back pain, and noncardiac chest pain (Table 4.14).

Table 4.14. AEs that occurred during the Phase III Trial of L-Glutamine[16]

	L-Glutamine (n=151) N (%)	Placebo (n=78) N (%)
Constipation	38 (25.2)	19 (24.4)
Nausea	34 (22.5)	13 (16.7)
Vomiting	22 (14.6)	10 (12.8)
Abdominal pain upper	16 (10.6)	6 (7.7)
Diarrhea	12 (7.9)	5 (6.4)
Chest pain (noncardiac)	21 (13.9)	7 (9.0)
Fatigue	9 (6.0)	1 (1.3)
Urinary tract infection	10 (6.6)	3 (3.8)
Pain in extremity	24 (15.9)	6 (7.7)
Back pain	20 (13.2)	5 (6.4)
Headache	32 (21.2)	14 (17.9)
Dizziness	8 (5.3)	4 (5.1)
Nasal congestion	11 (7.3)	5 (6.4)
Tachycardia	8 (5.3)	4 (5.1)

Uncertainty and Controversies

Generalizability of Patient Populations Studied

Because there are so few therapies available for patients with SCD, there may be a tendency to prescribe these three new therapies to similar patient populations. However, there are important patient subpopulations with SCD that may have different responses to each of the three therapies.

Although patients with SCD may experience their first acute pain crisis or other important clinical manifestation before their first birthday, very few children, and no infants were included in these studies. The youngest ages included in the available studies were 16 years for crizanlizumab, 12 years for voxelotor, and 5 years for L-glutamine. These inclusion criteria make it difficult to generalize results to pediatric patients with SCD, all of whom will likely experience anemia and/or pain. There are several ongoing trials of crizanlizumab and voxelotor (Appendix C), which are enrolling patients as young as 2 years of age. These trials should help to fill in some of the current knowledge gaps about the efficacy and safety of these agents in pediatric patients.

Patients in these trials differed by factors other than age. Most patients in the studies were homozygous for hemoglobin S, though a minority of patients with other genotypes such as hemoglobin $S\beta^0$ or $S\beta^+$ thalassemia, hemoglobin SC, and other variants were included. None of the trials reported details about subphenotypes. Because the majority enrollment was hbSS in the clinical trials, there are insufficient data available to determine whether the risk/benefit profile of the agents of focus differs across genotypic subpopulations.

The definition of acute pain crisis, baseline hemoglobin levels, and baseline number of pain crises also differed across studies. All of these factors are important as clinicians make prescribing decisions.

Generalizability of Results Based on "Optimal Usual Care" Control Arms

It is evident from input from clinical experts and patient advocates that the quality and intensity of "usual care" delivered to patients in the control arms of the clinical trials we reviewed was far better than the usual care received by the vast majority of patients with SCD in the US. For example, approximately 63% of patients in the RCT of crizanlizumab received hydroxyurea, whereas our best estimates of real-world usual care suggest that at most 15% are likely to receive this drug. The level of attention given to hydration, oxygenation, transfusion needs, and other clinical aspects of care was likely far higher than the norm in real-world practice. This is the primary reason we have labeled usual care in this report as "optimal usual care."

How this lack of generalizability affects the magnitude of the relative benefits of treatment with these new interventions is difficult to judge. It seems likely, however, that any bias would be to reduce the magnitude of the incremental benefits measured for patients in the intervention arms of the clinical trials. The relative reduction in acute pain crises with crizanlizumab, for example, may prove to be higher in real-world practice between those patients who receive the drug and those who do not since those who do not are not receiving the background benefits of optimal usual care. On the other hand, it is perhaps equally possible that the magnitude of the benefits of the new agent seen in the clinical trials is only realized if other elements of background care are excellent, which would tend to reduce the incremental benefits of a drug like crizanlizumab if it is given in real-world practice as an adjunct to less than optimal usual care. What is certain, however, is that the introduction of new, effective treatments for SCD serves as an opportunity for the overall care of patients with SCD to be re-imagined and improved from top to bottom.

Quality of Life

None of the trials demonstrated an improvement in quality of life based on the instruments chosen by the investigators and studies for L-glutamine did not include any measures of quality of life. This is an especially important consideration in SCD as patients and caregivers have repeatedly reported

on the devastating impact of pain on their QOL. It also calls into the question the relevance to patients of the clinical benefits observed in the trials.

Drop Out

All studies reviewed had significant rates of attrition. If drop-out rates in real-world practice are even higher than those seen in the clinical trials, which is likely, it is possible that the magnitude of longer-term benefits seen with treatment in the studies would not be realized. Some clinical experts also expressed concern that sudden withdrawal or noncompliance with voxelotor might result in a high rate of hemolysis, potentially worsening vasculopathy. Other experts reported relatively poor compliance with L-glutamine in some of their patients due to the dosing regimen. There is currently no information on how to safely discontinue any of these medications should that be necessary.

Durability of Benefits

At this time there is no data on the durability of the effects observed in the clinical trials. We do not know if positive effects will continue to be seen in patients over the course of several years or a lifetime.

Long-term Safety

All three therapies are relatively new, each with a novel mechanism of action. We lack long-term safety data and it is possible that undetected safety events will be identified over time or that the benefit/risk profile might change over time. There is also uncertainty as to which subpopulations of patients may have an increased risk of AEs. For example, some clinical experts expressed concern about a potential risk of hyperviscosity in patients with relatively high levels of hemoglobin who might be prescribed voxelotor. Other experts were concerned about the safety implications of the differential drop-out rates in the L-glutamine trial.

Combination Therapy

From a clinical perspective these therapies might be used in various combinations with hydroxyurea, chronic transfusion, and each other as they all have different mechanisms of action. Without data to help clinicians understand the optimal way to combine therapies, there is uncertainty about whether combination therapy represents an optimal approach for some patients or whether combining therapies will increase AEs (and costs) without commensurate clinical benefit.

Impact of Therapy on Acute and Chronic Outcomes and Mortality

The full clinical benefit of these therapies is unclear. Although crizanlizumab reduced acute pain crises it is unclear if the reduction seen (approximately one fewer crises per year) is enough to produce a meaningful improvement in quality of life for patients. And although acute pain crises have been associated with an increased risk of other acute and chronic conditions, it is not possible to know at this time if treatment with crizanlizumab will decrease the rates of these conditions or will improve overall survival in treated patients. For all three treatments reviewed in this report there are reasons to be optimistic about beneficial long-term effects, and our economic model has made favorable assumptions about the linkage between short-term outcomes and longer-term health benefits. Nevertheless, there remains significant uncertainty about the true magnitude of the benefits that patients will receive.

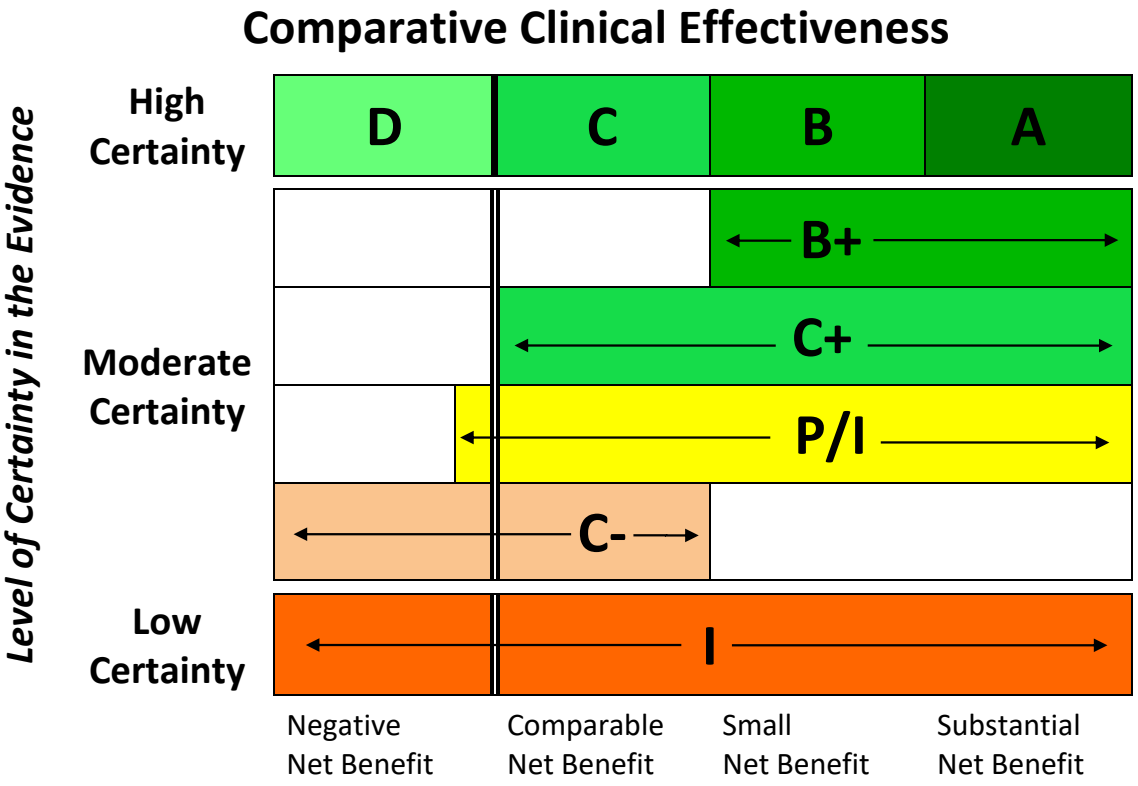
For patients treated with voxelotor there is an additional concern that adds to the uncertainty about long-term benefits: the trial result demonstrating that while hemoglobin levels were modestly increased with treatment, pain crises were not decreased, nor was there any difference in quality of life. There was also a numerically higher rate of transfusion in the treated group compared to the placebo group, a puzzling finding given that voxelotor did increase average hemoglobin levels, but one most likely due to a higher rate of pain crises among treated patients. As with crizanlizumab, there are no data on whether treatment with voxelotor will improve acute or chronic complications of SCD or increase survival.

For patients treated with L-glutamine an additional layer of uncertainty is created by the significant differential drop-out rate that saw treated patients dropping out at a higher rate than patients receiving placebo. Furthermore, the impact of L-glutamine on pain crises differed based on the imputation method used to account for those patients who dropped out. As reported in Table 4.11 the investigator's imputation method resulted in a median count of 3 crises in those treated with L-glutamine versus 4 in those treated with placebo. However sensitivity analyses conducted by the FDA systematically adjusting for non-completers, study group, stratification factors, time on study, baseline age, and baseline crisis counts resulted in a median count of 3.9 crises in those treated with L-glutamine and 4.3 in those treated with placebo, with a rate ratio of 0.91 (0.73-1.12). Other imputation methods also conducted by FDA, with fewer adjustment factors resulted in median rates in between the investigator's rates and median rates using all adjustment factors. As with crizanlizumab and voxelotor, there are no data on whether treatment with L-glutamine will improve acute or chronic complications of SCD or increase survival.

4.4 Summary and Comment

Using the ICER Evidence Matrix (Figure 4.1.), we assigned independent evidence ratings for crizanlizumab, voxelotor, and L-glutamine, each compared to optimal usual care as defined by the placebo arm of their respective clinical trials.

Figure 4.1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable"*- High certainty of a comparable net health benefit*
D = "Negative"*- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Table 4.15. ICER Evidence Ratings

Intervention	ICER Evidence Rating
Crizanlizumab	B+
Voxelotor	P/I
L-Glutamine	P/I

Crizanlizumab versus Optimal Usual Care

The primary source of evidence for our evaluation of crizanlizumab was a single Phase II trial (SUSTAIN).[17] Compared to optimal usual care, crizanlizumab statistically significantly reduced the rate of acute pain crises in patients with SCD and prolonged the time to first and second crisis. Patients treated with crizanlizumab experienced approximately one fewer pain crisis per year, from approximately 3 in optimal usual care to approximately 2 with treatment.

Although rates of acute pain crises were reduced, statistically significant improvements in the annual rate of days hospitalized and quality of life were not observed in the SUSTAIN trial. Questions about safety also remain. Crizanlizumab was relatively well-tolerated during SUSTAIN's 52-week treatment phase, however risks for long-term adverse outcomes are hard to judge, a problem common to all newly introduced treatments with a new mechanism of action. The FDA is requiring several postmarketing studies, including a clinical trial to assess the risk of infusion-related reactions and immunogenicity, bleeding complications, and infections.

Overall, we judged that the statistically significant reduction in pain crises was enough to give adequate certainty that crizanlizumab will provide a positive net health benefit. However, the difficulty in estimating the amount of longer-term organ system benefit conveyed by this relatively modest absolute reduction in acute pain crises, coupled with uncertainty about long-term safety, gives us only moderate certainty overall in the magnitude of net health benefit, which seems likely to range from small to moderate, a "B+" rating in the ICER Evidence Matrix.

Voxelotor versus Optimal Usual Care

Compared to optimal usual care alone, voxelotor improved laboratory parameters, including an increase in hemoglobin and reductions in hemolysis markers such as bilirubin and percent reticulocytes. But voxelotor did not significantly reduce the annualized incidence rate of acute pain crises and did not improve quality of life. Annualized incidence rates of acute pain crises were very similar across the voxelotor arms and placebo arms, such that the best suggestion of a trend toward improvement might be an approximate risk reduction of 13% with a confidence interval that crosses one (incidence rate ratio 0.87 [95% CI 0.61 to 1.23]); a longer duration of follow-up will be necessary to determine whether voxelotor improves this important outcome. Although the rate of acute pain crises and quality of life were secondary outcomes, they are important outcomes to

patients and linking an increase in hemoglobin levels to these or other patient-important outcomes will be helpful over time. We did not identify any data related to health care utilization for voxelotor that would indicate a reduction in transfusions. Although it seems logical to assume that for some patients there will be reductions in transfusions over time, the clinical trial reported more transfusions in the group who received voxelotor than in the placebo group.

Does an increase of 1g/dL of hemoglobin improve short or long-term health outcomes? There are reasons on both sides of this question. From some clinical experts we heard that even 1g of hemoglobin can reduce patient fatigue and likely reduce the risks for specific longer-term harms such as high-output congestive heart failure. It is also likely that some patients will get far more than the average 1g improvement in hemoglobin, and therefore benefit greatly, even though the available data do not allow us to identify the heterogeneity of treatment effect in the clinical trial.

Separate from questions about increases in hemoglobin is the extent to which reduction in hemolysis improves short or long-term outcomes. Again, some clinical experts feel there are strong correlational data to support the benefits of reduced hemolysis. For example, several studies have shown higher rates of leg ulcers, priapism, renal dysfunction, stroke and mortality with higher rates of hemolysis and hemolytic byproducts, and there may be broader clinical implications as well.[15] But on the other side of this issue lies the uncertainty of whether there is a threshold of reduced hemolysis required to achieve clinical benefit, and the short-term data available make it impossible to determine the answer to this question.

Safety issues, including rates of SAEs and treatment discontinuation due to an AE were relatively low in the HOPE trial. Further study of the long-term safety of voxelotor, however, is required.

Overall, we felt that it was difficult to ascertain the net health benefit of voxelotor with available data at its launch. Nonetheless, we feel that there is less than a 10% chance that treatment will lead to net harm over a broad population. Given that we cannot determine the magnitude of the clinical benefits but feel they are likely to be somewhat greater than usual care, we have assigned a rating of "Promising but Inconclusive" (P/I) to the comparative clinical effectiveness of voxelotor at this time.

L-Glutamine versus Optimal Usual Care

The Phase II and Phase III trials of L-glutamine showed reductions in the number of acute pain crises and hospitalizations, although these results were not robust to different analytic methods needed to account for a large and differential rate of trial withdrawal across treatment arms. This led the FDA to conclude that results trended in favor of L-glutamine but that the magnitude of benefit was likely modest.[61] L-glutamine is considered to have a relatively benign safety profile, with few SAEs in the Phase III trial determined to be related to therapy. Nevertheless, a trial of intravenously administered L-glutamine in critically ill patients (without SCD) with multiorgan failure found that L-

glutamine increased mortality. Overall, there were problems with the conduct and analyses of the available phase II and phase III trials that lead to uncertainty about the magnitude of clinical benefit as well as some *a priori* safety concerns from the use of L-glutamine in other clinical settings. Additionally, we identified two phase II trials of L-glutamine that met our inclusion criteria but for which the results were not published, raising concerns about publication bias.

Overall, we judged that the findings on clinical benefit are too uncertain to allow a clear determination of their magnitude, but it appears most likely that L-glutamine does provide some clinical benefit. However, with residual safety concerns and uncertainty about the clinical benefits due to trial limitations, we feel there remains a small risk that L-glutamine produces net harm overall, but that this risk is less than 10%. In our view, therefore, we rate the evidence on the comparative clinical effectiveness of L-glutamine to be "Promising but Inconclusive" (P/I) within the parameters of the ICER Evidence Matrix.

5. Long-Term Cost Effectiveness

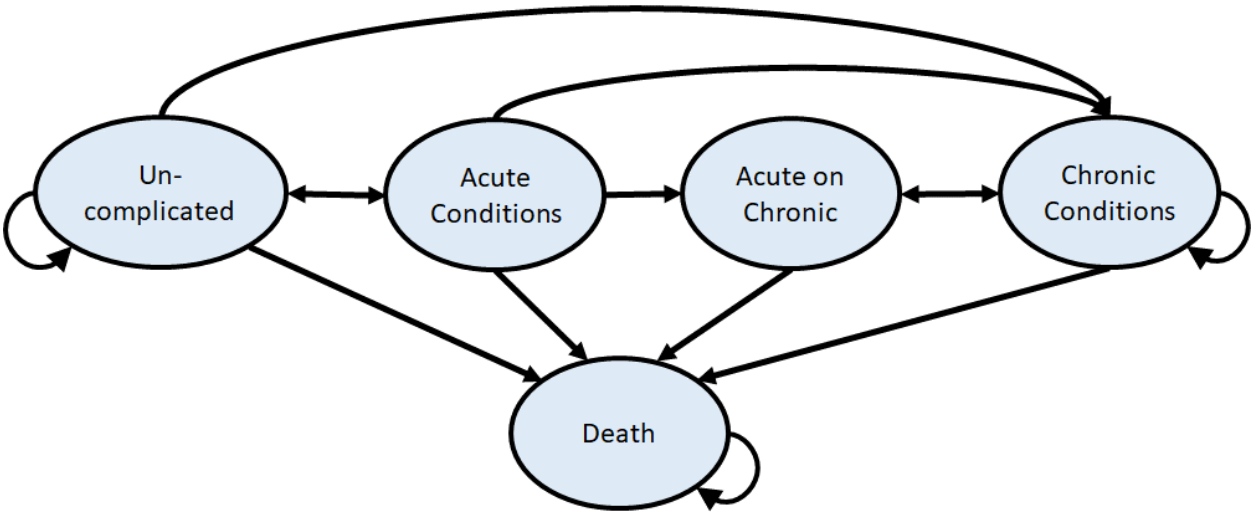
5.1 Overview

The primary aim of this analysis was to estimate the lifetime cost effectiveness of treatments for SCD using a decision analytic model. Crizanlizumab, L-glutamine and voxelotor, each combined with optimal usual care, were compared to optimal usual care alone. The model estimates outcomes that include life years gained, quality-adjusted life years (QALYs) gained, equal value life years gained (evLYGs), clinical events, pain crises avoided, change in hemoglobin, and total costs for each intervention over a lifetime time horizon. The base-case analysis used a health care sector perspective (i.e., direct medical care costs only), and a lifetime time horizon. We also modeled a variety of scenarios beyond the base case, including a modified societal perspective. (See Appendix Table E1 for an inventory of items included in the health care sector and modified societal perspective analyses.) All costs and outcomes were discounted at 3% per year.

This model focuses on improvements in both quality of life and length of life. SCD has a large impact on patients' psychosocial well-being. Many of these impacts are captured in the outcomes and measures of quality of life included in the model. It is important to note that economic models such as this one cannot capture the full psychosocial impact of systemic issues such as racism that may impact underserved populations such as patients with SCD. It is also unclear what impact treatments for these populations will have on those systemic issues, or vice versa. Further improvements from treatments for SCD that may not be captured by the model are discussed in other sections of the report.

The analytic framework for this assessment is depicted in Figure 5.1 below.

Figure 5.1. Model Framework



5.2 Methods

We developed a *de novo* decision analytic model for this evaluation, informed by the SUSTAIN trial, HOPE trial, and Niihara et al. 2018, relevant quality of life literature, and other prior economic models. The model was developed in Microsoft Excel for Office MSO (ver. 16.0.11328.20390 64-bit).

Model Structure

The model (Figure 5.1) is a cohort-level, Markov simulation of costs, quality of life, clinical events, and mortality associated with SCD among children and adults in the US diagnosed with the disease, using a 2-week cycle length. This modeling approach was chosen due to the chronic nature of disease and the multiple re-occurring events in SCD. The model focuses on transitions between acute and chronic health states, as well as including the risk of death. The acute and chronic conditions considered in the model are listed in Table 5.1. Treatments that delay or avoid acute and chronic conditions will improve patients' health and health care costs. Evidence of treatment effects on acute pain crises and level of hemoglobin come directly from the trials. The model included the impact of these treatment effects on other acute and chronic outcomes. Evidence linking the relationship between acute pain crises and levels of hemoglobin to other acute and chronic conditions come from multiple sources (detailed below), as these were not directly measured in the clinical trials. In the model, an acute pain crisis is defined similarly to the trial definitions and includes hepatic sequestration, splenic sequestration, and priapism; ACS was modelled separately.

Table 5.1. Acute and Chronic Conditions Included in the Model

Clinical Outcomes	
Ischemia-Related Outcomes	
Acute	**Chronic**
Acute Pain Episode (including hepatic sequestration, splenic sequestration and priapism)	Opioid Tolerance/Dependence
Acute Chest Syndrome	Pulmonary Hypertension
Myocardial Infarction (MI)	Heart Failure
AKI/Renal Infarction	Nephropathy, Chronic Kidney Disease
Stroke	Neurocognitive Impairment
Mortality	Mortality
Anemia-Related Outcomes	
Acute	**Chronic**
Acute Pain Episode (including hepatic sequestration, splenic sequestration and priapism)	Opioid Tolerance/Dependence
Acute Chest Syndrome	Pulmonary Hypertension
Stroke	Heart Failure
Mortality	Nephropathy, Chronic Kidney Disease
	Neurocognitive Impairment
	Fatigue
	Mortality
	Iron Overload Due to pRBCs

pRBC: packed red blood cells

Target Population

The base-case model uses the average of the median ages reported in the trials, 24 years. The proportion of females used in the model was 52%, as this was reported in both the HOPE and SUSTAIN trials. The base-case model evaluated a population with a baseline rate of 3 acute pain crises per year. Prevalence of chronic conditions was estimated by using the Markov model to simulate a cohort of patients from birth to the starting age of the analysis. For instance, to estimate the prevalence of each chronic condition at age 24 years, the Markov model was run from birth for 24 years, and the proportion of patients in each chronic condition at 24 years was reported and then used in the base-case analysis. In scenario analyses, we explored results for younger populations, beginning treatment at age 16. We also include subgroup analyses based on frequency of acute pain crises. The demographic and clinical characteristics of the patient population for our analyses are summarized and compared to those reported in the trials in Table 5.2.

Table 5.2. Base-Case Model Cohort Characteristics

	Model Inputs for Base Case	Standard of Care in SUSTAIN trial[17]	Standard of Care in HOPE trial[59]	Standard of Care in Niihara 2018 trial[16]
Age at enrollment	24	16	12	5
Median age (years)		29	24	19
Female, %	52	52	64	52
Frequency of Acute Pain Crises (per year)	3	2.98	3.19	4.3
Prevalence of Chronic Conditions				
Opioid Tolerant/Dependent (per 1000)	18	NR	NR	NR
Pulmonary Hypertension (per 1000)	342	NR	NR	NR
Heart Failure (per 1000)	130	NR	NR	NR
Chronic Kidney Disease (per 1000)	214	NR	NR	NR
Post-stroke (per 1000)	243	NR	NR	NR
Neurocognitive Impairment alone (per 1000)	63	NR	NR	NR
Fatigue alone (per 1000)	285	NR	NR	NR

NR: not reported

Treatment Strategies

The list of treatment strategies was developed with input from patient organizations, clinicians, manufacturers, and payers, and were chosen to optimal reflect real-world treatment decisions and those in the clinical trials. The list of interventions is presented below:

- Crizanlizumab in addition to optimal usual care
- Voxelotor in addition to optimal usual care
- L-glutamine in addition to optimal usual care

In the main analysis each intervention is compared to optimal usual care, which can include hydroxyurea and/or acute and chronic transfusions. As noted previously, optimal usual care here is meant to correspond to the treatment received in the comparator arms of the trials, and may differ from the care received by many patients in actual practice.

Doses for each treatment used in the model are shown in Table 5.3. Given that some of the treatments are weight-based, the doses of treatments change over time as the modeled population ages and the average weight increases.

Table 5.3. Treatment Regimen Modeled Dosages

Generic Name	Crizanlizumab	Voxelotor	L-glutamine
Brand Name	Adakveo	Oxbryta	Endari
Generic Name	Crizanlizumab	Voxelotor	L-glutamine
Manufacturer	Novartis	Global Blood Therapeutics	Emmaus Life Sciences
Route of Administration	Intravenous	Oral	Powder, for oral solution
Dosing	5.0 mg/kg, administered at weeks 0, 2, and then every 4 weeks	1500 mg, once daily	5-15 grams, twice daily

mg: milligram, kg: kilogram

Key Model Characteristics and Assumptions

Key model assumptions are listed in Table 5.4, along with the rationale for each. In general, where there was uncertainty in the evidence, we made assumptions that tended to favor the treatments.

Table 5.4. Key Model Assumptions

Assumptions	Rationale
Risk factors were multiplicative, i.e. risk factors were multiplied together to estimate a combined risk factor.	To estimate the likelihood of an event for those with multiple risk factors and to avoid the probability of an event being greater than 1.
Health-related quality of life is multiplicative.	To estimate the health-related quality of life of patients with multiple health states, it is recommended that a multiplicative assumption is used to reflect overlap in symptoms and to avoid implausibly low quality of life estimates.
All discontinuation occurs within the first year of treatment.	The trials report discontinuation at 48 or 52 weeks. It is assumed that patients that stay on treatment for 1 year will remain on treatment.
Opioid tolerance or dependence was only possible after patients had experienced 3 acute pain crises.	This assumption was instituted to recognize a potential consequence of the accumulation of acute pain crises.
The effects of baseline treatment (i.e., chronic transfusion, hydroxyurea, chelation therapy, etc.) were assumed to be captured in the optimal usual care population.	Treatment rates in the source population used for optimal usual care were similar to those for populations reported in the literature.
Treatment-related adverse events were treated with a physician visit, but were not modeled as having a significant effect on the health-related quality-of-life.	Treatment-related adverse events reported in the trials were expected to be transitory and treatable with over-the-counter medication or a visit to the physician.
Model results represent a mixed genotype population.	Model inputs are not available from data and published literature by genetic mutation. Treatment effects from the trials are representative of a mixed genotype population.

Model Inputs

Clinical Inputs – Use of Real-World Data

A comprehensive literature review was undertaken to identify baseline rates of acute and chronic conditions of interest for the comparative cost-effectiveness model. Since the majority of patients with SCD receive health care coverage under Medicaid and/or Medicare, baseline rates were taken from CMS data when possible. The CMS report[67] summarized all patients with SCD over the age of 18 years with Medicare coverage as well as dual Medicaid and Medicare coverage.

Rates for baseline conditions of interest not available through CMS data reports, incidence rates of acute and chronic conditions in the model, and actual costs of both acute and chronic events were obtained through *de novo* evidence generation from a series of analyses using the Aetion Evidence Platform on a MarketScan claims dataset using the most recent data available, from Dec 31, 2002 to Dec 31, 2017. The Truven MarketScan databases capture longitudinal, individual-level administrative claims data from the United States. The data available for this study included the Commercial Claims and Encounters (CCAE) Database and Medicare Supplemental and Coordination of Benefits Database, IBM MarketScan Research Databases for Life Sciences Researchers.[68](See Appendix F for full study protocol). Data from the Truven MarketScan database covered approximately one-third of patients in the US with SCD and demonstrated a patient geographic distribution across the US in a similar pattern to the CMS data.

Baseline annual rates of acute and chronic events used in the model are presented in Tables 5.5 through 5.9 below. Inputs not available from the CMS report or MarketScan data were obtained from the literature.

Table 5.5. Baseline Rates of Acute Chest Syndrome by Age

Age	Mean	Lower	Upper	Source[68]
0-1	0.075	0.07	0.09	MarketScan
2-4	0.101	0.09	0.12	MarketScan
5-12	0.107	0.10	0.11	MarketScan
13-17	0.092	0.09	0.11	MarketScan
18+	0.051	0.049	0.053	MarketScan

Table 5.6. Baseline Rates of Stroke by Age*

Age	Mean	Lower	Upper	Source[68]
0-1	0.005	0.00	0.01	MarketScan
2-5	0.007	0.00	0.01	MarketScan
6-9	0.010	0.008	0.012	MarketScan
10-19	0.011	0.01	0.02	MarketScan
20+	0.021	0.020	0.023	MarketScan

*It was assumed that 35% of strokes would be major strokes resulting in more severe outcomes and higher costs.

Table 5.7. Baseline Rates of Myocardial Infarction by Age

Age	Mean	Lower	Upper	Source[68]
0-12	0.000	0.000	0.000	MarketScan
13-17	0.0009	0.0004	0.0017	MarketScan
18+	0.0069	0.0062	0.0077	MarketScan

Table 5.8. Baseline Rates of AKI/Renal Infarction by Age

Age	Mean	Lower	Upper	Source[68]
0-17	0.000	0.000	0.000	MarketScan
18+	0.0006	0.0004	0.0009	MarketScan

Table 5.9. Baseline Chronic Complication Risks

Complication	Mean	Source
Opioid tolerance/dependence*	0.011	Elander et al. 2003[69]
Neurocognitive impairment	0.04	Schatz et al. 2001[70]
Fatigue	0.18	Vichinsky et al. 2019[59]
Pulmonary hypertension		
Age 0-1	0.0176	CMS 2016[71]
Age 2-4	0.0176	
Age 5-12	0.0176	
Age 13-17	0.0176	
Age 18-30	0.0176	
Age 31-45	0.0609	
Age 46-54	0.1598	
Age 55-64	0.2018	
Age 65+	0.2289	
Heart failure		
Age 0-1	0.0033	MarketScan[68]
Age 2-4	0.0035	MarketScan[68]
Age 5-12	0.0022	MarketScan[68]
Age 13-17	0.0075	MarketScan[68]
Age 18-30	0.0075	MarketScan[68]
Age 31-45	0.0320	CMS 2016[71]
Age 46-54	0.0772	
Age 55-64	0.0785	
Age 65+	0.0632	
Nephropathy, CKD		
Age 0-1	0.0038	MarketScan[68]
Age 2-4	0.0035	MarketScan[68]
Age 5-12	0.0077	MarketScan[68]
Age 13-17	0.0143	MarketScan[68]
Age 18-30	0.0143	MarketScan[68]
Age 31-45	0.0381	CMS 2016[71]
Age 46-54	0.0945	
Age 55-64	0.1015	
Age 65+	0.0974	

*Opioid tolerance/dependence was estimated for patients that had experienced 3 or more acute pain crises in a year.

Risk Factors and Correlations Between Conditions

An attempt was made to capture the risks of the different acute and chronic conditions. This was considered particularly important due to the multifaceted nature of the disease. Where available in the published literature, risk factors correlating each of the conditions were included in the model, as shown in Table 5.10. Much of the data demonstrated associations between conditions, rather than causation. In the base-case model, we made the assumption that these correlations would be causative to model the potential benefit of these treatments beyond the outcomes reported in the trials.

Table 5.10. Risk Factors for Acute and Chronic Conditions

Determinant	Consequence	Relative Effect	Source
Pulmonary hypertension	Acute Chest Syndrome	1.74	Agarwal et al. 2018[72]
Pulmonary hypertension	AKI/Renal infarction	1.70	Yeruva et al. 2016[73]
Nephropathy/CKD	AKI/Renal infarction	2.00	Yeruva et al. 2016[73]
Heart failure	AKI/Renal infarction	1.70	Yeruva et al. 2016[73]
Nephropathy/CKD	Myocardial infarction	2.26	Kokubo et al. 2009[74]
Pulmonary hypertension	Stroke	2.52	Agarwal et al. 2018[72]
Nephropathy/CKD	Stroke	1.25	Lee et al. 2010[75]
AKI/Renal infarction	Nephropathy/CKD	3.00	Yeruva et al. 2016[73]
Myocardial infarction	Heart Failure	2.67	Tofovic et al. 2017[76]

AKI: acute kidney injury, CKD: chronic kidney disease

For example, pulmonary hypertension and chronic kidney disease are correlated with, and are considered in the model as risk factors for, stroke. In the model, those with pulmonary hypertension were 2.52 times more likely to experience stroke, those with CKD were 1.25 times more likely to experience a stroke. To estimate the likelihood of an event for those with multiple risk factors, we assumed that the risk was multiplicative, i.e., risk factors were multiplied together to estimate a combined risk factor.

The above risk factors were applied to the baseline rates previously reported. The use of these risk factors resulted in a population similar to that reported by CMS in 2016[67] (see the validation section below).

Mortality Probabilities

Annual mortality probabilities were estimated from Hassell et al. 2010 (Appendix Table E2). The model allows for increases in mortality due to acute pain crises, ACS, myocardial infarction, AKI/renal infarction, pulmonary hypertension, heart failure, chronic kidney disease, and stroke. To risk adjust the mortality probabilities for each additional risk factor in the model, the age-specific estimates from the literature were divided by the risk of death from each of the chronic conditions.

$$\frac{Death\ Age}{(pHTN_{RF} \times HF_{RF} \times CKD_{RF})}$$

pHTN: pulmonary hypertension, HF: heart failure, CKD: chronic kidney disease, RF: risk factor for death

The annual relative effect of acute pain crises was found to range from 1.2 to 2.68[77-79] and ACS from 1.03 to 1.5[79,80] (Table 5.11). A relative effect of 1.2 was used for acute pain crises, as it best represented the annual risk of death per event. Using the baseline annual risk of death estimated from Hassell et al. 2010, the annual risk was converted to a 2-week risk to reflect the cycle length of the model. This conversion means that deaths that would really happen over the year occur in the model during the two-week cycle in which the acute pain crisis occurs; this has the effect of decreasing life-expectancy after an acute pain crisis. The same conversion was used for ACS using the average of the two published risk factors. There is also an increased probability of death included in the model for those who experience a stroke. In the first two weeks after a stroke there is a 0.074 probability of death. No published risk factors were found for heart failure or myocardial infarction in patients with SCD, so it was assumed that these risk factors were the same as for pulmonary hypertension. The results of combining these data are reported in the validation section below.

Table 5.11. Risk Factors for Death

Complication	Relative Effect	Source
Acute pain crisis	1.2	Darbari et al. 2013[78]
Acute chest syndrome	1.27	Average of Platt et al. 1994 and Maitra et al. 2017[79,80]
Myocardial infarction	12.57	Assumption
AKI/Renal infarction	9.57	Lanzkron et al. 2013[81]
Pulmonary hypertension	12.57	Gladwin et al. 2012[82]
Heart failure	12.57	Assumption
Nephropathy, CKD	9.57	Lanzkron et al. 2013[81]

AKI: acute kidney injury, CKD: chronic kidney disease

Risk factors for death are applied during each cycle that a patient is considered to have the health state. Once a chronic condition occurs, the patients will have it for life, so the risk factor is applied in every cycle for the rest of their life. For acute conditions, they are applied for the cycle in which the acute condition occurs, but then patients go back to having the baseline probability of death. This mean that when a patient with heart failure has a myocardial infarction, they have the risk factor for both myocardial infarction and heart failure for that cycle and then go back to having only the heart failure risk.

Treatment Effect

We used treatment effects from the clinical trials (Table 5.12). Each trial reported the relative effect of treatment on acute pain crises. In the base-case analysis, the reported magnitude of effect for voxelotor was used, although the trial results were not statistically significant. The relative effect on acute pain crisis was used directly in the model. Despite the lack of information of treatment effect on other outcomes of interest, we assumed that acute events and chronic conditions could also be impacted by reducing the number of acute pain crises. Voxelotor was the only treatment to report a statistically significant difference in hemoglobin. The model was programmed to also allow for the effect of changes in hemoglobin on risk for acute and chronic conditions. The relative effect of hemoglobin level on stroke, fatigue, chronic kidney disease, and pulmonary hypertension were obtained from the literature and included in the model.

Table 5.12. Treatment Effects

Treatments	Relative Effect on Acute Pain Crises	Change in Hemoglobin (g/dL)	Source
Crizanlizumab	0.547	0	SUSTAIN trial[17]
Voxelotor	0.868	1.2	HOPE trial[59]
L-glutamine	0.910	0	FDA Multiple Imputation Analysis[61]

g/dL: grams per deciliter

The effect of acute pain crises on acute events and chronic conditions were found in the literature, and are shown in Table 5.13. For example, patients who experience an acute pain crisis are 58.67 times more likely to have an ACS in the next cycle and patients who experience an acute pain crisis are 4.12 time more likely to develop pulmonary hypertension in the next cycle.

Table 5.13. Acute Pain Crisis as a Risk Factor for Acute and Chronic Conditions Used in the Model

Treatments	Risk Factor Used in Model	Source
Acute Events		
Acute chest syndrome	58.67	Shah et al. 2019[77]
Myocardial infarction	3.00	Bode-Thomas 2011[83]
AKI/Renal infarction	3.00	Assumption
Stroke	2.26	Shah et al. 2019[77]
Chronic Conditions		
Pulmonary hypertension	4.12	Shah et al. 2019[77]
Heart Failure	1.185	Van Tuijn et al. 2010[84]
Nephropathy, CKD	1.185	Van Tuijn et al. 2010[84]

AKI: acute kidney injury, CKD: chronic kidney disease

The relative effect of hemoglobin level on stroke and fatigue were obtained from the literature and included in the base case of the model. The reported difference of 1.2 g/dL for voxelotor was used

in the model. It was assumed there would be a constant treatment effect as long as patients continued to use voxelotor, i.e., that patients maintained a 1.2 g/dL effect as long as they continued treatment. To estimate the effect of 1.2 g/dL change in hemoglobin, the effect size was assumed to be exponential:

$$RE^H = 0.602^{1.2} = 0.544$$

where RE is the relative effect reported in the literature and H is the hemoglobin difference reported in the trial (Table 5.14).

There was mixed evidence on the relation between hemoglobin level and chronic kidney disease and pulmonary hypertension. One study suggested that lower hemoglobin was associated with hyperfiltration; however no data were reported.[85] Another study showed no difference in hemoglobin levels between patients with normoalbuminuria and those with micro- or macroalbuminuria.[86] Mixed results were reported on the association of hemoglobin and eGFR.[87] Derebail et al. used a multiregression analysis and reported that a 1 g/dL increase in hemoglobin was associated with 0.64 odds of chronic kidney disease in hemoglobin SC disease and sickle-β+-thalassemia but no effect in homozygous SCD or sickle-β0-thalassemia.[88] To capture the possibility of an effect on chronic kidney disease, we assumed that a 1 g/dL increase in hemoglobin would decrease the risk of chronic kidney disease by a factor of 0.64. Adjusted for a 1.2 g/dL increase, this resulted in a risk factor of 0.56.

We also explored the effect of hemoglobin changes on pulmonary hypertension. Generally, studies evaluated the difference between those with less than 2.5 m/s tricuspid regurgitant jet velocity and those with 2.5 or more. Four studies showed no statistically significant differences in average hemoglobin between groups.[89-92] One study found that for every 1.0 g/dL increase in hemoglobin, TRV decreased by 13%.[93] To capture the possibility of an effect on pulmonary hypertension, we used the results of a meta-regression which reported a 1% (95%CI, -8% to 6%) higher prevalence of tricuspid regurgitant velocity of 2.5 m/s or greater. This 1% difference was reported for a population with an average age of 22 years, so an annual difference was estimated by assuming the difference would accumulate over the 22 years and then be constant for a patient's life.

Table 5.14. Effects of a 1 g/dL Change in Hemoglobin

Condition	Relative Effect	Effect for Voxelotor Used in Model	Source
Stroke	0.602	0.544	Ohene-Frempong et al. 1998[94]
Fatigue	0.06	0.034	Vichinsky et al. 2019[59]
Nephropathy, CKD	0.62	0.56	Derebail et al. 2019[88]
	Reduction in Annual Probability	Effect for Voxelotor Used in Model	Source
Pulmonary hypertension	0.0005	0.0006	Caughey et al. 2015[89]

CKD: chronic kidney disease

AEs

We included serious treatment-related adverse events in the model as reported in the respective clinical trials (Table 5.15). Each AE was assumed to require a physician visit at a cost of $175 per visit, based on the cost of a level 5 physician visit. We did not model any quality of life impacts due to AEs, as these were generally transitory.

Table 5.15. Treatment-Related Adverse Events

Treatment	Treatment-related Adverse Events	Comment	Source
Crizanlizumab	0.15	Annual rate of serious AEs during the trial	Kutlar et al. 2019[58]
Placebo arm of SUSTAIN trial	0.05		
Voxelotor	0.034	Proportion of patients that experienced a serious AE during the trial	Vichisky et al. 2019[59]
Placebo arm of HOPE trial	0.011		
L-glutamine	0.021	Proportion of patients that experienced a severe AE during the trial	L-Glutamine Sponsor Briefing Document[95]
Placebo arm of trial	0.018		

AE: adverse event

Utilities

A systematic literature review was undertaken to investigate data on the health-related quality of life for patients with SCD. Much of the literature was collected on patients from the United Kingdom. Where possible values from the US were prioritized for use in the model; however, US and UK values were generally similar.

Utilities were applied to the proportion of the cohort in each health state in the model. For example, an otherwise healthy patient who experienced ACS would have a utility of 0.581 for the 2-week cycle that they experienced ACS. In the base-case for patients experiencing multiple conditions, it was assumed that utilities were multiplicative. For example, a patient with opioid tolerance or dependence would have a utility of 0.64, but during an ACS the utility would be 0.64 X

0.581 = 0.37. Alternatively, an additive assumption can be made; using the reported disutilities, this would result in the same patient having a utility of 0.64 – 0.129 = 0.51. The additive assumption was tested in a sensitivity analysis.

Anie et al. 2012 reported utilities for acute pain crisis at admission to hospital, discharge and 1 week after discharge. We assumed that patients experiencing an acute pain crisis would have the admission utility for 1 week and the discharge utility for 1 week.

Table 5.16. Utility Estimates for Health States

Health State	Model Utility	Model Disutility	Source Value	Source
Uncomplicated SCD	0.71		0.71	NICE CG 143[96]
Acute pain crisis (admission)	0.35	0.36	0.39	Anie et al. 2012 [97]
Acute pain crisis (discharge)	0.61	0.1	0.65	
Acute pain crisis (1 week follow-up)			0.75	
Two-week crisis assuming 7 days of severe pain (admission) and 7 days of less severe pain (discharge)*	0.48	0.23		Calculated
Acute chest syndrome	0.581	0.129	0.56	NICE CG 143[96]
Myocardial infarction	0.581	0.129	0.129	Clarke et al. 2002 [98]
AKI/Renal infarction	0.581	0.129		Assumption
Stroke (major)	0.145	0.565	0.565	NICE CG 143[96]
Stroke (minor)	0.548	0.162	0.162	
Post-stroke based on the proportion of major stroke (0.35)	0.407	0.303		Calculated
Opioid tolerance/dependence	0.64	0.07	0.07	Krebs et al. 2018 [99]
Pulmonary hypertension	0.59	0.12		Assumption
Heart failure	0.589	0.121	0.121	Clarke et al. 2002 [98]
Nephropathy, CKD	0.575	0.135	0.135	Villeneuve et al. 2016 [100]
Neurocognitive impairment	0.68	0.03	0.03	Stites et al. 2018 [101]
Fatigue	0.59	0.12	0.12	Naess et al. 2012 [102]

AKI: acute kidney injury, CKD: chronic kidney disease, SCD: sickle cell disease

*The model allows for the length of severe pain to be adjusted, currently it is assumed to be 7 days.

Economic Inputs

Drug Acquisition Costs

We obtained the list prices for crizanlizumab and L-glutamine.[103] The reported list price of voxelotor (Oxbryta) is $10,417 per month, based on online reports.[104]

We applied estimated branded drug discount rates to obtain net pricing estimates. Because crizanlizumab and voxelotor were recently approved, there are no data on net price available yet.

Because net prices are not yet known, we used the average branded drug discount in the US of 27% as an estimate of these drug's net prices.[105] Net price data for L-glutamine were not available in the SSR net price database,[106] so we used the FSS price as the net price for this drug.[107] As part of optimal usual care, we used the average of generic prices for hydroxyurea.

Table 5.17. Drug Costs

Drug	WAC per Package/Vial	Discount From WAC	Net Price Per Package/Vial	Net Price per Year§
Crizanlizumab (Adakveo®)	$2,357/vial	27%	$1,721	$120,470
Voxelotor (Oxbryta®)	$10,417	27%	$7,604	$99,197
L-glutamine (Endari®)*	$1,110/package	26%	$823.88†	$30,092
Hydroxyurea‡	$88.05/100 capsules	--	--	$322 - $2,251

NA: not available, WAC: wholesale acquisition cost
*Price per package of 60 5g packets
†Federal Supply Schedule (FSS) price as of November 2019
‡Average of generic prices for 100 500mg oral capsules
§1 year = 365.25 days or 52 weeks

Non-Drug Costs

As described above, actual costs of both acute (Table 5.18) and chronic (Table 5.19) events were obtained through *de novo* evidence generation from a series of analyses using the Aetion Evidence Platform on a Marketscan claims dataset using the most recent data available, from Dec 31, 2002 to Dec 31, 2017. The Truven MarketScan databases capture longitudinal, individual-level administrative claims data from the United States. The data available for this study included the Commercial Claims and Encounters (CCAE) Database and Medicare Supplemental and Coordination of Benefits Database. (See Appendix F for full study protocol).

Table 5.18. Cost per SCD Complication

Incremental Cost in the Year of Event/Diagnosis (per Event)	Estimate	SD	Source
Acute Pain Crisis			
Age < 18	$12,980	$33,604	MarketScan[68]
Age ≥ 18	$13,735	$24,576	MarketScan[68]
Acute Chest Syndrome			
Age < 18	$22,701	$24,332	MarketScan[68]
Age ≥ 18	$29,896	$49,104	MarketScan[68]
Myocardial infarction	$53,458	$81,781	MarketScan[68]
Acute kidney injury/Renal infarction	$8,205	NR	Yeruva et al. 2016[73]
Stroke			
Age < 18	$129,956	$243,770	MarketScan[68]
Age ≥ 18	$57,780	$94,745	MarketScan[68]

NR: not reported

Table 5.19. Annual Cost of Chronic Complications

	Estimate	(95% CI)	Source
Pulmonary hypertension	$19,343	(10,697, 27,989)	MarketScan[68]
Heart failure	$32,505	(21,405, 43,605)	MarketScan[68]
Nephropathy, CKD	$20,708	(13,947, 27,468)	MarketScan[68]
Neurocognitive impairment	$11,687	(1,430, 21,944)	MarketScan[68]
Fatigue	$4,398	(588, 8,208)	MarketScan[68]
Post-stroke	$9,807	NR	MarketScan[68]
Opioid tolerance/dependence	$17,345	(-1,151, 35,841)	MarketScan[68]

CI: confidence interval, CKD: chronic kidney disease, NR: not reported

According to the MarketScan data, 11% to 29% of patients are on chronic transfusion and up to 5 in 10,000 experience iron overload, depending on their age. Age-specific proportions were used to calculate chronic transfusion costs using the annual cost of chronic transfusion from Blinder et al. 2013 and iron overload costs using costs calculated from the MarketScan data (Table 5.20).

Table 5.20. Other Health Care Cost Parameters

	Estimate	Lower (-20%)	Upper (+20%)	Source
Physician Visit	$175	$140	$210	Level 5 Physician Visit
Transfusion Cost (per year)	$36,305	$29,044	$43,566	Blinder et al. 2013 [108]
Iron Overload (per event)	$9,137	$7,309	$10,964	MarketScan Data[68]

Model Analysis

The model estimated the average survival, quality-adjusted survival, drug cost, complication cost, and number of acute complications per patient. Time spent in each health state was summed to provide estimates of life expectancy and quality-adjusted life expectancy. Long-term estimates of costs, QALYs, evLYG, and LYs were discounted at 3% per year. A more detailed description of the evLYG calculations can be found in Appendix E. We calculated the incremental results for each intervention versus optimal usual care alone as the incremental cost per LY, evLYG, and QALY, and also the incremental cost per pain crisis avoided and per 1 g/dL increase in hemoglobin.

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be performed by jointly varying all model parameters over the minimum numbers of simulations necessary to achieve

statistical convergence, then calculating 95% credible range estimates for each model outcome based on the results.

Scenario Analyses

A modified societal perspective will be applied to the base case, using components such as out-of-pocket costs, productivity losses, caregiver HRQoL, and school attendance. This analysis will be completed using data from a survey being conducted by ICER and Sick Cells, scheduled to be complete by February 12th, 2020.

Two scenario analyses have been provided to demonstrate the cost-effectiveness of treatments in different populations. The first population had a higher pain crisis rate, with a baseline of 10 acute pain crises per year. The second population reflects a younger cohort, using the starting age of 16 years, the minimum age for which crizanlizumab is indicated. We also performed threshold analyses to determine drug prices that would achieve a range of incremental cost-effectiveness ratios (from $50,000 to $150,000 per QALY).

Model Validation

We used several approaches to validate the model. First, we shared preliminary methods, inputs, and model assumptions with manufacturers, patient groups, and clinical experts. Based on feedback from these different groups on our methodology and calculations, we refined our approach and data inputs used in the model, as relevant. Second, we varied model input parameters to evaluate face validity of changes in results. Third, we performed model verification for model calculations using internal reviewers. Fourth, we compared results to other cost-effectiveness models in this therapy area. Finally, following publication of this draft report, we will share the model with the manufacturers for a review period of three weeks. Feedback from review of the model and draft report will be considered when revising the draft report.

5.3 Results

Base-Case Results

All base-case results shown here are discounted at 3% for both costs and outcomes. (Undiscounted results for each drug are shown in Appendix Tables E3-E5.) The base-case results show the life-time costs for a patient on optimal usual care from age 24 are approximately $1.1 million. The model estimates that optimal usual care patients with a baseline risk of 3 acute pain crises per year are expected to experience 46 acute pain crises over their lifetime. Not all patients will have a myocardial or AKI/renal infarction or stroke; the model estimates a rate of 15 per 100 myocardial infarctions, 2 per 100 AKI/renal infarctions, and 61 per 100 with stroke. Patients with SCD on optimal usual care are predicted to live to 45 years old, which when discounted at 3% per year equates to approximately 15 additional life-years, 8 additional evLYG, and 8 additional QALYs. Each treatment below is compared to the same optimal usual care.

Treatment costs for crizanlizumab are approximately $1.2 million over the lifetime, with cost-savings of approximately $115,000 from avoided acute and chronic conditions (Table 5.21). Cost off-sets are due to avoiding costs of acute and chronic conditions, which are lower for patients on crizanlizumab than with optimal usual care alone. However, these cost off-sets are attenuated by the additional costs of longer life with costly chronic conditions. The model estimates that crizanlizumab patients will experience 29 acute pain crises over their lifetime and have fewer episodes of ACS, myocardial infarction, AKI/renal infarction and stroke (Table 5.21). Patients on crizanlizumab are expected to live to 50 years old, with approximately 2.3 life-years gained, 2.0 evLYG, and 0.85 QALYs gained compared to optimal usual care. Incremental cost-effectiveness of crizanlizumab compared to optimal usual care is estimated to be $444,000 per life year (LY) gained, $520, 000 per evLYG and $1.2 million per QALY gained.

Table 5.21. Results for the Base Case for Crizanlizumab versus Optimal Usual Care Alone

Treatment	Optimal Usual Care	Crizanlizumab	Difference	ICER	
Treatment Cost	-	$1,150,000	$1,150,000	-	
Other Cost	$1,145,000	$1,030,000	-$115,000	-	
Total Cost	$1,145,000	$2,180,000	$1,035,000	-	
Acute Pain Crises	45.56	28.75	-16.81	$62,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
Life-years	15.19	17.52	2.33	$444,000	per LY gained
evLYG	7.64	9.64	1.99	$520,000	per evLYG gained
QALYs	7.64	8.50	0.85	$1,212,000	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year

Treatment costs for voxelotor are approximately $1.3 million over the lifetime (Table 5.22). The model estimates that voxelotor patients will experience 44 acute pain crises over their lifetime (Table 5.22), and have fewer episodes of ACS, myocardial infarction, AKI/renal infarction and stroke. Patients on voxelotor also experience an average increase in hemoglobin levels of 1.2 g/dL. Given the assumption that rises in hemoglobin with voxelotor produce benefits analogous to higher hemoglobin levels in other settings, this results in patients on voxelotor having the fewest stroke events over their lifetime, 38 per 100 patients. Patients on voxelotor are expected to live to 50 years old, with approximately 2.1 life-years gained, 1.9 evLYG, and 0.96 QALYs gained compared to optimal usual care. Incremental cost-effectiveness of voxelotor compared to usual care is estimated at approximately $600,000 per LY gained, $650,000 per evLYG, and $1.3 million per QALY gained. Note that these results rely on the inclusion of several assumptions that tended to favor the treatment. Despite the lack of information of treatment effect on other outcomes of interest, we assumed that acute events and chronic conditions would be impacted by the (non-significant) reduction in number of acute pain crises, and that there was an effect of changes in hemoglobin on risk for acute and chronic conditions including stroke, fatigue, chronic kidney disease, and pulmonary hypertension.

Table 5.22. Results for the Base Case for Voxelotor versus Optimal Usual Care Alone

Treatment	Usual Care	Voxelotor	Difference	ICER	
Treatment Cost	-	$1,260,000	$1,260,000	-	
Other Cost	$1,209,000	$1,214,000	$4,000	-	
Total Cost	$1,209,000	$2,474,000	$1,264,000	-	
Acute Pain Crises	45.56	43.86	-1.70	$742,000	per acute pain crisis avoided
Hemoglobin (g/dL)	-0.10	1.10	1.20	$61,000	per g/dL per year
LYs	15.19	17.30	2.11	$600,000	per LY gained
evLYG	7.64	9.59	1.94	$651,000	per evLY gained
QALYs	7.64	8.60	0.96	$1,321,000	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year

* It is assumed that patients on voxelotor maintain the 1.2 g/dL hemoglobin improvement throughout their life. This number is the total incremental cost divided by the improvement in hemoglobin divided by life-expectancy or the number of years it is assumed the improvement will be maintained. This represents the cost of improving an individual's hemoglobin by 1g/dL each year.

Treatment costs for L-glutamine are approximately $302,000 over the lifetime, with cost-savings of approximately $23,000 from avoided acute and chronic conditions (Table 5.23). The model estimates that L-glutamine patients will experience 42 acute pain crises over their lifetime and have fewer episodes of stroke (Table 5.23). Patients on L-glutamine are expected to live to 46 years old,

with approximately 0.29 life-years gained, 0.33 evLYG, and 0.10 QALYs gained compared to optimal usual care. Incremental cost-effectiveness of L-glutamine compared to usual care is estimated to be approximately $965,000 per LY gained, $847, 000 per evLYG, and $2.7 million per QALY gained.

Table 5.23. Results for the Base Case for L-glutamine versus Optimal Usual Care Alone

Treatment	Usual Care	L-glutamine	Difference	ICER	
Treatment Cost	-	$302,000	$302,000	-	
Other Cost	$1,145,000	$1,121,000	-$23,000	-	
Total Cost	$1,145,000	$1,423,000	$278,000	-	
Acute Pain Crises	45.56	42.25	-3.31	$84,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
LYs	15.19	15.48	0.29	$965,000	per LY gained
evLYG	7.64	7.97	0.33	$847,000	per evLY gained
QALYs	7.64	7.75	0.10	$2,717,000	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year

Table 5.24 reports the life-time discounted acute events. In all cases patients with optimal usual care alone are more likely to experience an acute event. Patients on crizanlizumab experience the fewest acute pain crises, ACS, MI and renal infarction events. This is because of the large treatment effect of crizanlizumab on acute pain crises and the relative effect of acute pain crises on each of the other acute events in the model. Patients on voxelotor experience the fewest stroke events because of the relative effect of improvements in hemoglobin on strokes, with smaller impacts on other events.

Table 5.24. Comparison of Acute Events

Treatment	Optimal Usual Care	Crizanlizumab	Voxelotor	L-glutamine
Acute Pain Crisis	45.56	28.75	43.86	42.25
ACS	0.99	0.75	0.93	0.99
MI	0.151	0.124	0.147	0.151
RI	0.022	0.020	0.021	0.022
Stroke	0.61	0.51	0.38	0.61

ACS: acute chest syndrome, MI: myocardial infarction, RI: renal infarction

Table 5.25 reports the prevalence of chronic diseases accounted for in the model at different ages. These results suggest crizanlizumab improves pulmonary hypertension after age 24 and heart

failure and CKD until after 50 years of age. Voxelotor improves pulmonary hypertension, chronic kidney disease, and heart failure until after 50 years of age. L-glutamine has no effect on pulmonary hypertension, and minimal effects on heart failure and CKD. The model assumes no direct treatment effects on chronic conditions. However, the model does assume that acute pain crises have a small effect on each of the chronic conditions. Therefore, treatments that reduce acute pain crises reduce chronic conditions, and treatments that reduce acute pain crises more have a larger impact on chronic conditions. The model also accounts for improvements in hemoglobin, as discussed above. In some cases, prevalence in the treated population is higher than the prevalence in the usual care group. This is due to longer life expectancy in the treatment arms.

Table 5.25. Comparison of Chronic Disease Prevalence at Different Ages in the Model

	Model			
	Optimal Usual Care	Crizanlizumab	Voxelotor	L-glutamine
Age	pHTN (%)			
24	34%	34%	34%	34%
38	56%	52%	51%	56%
50	77%	73%	72%	77%
59.5	89%	86%	85%	89%
70	97%	95%	95%	97%
	HF (%)			
24	13%	13%	13%	13%
38	32%	29%	28%	32%
50	50%	46%	46%	50%
59.5	49%	51%	50%	49%
70	51%	54%	54%	52%
	CKD (%)			
24	21%	21%	21%	21%
38	41%	37%	32%	40%
50	57%	53%	45%	57%
59.5	60%	60%	46%	60%
70	66%	66%	51%	66%

CKD: chronic kidney disease, HF: heart failure, pHTN: pulmonary hypertension

Sensitivity Analysis Results

Sensitivity analysis demonstrates that increasing the baseline risk of acute and chronic conditions (including the rate of acute pain to 6 per year) and baseline death rates results in lower incremental cost-effectiveness ratios (Table 5.26-5.28). Increasing the baseline utility for patients with uncomplicated SCD decreased the incremental cost-effectiveness ratio, however, an increase of 20% did not result in any treatment being less than $1 million per additional QALY. Changes to the

health state costs of plus or minus 20% had very small effects on the incremental cost-effectiveness ratios, less than $2,000 difference in the cost per QALY. The lowest cost per QALY for the crizanlizumab and L-glutamine comparisons occurred when the baseline risk of acute and chronic conditions was doubled. The comparison with voxelotor had the lowest cost per QALY when the baseline utility for uncomplicated SCD was increased by 20%.

Table 5.26. Sensitivity Analysis of Crizanlizumab Compared to Usual Care

Analysis	Treatments	Outcomes			Costs		Incremental Cost-Effectiveness Ratios		
		LYG	evLYG	QALYs	Treatment	Total	$/LYG	$/evLYG	$/QALY
Base case	Usual Care	15.19	7.64	7.64	-	$1,144,760	-	-	-
	Crizanlizumab	17.52	9.64	8.50	$1,150,054	$2,180,243	$444,226	$520,294	$1,212,097
Double baseline risks	Usual Care	11.13	5.32	5.32	-	$1,365,672	-	-	-
	Crizanlizumab	13.41	7.28	6.14	$886,009	$2,084,024	$315,237	$365,890	$875,716
Half baseline risks	Usual Care	19.32	10.09	10.09	-	$983,045	-	-	-
	Crizanlizumab	21.44	11.91	10.89	$1,402,592	$2,309,791	$624,169	$726,873	$1,642,256
Double baseline death risk	Usual Care	14.08	7.24	7.24	-	$1,017,672	-	-	-
	Crizanlizumab	16.30	9.09	8.06	$1,071,414	$1,981,530	$435,710	$519,712	$1,169,691
Half baseline death risk	Usual Care	16.59	8.12	8.12	-	$1,312,989	-	-	-
	Crizanlizumab	19.03	10.27	9.01	$1,247,329	$2,434,265	$459,163	$522,259	$1,270,306
Baseline HRQoL +20%	Usual Care	15.19	9.17	9.17	-	$1,144,760	-	-	-
	Crizanlizumab	17.52	11.16	10.20	$1,150,054	$2,180,243	$444,226	$519,736	$1,009,556
Baseline HRQoL -20%	Usual Care	15.19	6.12	6.12	-	$1,144,760	-	-	-
	Crizanlizumab	17.52	8.11	6.80	$1,150,054	$2,180,243	$444,226	$520,781	$1,515,910
Health State Costs +20%	Usual Care	15.19	7.64	7.64	-	$1,151,162	-	-	-
	Crizanlizumab	17.52	9.64	8.50	$1,150,054	$2,187,275	$444,496	$520,611	$1,212,836
Health State Costs -20%	Usual Care	15.19	7.64	7.64	-	$1,138,358	-	-	-
	Crizanlizumab	17.52	9.64	8.50	$1,150,054	$2,173,210	$443,955	$519,977	$1,211,359

evLYG: equal value life years gained, HRQoL: health-related quality of life, LYG: life years gained, QALY: quality-adjusted life year

Table 5.27. Sensitivity Analysis of Voxelotor Compared to Usual Care

Analysis	Treatments	Outcomes			Costs		Incremental Cost-Effectiveness Ratios		
		LYG	evLYG	QALYs	Treatment	Total	$/LYG	$/evLYG	$/QALY
Base case	Usual Care	15.19	7.64	7.64	-	$1,209,430	-	-	-
	Voxelotor	17.30	9.59	8.60	$1,260,291	$2,473,793	$599,508	$650,585	$1,321,248
Double baseline risks	Usual Care	11.13	5.32	5.32	-	$1,419,163			
	Voxelotor	13.12	7.14	6.19	$958,704	$2,394,965	$492,017	$537,090	$1,127,033
Half baseline risks	Usual Care	19.32	10.09	10.09	-	$1,055,655	-	-	-
	Voxelotor	21.31	11.95	11.02	$1,550,084	$2,601,140	$775,607	$831,101	$1,650,922
Double baseline death risk	Usual Care	14.08	7.24	7.24	-	$1,073,898	-	-	-
	Voxelotor	16.12	9.07	8.15	$1,175,477	$2,258,149	$581,187	$647,001	$1,294,053
Half baseline death risk	Usual Care	16.59	8.12	8.12	-	$1,389,972	-	-	-
	Voxelotor	18.69	10.14	9.10	$1,361,084	$2,742,868	$642,955	$671,051	$1,388,543
Baseline HRQoL +20%	Usual Care	15.19	9.17	9.17	-	$1,209,430	-	-	-
	Voxelotor	17.30	11.14	10.32	$1,260,291	$2,473,793	$599,508	$640,639	$1,100,937
Baseline HRQoL -20%	Usual Care	15.19	6.12	6.12	-	$1,209,430	-	-	-
	Voxelotor	17.30	8.03	6.88	$1,260,291	$2,473,793	$599,508	$660,795	$1,651,715
Health State Costs +20%	Usual Care	15.19	7.64	7.64	-	$1,215,832	-	-	-
	Voxelotor	17.30	9.59	8.60	$1,260,291	$2,480,844	$599,816	$650,919	$1,321,927
Health State Costs -20%	Usual Care	15.19	7.64	7.64	-	$1,203,028	-	-	-
	Voxelotor	17.30	9.59	8.60	$1,260,291	$2,466,742	$599,200	$650,251	$1,320,570

evLYG: equal value life years gained, HRQoL: health-related quality of life, LYG: life years gained, QALY: quality-adjusted life year

Table 5.28. Sensitivity Analysis of L-Glutamine Compared to Usual Care

Analysis	Treatments	Outcomes			Costs		Incremental Cost-Effectiveness Ratios		
		LYG	evLYG	QALYs	Treatment	Total	$/LYG	$/evLYG	$/QALY
Base case	Usual Care	15.19	7.64	7.64	-	$1,144,760	-	-	-
	L-glutamine	15.48	7.97	7.75	$301,804	$1,423,237	$965,048	$847,412	$2,716,536
Double baseline risks	Usual Care	11.13	5.32	5.32	-	$1,365,672	-	-	-
	L-glutamine	11.40	5.61	5.42	$223,648	$1,555,096	$701,522	$654,689	$1,960,283
Half baseline risks	Usual Care	19.32	10.09	10.09	-	$983,045	-	-	-
	L-glutamine	19.59	10.43	10.19	$380,855	$1,348,905	$1,329,760	$1,048,609	$3,665,503
Double baseline death risk	Usual Care	14.08	7.24	7.24	-	$1,017,672	-	-	-
	L-glutamine	14.35	7.54	7.34	$280,183	$1,275,481	$968,987	$850,550	$2,640,458
Half baseline death risk	Usual Care	16.59	8.12	8.12	-	$1,312,989	-	-	-
	L-glutamine	16.90	8.49	8.23	$329,214	$1,617,465	$966,176	$839,404	$2,808,248
Baseline HRQoL +20%	Usual Care	15.19	9.17	9.17	-	$1,144,760	-	-	-
	L-glutamine	15.48	9.52	9.29	$301,804	$1,423,237	$965,048	$806,578	$2,263,558
Baseline HRQoL -20%	Usual Care	15.19	6.12	6.12	-	$1,144,760	-	-	-
	L-glutamine	15.48	6.43	6.20	$301,804	$1,423,237	$965,048	$892,577	$3,396,004
Health State Costs +20%	Usual Care	15.19	7.64	7.64	-	$1,151,162	-	-	-
	L-glutamine	15.48	7.97	7.75	$301,804	$1,429,717	$965,318	$847,649	$2,717,296
Health State Costs -20%	Usual Care	15.19	7.64	7.64	-	$1,138,358	-	-	-
	L-glutamine	15.48	7.97	7.75	$301,804	$1,416,758	$964,778	$847,175	$2,715,777

evLYG: equal value life years gained, HRQoL: health-related quality of life, LYG: life years gained, QALY: quality-adjusted life year

Scenario Analyses Results

Modified Societal Perspective

We are currently undertaking a survey of patients living with SCD to understand the impact of their disease on their education, their ability to work, the effect on caregivers, and other costs not covered by commercial insurance or the government. These values will be added to the model to estimate a societal perspective. It is expected that a treatment that avoids acute events and chronic conditions will allow students to attend more school, will decrease the number of missed days from work, will have fewer demands on the caregiver, and will have lower out-of-pocket costs. These additional societal benefits not currently included in the health care perspective are important for understanding the full potential impact of treatments and their value.

Population with Higher Acute Pain Crisis Rate

Analysis of a population with 10 acute pain crises per year results in a larger difference in acute pain crises avoided and lower incremental cost-effectiveness ratios for all treatments, Tables 5.26-5.28.

Lifetime treatment costs for crizanlizumab in this population are slightly lower than in the base-case population due to the higher mortality rate resulting in a shorter length of treatment, approximately $1.0 million over the lifetime, with cost-savings of approximately $396,000 from avoided acute and chronic conditions (Table 5.29). The model estimates that crizanlizumab patients will experience 87 acute pain crises over their lifetime, 48 fewer than with optimal usual care. These patients on crizanlizumab are expected to live to 46 years old, compared to 42 years old for these patients on optimal usual care and 50 years old for the base-case population. These patients on crizanlizumab have approximately 2.4 life-years gained, 2.0 evLYG, and 0.97 QALYs gained compared to usual care. The decreased treatment costs and improved outcomes compared to the base-case result in improved incremental cost-effectiveness of crizanlizumab compared to usual care, at approximately $273,000 per LY gained, $309,000 per evLYG, and $664,000 per QALY gained. To reduce the ICER to $150,000 per QALY, the baseline acute pain crisis rate would have to be 21 per year.

Table 5.29. Results for Crizanlizumab versus Optimal Usual Care Alone in a Population with 10 Acute Pain Crises per Year

Treatment	Optimal Usual Care	Crizanlizumab	Difference	ICER	
Treatment Cost	-	$1,042,000	$1,042,000	-	
Other Cost	$2,254,000	$1,858,000	-$396,000	-	
Total Cost	$2,254,000	$2,900,000	$646,000	-	
Acute Pain Crises	134.69	86.61	-48.08	$13,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
LYs	13.47	15.83	2.37	$273,000	per LY gained
evLYG	6.53	8.63	2.09	$309,000	per evLY gained
QALYs	6.53	7.50	0.97	$664,000	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year

Lifetime treatment costs for voxelotor in this population with 10 acute pain crises are also lower than in the base-case population, at approximately $1.1 million over the lifetime (Table 5.30). The model estimates that voxelotor patients will experience 132 acute pain crises over their lifetime, 3 fewer than with optimal usual care. These patients on voxelotor are expected to live to 45 years old, compared to 42 years old for these patients on optimal usual care and 47 years old for the base-case population. These patients on voxelotor have approximately 1.7 life-years gained, 1.6 evLYG, and 0.77 QALYs gained compared to optimal usual care. The incremental cost-effectiveness of voxelotor compared to usual care is approximately $643,000 per LY gained, $698,000 per evLYG, and $1.4 million per QALY gained. There was no number of acute pain crises that would reduce the cost per QALY to $150,000.

Table 5.30. Results for Voxelotor versus Usual Care Alone in a Population with 10 Acute Pain Crises per Year

Treatment	Optimal Usual Care	Voxelotor	Difference	ICER	
Treatment Cost	-	$1,107,000	$1,107,000	-	
Other Cost	$2,306,000	$2,298,000	-$8,000	-	
Total Cost	$2,306,000	$3,405,000	$1,099,000	-	
Acute Pain Crises	134.69	131.75	-2.93	$375,000	per pain crisis avoided
Hemoglobin (g/dL)	-0.10	1.10	1.20	$60,000	per g/dL per year
LYs	13.47	15.18	1.71	$643,000	per LY gained
evLYG	6.53	8.11	1.57	$698,000	per evLY gained
QALYs	6.53	7.30	0.77	$1,423,000	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year

Lifetime treatment costs for L-glutamine in a more frequent pain crisis population are also lower than in the base-case population, approximately $269,000 over the lifetime, with cost-savings of approximately $80,000 from avoided acute and chronic conditions (Table 5.31). The model estimates that L-glutamine patients will experience 125 acute pain crises over their lifetime, 10 fewer than usual care. These patients on L-glutamine are expected to live to approximately 42 years old, with only a 0.29 improvement compared to patients on optimal usual care. Severe patients on L-glutamine have approximately 0.29 life-years gained, 0.34 evLYG, and 0.13 QALYs gained compared to optimal usual care. The incremental cost-effectiveness of L-glutamine compared to optimal usual care is estimated as approximately $657,000 per life year gained, $564,000 per evLYG, and $1.5 million per QALY gained. There is no number of acute pain crises that will reduce the cost per QALY to $150,000.

Table 5.31. Results for L-Glutamine versus Optimal Usual Care Alone in a Population with 10 Acute Pain Crises per Year

Treatment	Optimal Usual Care	L-glutamine	Difference	ICER	
Treatment Cost	-	$269,000	$269,000	-	
Other Cost	$2,254,000	$2,174,000	-$80,000	-	
Total Cost	$2,254,000	$2,443,000	$189,000	-	
Acute Pain Crises	134.69	125.17	-9.52	$20,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
Lys	13.47	13.76	0.29	$657,000	per LY gained
evLYG	6.53	6.87	0.34	$564,000	per evLY gained
QALYs	6.53	6.66	0.13	$1,511,000	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year

Younger Population

Analyses of a younger population, starting treatment at 16 years old, resulted in a slightly higher cost per QALY for crizanlizumab and voxelotor and a lower cost per QALY for L-glutamine (Tables 5.32-5.34). This is likely due to the lower baseline risk of acute events and chronic conditions in the younger population. This results in improvements in acute pain crises having less of an impact on acute events and chronic conditions at these younger ages.

These results suggest that 16-year-old patients who start crizanlizumab would have 34 acute pain crises over their lifetime, which is 22 acute pain crises fewer than patients on optimal usual care. Lifetime cost would be approximately $1.3 million, with $174,000 cost-saving from other costs. This results in incremental cost-effectiveness ratios of approximately $522,000 per life-year gained, $578,000 per evLYG, and $1.3 million per QALY gained.

Table 5.32. Results for Crizanlizumab versus Optimal Usual Care Alone with a Starting Age of 16 Years

Treatment	Optimal Usual Care	Crizanlizumab	Difference	ICER	
Treatment Cost	-	$1,308,000	$1,308,000	-	
Other Cost	$1,328,000	$1,154,000	-$174,000	-	
Total Cost	$1,328,000	$2,463,000	$1,135,000	-	
Acute Pain Crises	56.18	34.30	-21.88	$52,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
Life Years	18.73	20.90	2.18	$522,000	per LY gained
evLYG	9.85	11.82	1.96	$578,000	per evLY gained
QALYs	9.85	10.73	0.88	$1,291,000	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year

This analysis suggests that 16-year-old patients who start voxelotor would have 53 acute pain crises over their lifetime, which is 3 acute pain crises fewer than patients on optimal usual care. Lifetime cost would be $1.5 million, with $27,000 cost-saving from other costs. This results in incremental cost-effectiveness ratios of $702,000 per life-year gained, $723,000 per evLYG, and $1.4 million per QALY gained.

Table 5.33. Results for Voxelotor versus Optimal Usual Care Alone with a Starting Age of 16 Years

Treatment	Optimal Usual Care	Voxelotor	Difference	ICER	
Treatment Cost	-	$1,516,666	$1,516,666	-	
Other Cost	$1,392,178	$1,364,770	-$27,408	-	
Total Cost	$1,392,178	$2,881,436	$1,489,258	-	
Acute Pain Crises	56.18	52.84	-3.34	$445,937	per pain crisis avoided
Hemoglobin (g/dL)	-0.10	1.10	1.20	$59,528	per g/dL per year
Lys	18.73	20.85	2.12	$701,912	per LY gained
evLYG	9.85	11.91	2.06	$723,240	per evLY gained
QALYs	9.85	10.91	1.05	$1,412,560	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year

This analysis suggests that 16-year-old patients who start L-glutamine would have 52 acute pain crises over their lifetime, which is 4 acute pain crises fewer than patients on optimal usual care. Lifetime treatment costs would be $349,000, with $34,000 cost-saving from other costs. This results in incremental cost-effectiveness ratios estimated to be approximately $1.2 million per life-year gained, $901,000 per evLYG, and $3.1 million per QALY gained.

Table 5.34. Results for L-Glutamine versus Optimal Usual Care Alone with a Starting Age of 16 Years

Treatment	Optimal Usual Care	L-glutamine	Difference	ICER	
Treatment Cost	-	$349,000	$349,000	-	
Other Cost	$1,328,000	$1,294,000	-$34,000	-	
Total Cost	$1,328,000	$1,643,000	$315,000	-	
Acute Pain Crises	56.18	51.83	-4.35	$72,000	per pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
Life years	18.73	18.99	0.26	$1,194,000	per LY gained
evLYG	9.85	10.20	0.35	$901,000	per evLY gained
QALYs	9.85	9.96	0.10	$3,074,000	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year

Threshold Analyses

The threshold analyses calculate the drug price at which each treatment would be cost-effective at different relevant thresholds (Table 5.35). For crizanlizumab to be cost-effective at $50,000 per QALY, the price would have to be $235 per vial or $16,450 annually, and $25,410 annually at $150,000 per QALY. For voxelotor to be cost-effective at $50,000 per QALY, the price would have to be $189 per package or $2,466 annually, and $5,842 annually at $150,000 per QALY. L-glutamine would be cost-effective at 50,000 per QALY at $78 per package or $2,837 annually, and at $3,859 annually at $150,000 per QALY.

Table 5.35. Annual Drug Costs at List and Discount Prices and at Prices at Which Each Treatment is Cost-effective at Specific Thresholds[71]

Treatments	Input Prices		Thresholds of Interest					
	List Price	Discount Price	$50K per QALY	$100K per QALY	$150K per QALY	$50K per evLYG	$100K per evLYG	$150K per evLYG
Crizanlizumab	$164,990	$120,470	$16,450	$20,930	$25,410	$22,400	$32,830	$43,260
Voxelotor	$135,886	$99,197	$2,466	$5,842	$9,218	$5,951	$12,810	$19,670
L-glutamine	$40,543	$30,092	$2,837	$3,348	$3,859	$3,964	$5,602	$7,241

evLYG: equal value life years gained, QALY: quality-adjusted life year

Model Validation

Wilson-Frederick et al. examined the demographic and health utilization patterns among Medicare Fee-for-Service beneficiaries with SCD using the CMS SCD indicator. The population included 11,790 SCD patients between the ages of 18 and 75, using claims data from 2012 through 2016. In 2016, patients had an average of 7.4 emergency department visits, 3.9 days of inpatient hospitalization, and 21.1 days of outpatient utilization. Table 5.36 reports the prevalence of pulmonary hypertension, heart failure, and chronic kidney disease as reported by CMS[71] and as estimated in the model using the average age of the CMS range, as reported in the brackets. This comparison suggests that the predicted prevalence in the model is very similar to that of the Medicare population in terms of chronic disease prevalence.

Table 5.36. Comparison of Prevalence Reported in a Medicare Population Compared to Prevalence Predicted by the Model

Age range from CMS (average age used in the model)	Medicare Population	Model
		Usual Care
	pHTN (%)	
18-30 (24)	35%	34%
31-45 (38)	59%	56%
46-54 (50)	75%	77%
55-64 (59.5)	87%	89%
65-75 (70)	93%	97%
	HF (%)	
18-30 (24)	18%	13%
31-45 (38)	37%	32%
46-54 (50)	47%	50%
55-64 (59.5)	52%	49%
65-75 (70)	48%	51%
	CKD (%)	
18-30 (24)	26%	21%
31-45 (38)	42%	41%
46-54 (50)	55%	57%
55-64 (59.5)	62%	60%
65-75 (70)	64%	66%

CKD: chronic kidney disease, CMS: Centers for Medicare and Medicaid services, HF: heart failure, pHTN: pulmonary hypertension

The national median life-expectancy for people with SCD is reported as being between 38 and 42 years old for men and between 42 and 48 years old for women.[79,81] The average patient in the optimal usual care arm of the model is predicted to live 21 an additional 25 years after entering the model in the base-case analysis, giving a life-expectancy of 45 years old.

The average utility for a patient with SCD on usual care was estimated to be 0.52. This is a very low health-related quality of life and reflects the very serious nature of the disease and the severity of the modelled population.

Model validation suggests that the usual care population is similar to the Medicare population in terms of prevalence of chronic conditions, and has a life-expectancy similar to that reported in the literature.

Limitations

To simplify the model, it was assumed that only one chronic condition and one acute condition could occur each cycle. This creates a situation where chronic conditions and acute conditions become competing events. Therefore, by decreasing one event in the model it allows other events to occur more frequently. To correct for the competing events, the model was calibrated to minimize the difference in the number of acute events and chronic conditions because of the reduction in acute pain crises in the treatment arm. The specific steps we followed to perform this calibration are described in Appendix E.

This method can be validated by investigating how the model predicts acute and chronic conditions compared to known SCD populations, as was done in the validation section above.

The event rates used in the model are from claims data. This has the potential to underestimate event rates, particularly those that do not result in hospitalization. However, claims data is expected to capture the most debilitating and costly events. Event rates were also tested in sensitivity analysis.

Due to the lack of published evidence, a number of assumptions had to be made. These include: the risk effects of acute pain crisis on AKI/renal infarction, the prevalence of opioid tolerance and dependence, the risk factors of myocardial infarction and heart failure on death, and the dis-utility of AKI/renal infarction and pulmonary hypertension in the SCD population.

In addition, a number of assumptions had to be made about how to combine risk factors and dis-utilities for patients experiencing multiple acute and chronic conditions. These assumptions were described previously and the justifications described.

This model focuses on improvements in health states and the quality-of-life and length-of-life from these improvements. SCD often has a broad and deep impact on patients'' psychosocial well-being. Some of these impacts are captured in measures of quality-of-life, such as anxiety and depression, the ability to take care of one's self, and to perform activities of usual care. Further improvements from treatments for SCD may occur in aspects that are not captured within the model; these potential other benefits are discussed in later sections, along with other contextual considerations.

Conclusions

The prevalence rates predicted in the model suggest a cohort similar to Medicare FFS patients with SCD. Reduction in acute pain crises and improvement in hemoglobin both result in fewer acute events and a lower prevalence of chronic conditions. These improvements extend life-expectancy and lead to an improvement in health-related quality of life. The lifetime total cost of a 24-year-old patient on optimal usual care is $1.1 million. The life-time treatment cost of crizanlizumab and voxelotor is over $1 million. L-glutamine costs approximately $304,000 for lifetime treatment.

Crizanlizumab treatment resulted in the fewest acute pain crises, with 29 over the patient's life compared to 46 for patients on optimal usual care, 44 for patients on voxelotor, and 42 for patient on L-glutamine. Voxelotor treatment resulted in the lowest rate of stroke, with a mean of 0.38 over the patient's lifetime compared to 0.61 for patients on optimal usual care or L-glutamine, and 0.51 for patients on crizanlizumab. There was very little difference in the prevalence of chronic conditions with crizanlizumab and L-glutamine, with treatments causing slightly higher prevalence in some age groups due to lower mortality on treatment. However, treatment with voxelotor resulted in lower prevalence of pulmonary hypertension and chronic kidney disease. All treatments resulted in higher life-expectancy than optimal usual care alone, with 2.33 years with crizanlizumab, 1.19 years with voxelotor, and 0.29 years with L-glutamine.

In the base case, cost per QALY estimates range from $1.2-2.7 million, while cost per life-years gained and cost per evLYG ranged from $444,000 to $997,000 and $520,000 to $1 million, respectively. None of the scenario analyses resulted in any of the treatments achieving cost-effectiveness thresholds of $150,000 per QALY.

Disparities

It is important to note that economic models such as this one cannot capture the full psychosocial impact of systemic issues such as racism that may impact underserved populations such as patients with SCD. It is also unclear what impact treatments for these populations will have on those systemic issues, or vice versa. For example, the majority of people with SCD in the US have African American heritage. Life expectancy at birth is 4.442% lower for blacks than for whites in the US (75.3 years vs. 78.8 years).[109] In an exploratory analysis, we estimated that if all people with SCD were treated with crizanlizumab and all were assumed to be African-American, the increase in life years would decrease the overall disparity in life expectancy by a relative 3.6% (i.e., to 4.426% lower rather than 4.442%).

5.4 Summary and Comment

Treatment costs were the main driver of the cost-effectiveness results, with average annual costs of $88,000 for crizanlizumab, $84,000 for voxelotor and $24,000 for L-glutamine, considering many will discontinue each treatment. Combined with relatively small improvements in QALYs gained (0.85 for crizanlizumab, 0.96 for voxelotor, and 0.10 for L-glutamine), all ICERs were estimated to be over $1 million per QALY. None of the scenario analyses undertaken lowered the estimated cost per QALY to less than $150,000 per QALY.

Although a reduction in acute pain crises and increase in hemoglobin will provide relief to patients, they will continue to suffer from other acute and chronic conditions that will have a significant impact on their quality of life. The impact of therapies on these other acute and chronic conditions has yet to be demonstrated in clinical trials, although we made assumptions that included impacts of these treatments on several of these conditions. As a result, there is currently a large difference

in the cost per QALY and the cost per life-year and evLYG. For example, cost per evLYG ranged from approximately $520,000 for crizanlizumab to $847,000 for L-glutamine.

Scenario analyses suggest treatment is most cost-effective for patients with higher rates of acute pain crises. Patients who experience 10 acute pain crises per year may have a cost per QALY as low as $615,000 with crizanlizumab.

6. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness or cost-effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that should influence the judgment of policymakers in their determination of the relative value of different interventions. Specific potential other benefits and contextual considerations that we evaluate for each intervention are listed in Table 6.1 below, and the subsequent text provides detail about the elements that are applicable to the comparison of crizanlizumab, voxelotor, and L-glutamine to optimal usual care. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 6.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 6.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to optimal usual care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to optimal usual care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

6.1 Potential Other Benefits

As noted in the Introduction and section on Patient Perspectives, the way patients with SCD have been treated in the US is a tragedy that has extended over many decades. Patients and their families have experienced neglect, racism, and total disregard. Research into treatment improvements has received less funding than many other conditions that affect fewer patients. The overall "system" of health insurance and care has betrayed the SCD community.

The potential other benefits of effective treatments for SCD therefore are highly relevant. Among those benefits that are routinely considered by ICER, it is clear that treatment may reduce important health disparities that exist across racial and socio-economic groups in the US. Specifically, effective treatment could potentially reduce the gap in life expectancy between black and white Americans and between the poor and rich in the US, although the magnitude of impact is likely to be relatively small given that SCD affects a relatively small population.

It also seems likely that new, effective treatments could reduce caregiver burden Questions will remain about whether the magnitude of the clinical benefits seen in the early trials of the drugs

under review will reach the threshold of having a noticeable effect on caregivers, but if patients have less pain, suffer fewer morbidities, have fewer hospitalizations, and need fewer doctor visits, then their families and caregivers would have more time to focus on their own education, careers, family, friends, and other interests. Improvement in caregivers' quality of life can have a rebound positive effect for the patient, improving further their own mental, emotional, and physical health.

Similarly, effective treatment could increase the chances for employment among patients with SCD and improve the productivity of all patients, whether they are working or performing family and community functions.

Crizanlizumab, voxelotor, and L-glutamine all have different mechanisms of action both from each other and from hydroxyurea. This is a significant step forward in the field of SCD. Patients who have not been able to tolerate hydroxyurea now have other treatment options. Equally important all three products have different mechanisms of action and work on different critical pathways that underlie the different phenotypic expressions of the disease. This now provides novel treatment options that can be tailored to the different phenotypes of the disease; options to provide a more targeted approach that have not been available before. It also provides an opportunity to potentially combine therapies to address multiple pathophysiological pathways as opposed to just one. While there is much to be learned about the potential benefits and harms of combination therapy, there remains significant potential for new understanding and hope for additive health benefit for patients. With these new treatment options, a more targeted approach, and the potential to deploy multiple concurrent therapies, comes the potential for a healthier patient.

Among possible additional "other benefits," these treatments may also bring more interest, enthusiasm, and perhaps support for the development of subsequent and possibly better treatments in the future. By providing a more hopeful outcome for patients these new treatments may improve the attractiveness of SCD care for clinicians, leading to a new influx of talent and resources. The terrible dysfunction and lack of coordination between the pediatric care of SCD patients and adult care may receive new focus and be subject to innovative care delivery changes. Thus, a suite of new treatments for SCD may have the potential to kickstart a long overdue revolution in the care of the total patient and family from diagnosis throughout the lifespan.

6.2 Contextual Considerations

As with potential other benefits, the contextual considerations related to SCD are significant. SCD is a condition that has both many acute, severe effects, and a litany of substantial negative effects throughout patients shortened lifespan. Patients experience tremendous physical pain beginning in the first year of life, progress to organ damage in childhood, organ failure in their teens, twenties, and thirties and early death. They find themselves in financial difficulty due to their disease, have difficulty accessing care because there are so few specialists trained to care for them, and when they do access care are often treated like drug addicts wanting nothing more than to get their next

high, left to suffer agonizing pain, even within hospital wards and emergency rooms, without relief. Once at the physician's office they have historically had few treatment options; bone marrow transplant, hydroxyurea, chronic transfusion, all at significant cost, some with significant risk, and/or side effects. Not surprisingly their very complex disease becomes further complicated by the added psychological and emotional toll of having to endure, interact with, and attempt to navigate a broken, dysfunctional, and dispassionate health care system. This is the context in which patients, their families, loved ones, and the few committed health care providers who care for them find themselves in the current landscape of SCD care.

7. Value-Based Price Benchmarks

Value-based price benchmarks will be included in the revised Evidence Report that will be released on or about March 12, 2020.

8. Potential Budget Impact

Potential budget impact will be calculated after considering revisions to the cost-effectiveness model following public comment. This will be included in the revised Evidence Report that will be released on or about March 12, 2020.

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This is the first ICER review of SCD.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
		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 (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., healthcare 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.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

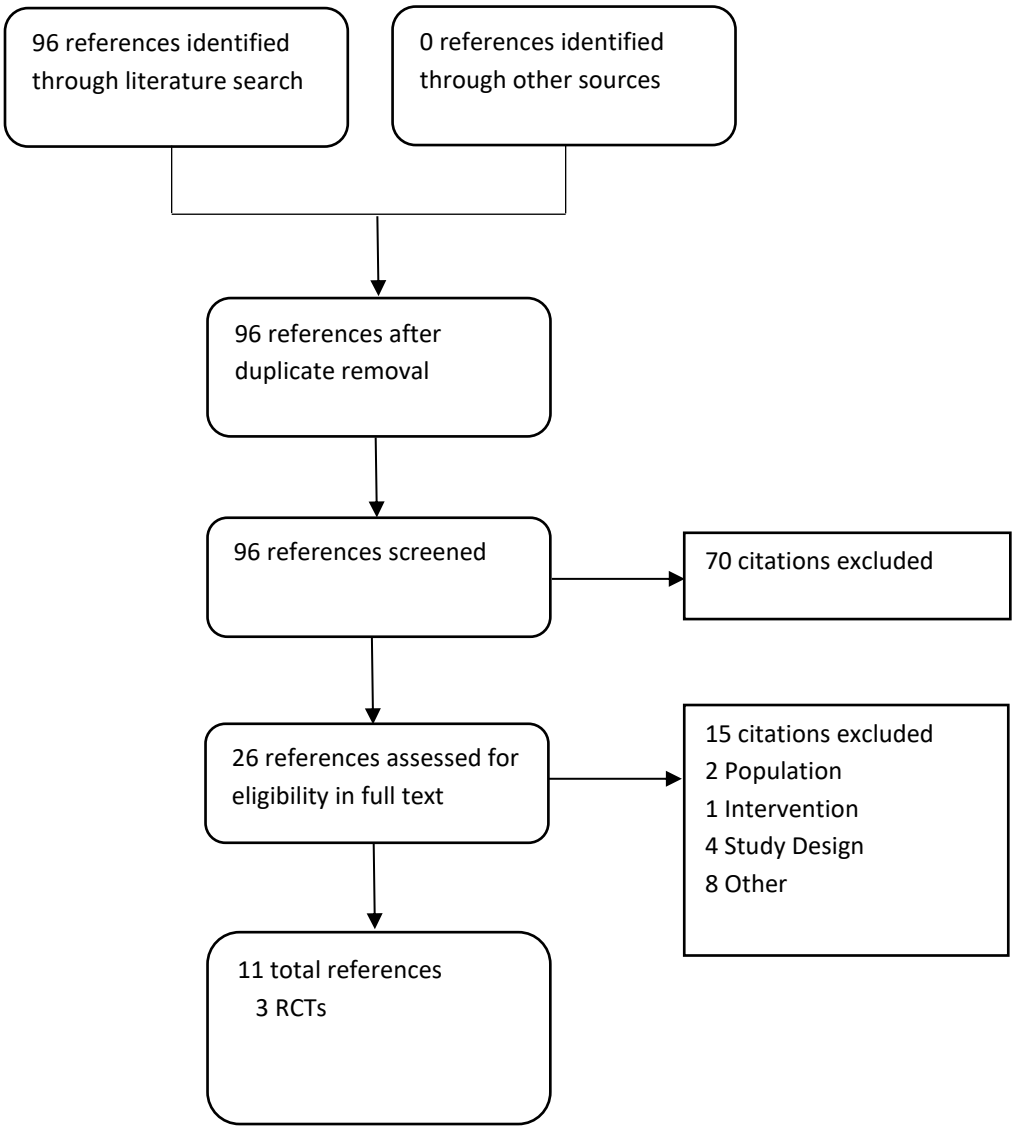
Table A2. Search Strategies for Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

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 A3. Search Strategy for 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

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Sickle Cell Disease



Appendix B. Previous Systematic Reviews and Technology Assessments

NICE: Crizanlizumab for preventing sickle cell crises in sickle cell disease (ID1406], Expected publication date: 24 March 2021

NICE is currently evaluating the clinical and cost effectiveness of crizanlizumab within its marketing authorization for preventing sickle cell disease. Proposed comparators include established clinical management without crizanlizumab including: hydroxycarbamide, blood transfusions, allogenic stem cell trasnplants, or optimal supportive care. Outcomes of interest being evaluated include mortality, number and severity of sickle cell crises, recurrent events, complications of SCD (stroke, acute chest syndrome, organ damage), adverse events, and health related quality of life outcomes.

NICE: Voxelotor for treating sickle cell disease [ID1403], Expected publication date: TBC

NICE is currently evaluating the clnical and economic effectiveness of voxelotor for the treatment of sickle cell disease.

Hutcherson et al. (2019). "Systematic Review of L-Glutamine for Prevention of Vaso-Occlusive Pain Crisis in Patients with Sickle Cell Disease".[110]

Investigators conducted a systematic review to evaluate the safety and efficacy of L-glutamine to prevent vaso-occlusive crises (VOCs) in patients with sickle cell disease (SCD). Select inclusion and exclusion criteria used to identify studies included randomized-controlled trials, observational studies, or case studies in patients with sickle cell disease, sickle cell anemia, or thalassemia taking l-glutamine. Studies were excluded if the primary outcomes were not related to the modification of one or more pain-related outcome related to acute pain crises. Ultimately three studies, published under the same author, were included in the review: one nonrandomized controlled trial (1998) and two randomized controlled trials (2014 and 2018). The randomized controlled studies (2014 and 2018) have been included in our review and will not be summarized here, however the 1998 nonrandomized controlled trial was not included in our review because it did not report outcomes of interest. The 1998 nonrandomized, single-center 4-week study evaluated the biochemical effects of oral l-glutamine in seven patients aged 18 and older with genotype HbSS. Patients were excluded if they were pregnant, had blood transfusions in the previous 3 months, or would be concurrently receiving hydroxyurea. After 4 weeks, there was a significant increase in NADH levels and NAD redox potential, with all patients (100%) reporting improvements in energy levels and a decrease in chronic pain levels and 6 (86%) reporting improvements in activity levels and decreased narcotics use.

Authors of the systematic review concluded that there is a limited amount of high-quality data to support the use of L-glutamine in patients with SCD and listed several limitations of the evidence supporting its use. Specifically, the studies were all conducted under the same principal

investigator, two trials recruited small sample sizes, and inclusion criteria were not generalizable to the broader SCD population.

Appendix C. Ongoing Studies

Title / Trial Sponsor	Study Design	Study Arms	Patient Population	Primary Outcomes	Estimated Completion Dates
Crizanlizumab					
Pharmacokinetics and Pharmacodynamics Study of SEG101 (Crizanlizumab) in Sickle Cell Disease (SCD) Patients with Vaso-Occlusive Crisis (VOC) NCT03264989 **Novartis Pharmaceuticals**	Phase II, Multicenter, Open-Label Estimated Enrollment: 57	Intervention: Crizanlizumab 5.0 mg/kg (or 7.5 mg/kg for exploratory group) by IV	Inclusion: 1. Male and non-pregnant female patients 16-70 years of age 2. Confirmed diagnosis of SCD 3. Experienced at least 1 acute pain crisis within the preceding 12 months prior to screening 4. If receiving HU/HC or erythropoietin stimulating agent, must have been receiving the drug for at least 6 months prior to screening Exclusion: 1. History of stem cell transplant 2. Acute pain crisis ending 7 days prior to first dosing 3. Ongoing hospitalization prior to screening 4. Received blood products within 30 days to first dosing	1. To characterize PK (AUC), PK (Ctrough), PK (Cmax), and PD (AUC for P-selectin inhibition) of crizanlizumab at 5.0 mg.kg	February 2021

			5. Participating in a chronic transfusion program		
Study of Dose Confirmation and Safety of Crizanlizumab in Pediatric Sickle Cell Disease Patients NCT03474965 **Novartis Pharmaceuticals**	Phase II, Multicenter, Open-Label Estimated Enrollment: 100	Intervention: Crizanlizumab 5.0 mg/kg	Inclusion: 1. Male or female patients who are 2 to <18 years 2. Confirmed diagnosis of SCD 3. Experienced at least 1 acute pain crisis within preceding 12 months, as determined by medical history 4. If receiving HU/HC or erythropoietin stimulating agent or L-glutamine, must have been receiving drug for at least 6 months prior to screening and plan to continue taking the same dose and schedule during the trial Exclusion: 1. History of stem cell transplant 2.Received any blood products within 30 days of Day 1 dosing 3. Participating in a chronic transfusion program 4. Patients with bleeding disorders	1. PK (AUCd15) after 1st dose 2. PD (AUCd15) after 1st dose 3. PK (AUCtau) after 5th dose 4. PD (AUCtau) after 5th dose 5. PK (Cmax) after 1st and 5th dose 6. PK pre-dose concentrations 7. Frequency of any adverse events (AEs) as a measure of safety and tolerability	August 2022
Study of Two Doses of Crizanlizumab Versus Placebo in	Phase III, Multicenter,	Intervention 1:	Inclusion: 1. Male or female aged 12 years and	1. Rate of acute pain crises events	November 2027

Adolescent and Adult Sickle Cell Disease Patients NCT03814746 **Novartis Pharmaceuticals**	Randomized, Double-Blind Estimated Enrollment: 240	Crizanlizumab 5.0mg/kg Intervention 2: Crizanlizumab 7.5 mg/kg Comparator: Placebo	older on day of signing informed consent 2. Confirmed diagnosis of SCD 3. Experienced at least 2 acute pain crises leading to healthcare visit within 12 months prior to screening visit as determined by medical history 4. If receiving HU/HC or erythropoietin stimulating agent or L-glutamine, must have been receiving drug for at least 6 months prior to screening Exclusion: 1.History of stem cell transplant 2. Participation in a chronic transfusion program 3. Contraindication or hypersensitivity to any drug or metabolites from similar class as a study drug or to any excipients of the study drug formulation 4. Received active treatment on another investigational trial within 30 days prior to screening	leading to healthcare visit	

A Study to Evaluate the Safety and Efficacy of Crizanlizumab in Sickle Cell Disease Related Priapism NCT03938454 **Novartis Pharmaceuticals**	Prospective Phase II, Multicenter, Open-Label, Single-Arm Estimated Enrollment: 56	Intervention: Crizanlizumab 5mg/kg IV	Inclusion: 1. Male patients aged 16 years and above 2. Confirmed diagnosis of SCD 3. Experienced 4 or more priapic events over the 14 weeks preceding study participation 4. Experienced at least 3 priapic events during the 12 week screening period with at least 1 event occurring within 4 weeks prior to the first treatment Exclusion: 1.Had penile prosthetic implants or shunts or any other surgical procedure on the penis 2. Took drugs/medications that may induce priapism over the 14 weeks preceding study entry 3. Received leuprolide acetate (Lupron) within 3 months before pre-screening 4. Had an erection lasting more than 12 hours over the 14 week preceding study entry	1. Percent change in priapic events from baseline to 26 weeks	March 2022

Study Exploring the Effect of Crizanlizumab on Kidney Function in Patients With Chronic Kidney Disease Caused by Sickle Cell Disease NCT04053764 **Novartis Pharmaceuticals**	Phase II, Randomized, Multicenter, Open-Label, Estimated Enrollment: 170	Intervention: Crizanlizumab (5mg/kg) + standard of care Comparator: Standard of care (HU/HC, ACE, and ARBs)	Inclusion: 1. Confirmed diagnosis of SCD 2. Patients with eGFR ≥ 45 ≤ 120 mL/min/1.73 m2 based on CKD EPI formula 3. Patients with ACR of ≥ 100 to ≤ 2000 mg/g 4. Receiving standard of care drugs for SCD and/or CKD for at least 6 months prior to study entry 5. Hb ≥ 4.0 g/dL, absolute neutrophil count (ANC) ≥ 1.0 x 109/L, and platelet count ≥ 75x109/L 6. Written informed consent prior to screening procedures Exclusion: 1. History of stem cell transplant 2. Patients with evidence of AKI within 3 months of study entry 3. Blood pressure > 140/90 mmHg despite treatment 4. Patients undergoing hemodialysis 5. Participating in chronic transfusion program 6. History of kidney transplant	1. Percentage of patients with ≥ 30% decrease in albuminuria (ACR)	July 2022

Voxelotor					
Study to Assess the Effect of Long-Term Treatment with GBT440 in Participants Who Have Completed Treatment in Study GBT 440-031 (034 OLE) NCT03573882 Global Blood Therapeutics	Phase III, Open-Label Estimated Enrollment: 179	Intervention: Voxelotor 300mg with or without food	Inclusion: 1. Participants with SCD who participated or received study treatment in study GBT440-031 Exclusion: 1. Participant who was lost to follow-up in previous study 2. Patient requiring chronic dialysis	1. Number of participants with treatment-related adverse events 2. Frequency of sickle-cell complications	December 2019
An Open-Label Extension Study of Voxelotor Administered Orally to Pediatric Participants With Sickle Cell Disease Who Have Participated in Voxelotor Clinical Trials **NCT04188509** **Global Blood Therapeutics**	Open-label Extension Estimated Enrollment: 50	Intervention: ≥ 12 years: 1500 mg QD < 12 years: weight-based dose	Inclusion: 1. Participants with SCD, aged ≥ 4 to ≤ 18 2. Participated and received study drug in GBT-sponsored voxelotor pediatric clinical study Exclusion: 1. Participant withdrew consent from GBT-sponsored voxelotor pediatric clinical study	1. Treatment-Emergent Adverse Events 2. Serious Adverse Events 3. Sickle Cell Disease-Related Complications	January 2026
Study to Evaluate the Effect of GBT440 on TCD in Pediatrics With Sickle Cell Disease (HOPE Kids 2) **NCT04218084** **Global Blood Therapeutics**	Phase III Double-Blind, Placebo-Controlled, RCT Estimated Enrollment: 224	Intervention: 1500mg voxelotor or equivalent daily as tablet or powder for oral suspension	Inclusion 1. Participants with SCA 2. Aged ≥ 2 to < 15 years 3. Hb ≥ 5.5 and ≤ 10.5 g/dL 4. TCD time averaged maximum of the mean velocity	1. Transcranial Doppler (TCD)	March 2026

		Comparator matching placebo	arterial cerebral blood blood ≥170 to <200 cm/sec during the screening period Exclusion 1. Body weight <5kg at screening visit 2.Hospitalization for acute pain crisis and ACS within the 14 days prior to execution of informed consent 3. More than 10 acute pain crises within past 12 months requiring hospitalization or clinic visit		
L-Glutamine					
No on-going trials at this time.					

Source: www.ClinicalTrials.gov (NOTE: studies

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to crizanlizumab, voxelotor, and L-glutamine (Endari). These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Tables D1, D7, and D13){, , U.S. Preventive Services Task Force Procedure Manual} Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

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 is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if 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: *Studies were graded "poor" if 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 analysis is lacking.*

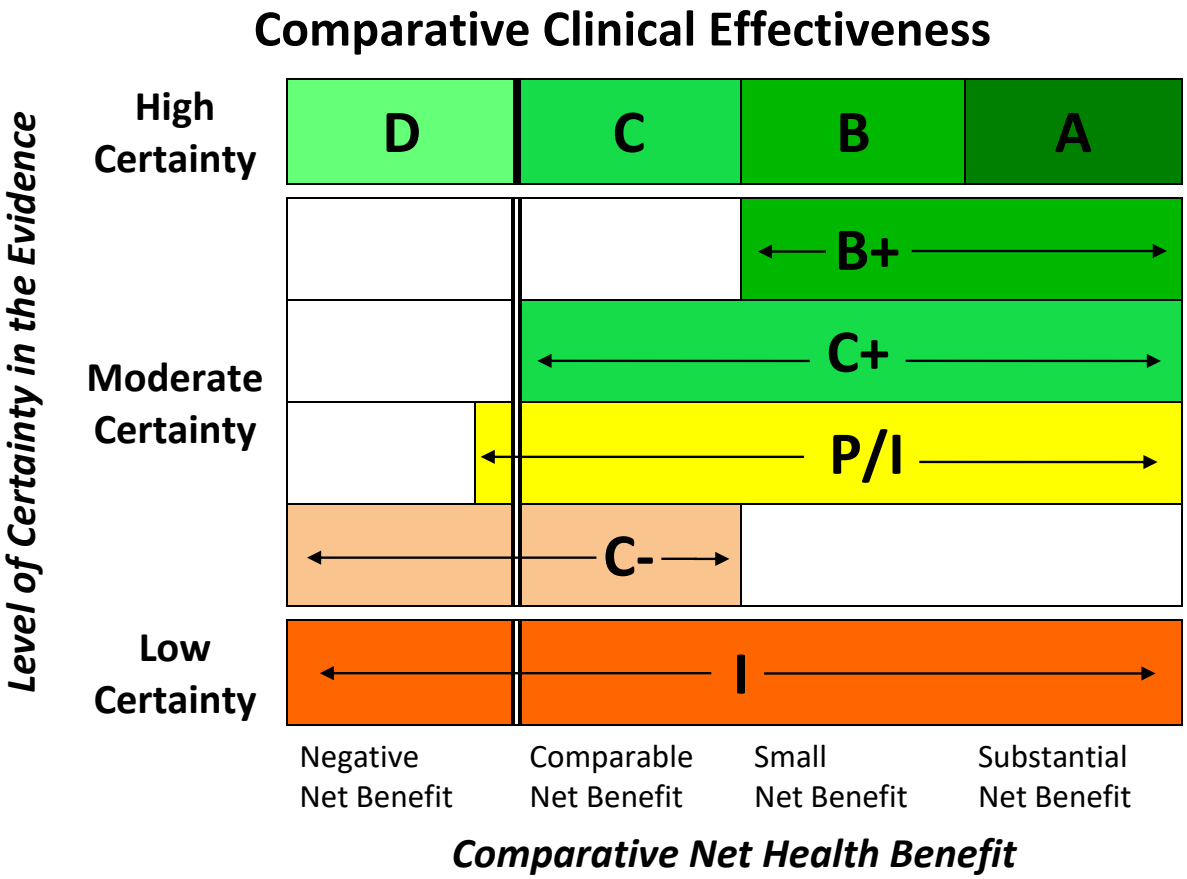
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.{Ollendorf, 2010, 79}

Figure D1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable"*- High certainty of a comparable net health benefit*
D = "Negative"*- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Table D1. Study Quality of Crizanlizumab SUSTAIN Trial{Ataga, 2017, 1001}

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
SUSTAIN Ataga 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

ITT: intent-to-treat

Table D2. Study Design of the SUSTAIN trial{Ataga, 2017, 1001}

Study	Crizanlizumab (SUSTAIN)
Design	Phase 2, double-blind, randomized, placebo-controlled trial. Patients were randomized 1:1:1 to receive low-dose crizanlizumab (2.5mg/kg of body weight), high dose crizanlizumab (5.0mg/kg of body weight) or placebo and were stratified by number of crises in the preceding year (2 to 4 or 5 to 10) and concomitant hydroxyurea use (yes or no).
Inclusion Criteria	• Sickle cell disease (homozygous hemoglobin S [HbSS], sickle hemoglobin C disease [HbSC], sickle β^0 thalassemia [HbSβ^0], sickle β^+ thalassemia [HbSβ^+] or other genotypes) • 16-65 years of age • 2 to 10 sickle-cell related pain crises in 12 months before enrollment • Patients on hydroxyurea were required to have been receiving the drug for at least 6-months and were not allowed to have any dose alteration during the 52-weeks. If patients were not on hydroxyurea, it could not be initiated.
Exclusion Criteria	• Patients undergoing long-term red-cell transfusion therapy were excluded
N	198
Interventions	• 2.5mg/kg Crizanlizumab (N=66) • 5.0 mg/kg Crizanlizumab (N=67) • Placebo (N=65)
Follow-up	30-day screening phase, 52-week treatment phase, and a 6-week follow-ep evaluation phase

Outcomes	• ***Primary Endpoint:*** Annual rate of sickle-cell related pain crises • ***Secondary Endpoints:*** ○ Annual rate of days hospitalized ○ Time to first and second crises ○ Annual rate of uncomplicated crises ○ Annual rate of acute chest syndrome ○ The Brief Pain Inventory Questionnaire

Table D3. Key Baseline Characteristics of the SUSTAIN Trial{Ataga, 2017, 1001}

Study		**Ataga 2017**		
Interventions		High-Dose Criz	Low-Dose Criz	Placebo
N		67	66	65
Age, Median (Range)		29 (16-63)	29 (17-57)	26 (16-56)
Female, n (%)		35 (52)	36 (55)	38 (58)
Black, n (%)		60 (90)	62 (94)	60 (92)
Concomitant Hydroxyurea, n (%)	Yes	42 (63)	41 (62)	40 (62)
	No	25 (37)	25 (38)	25 (38)
HbSS Genotype, n (%)	HbSS	47 (70)	47 (71)	47 (72)
	HbSC	9 (13)	15 (23)	8 (12)
	HbSβ0	3 (4)	2 (3)	7 (11)
	HbSβ+	7 (10)	2 (3)	1 (2)
	Other	1 (1)	0 (0)	2 (3)
Sickle-Cell Related Pain crises in past 12 months	2-4	42 (63)	41 (62)	41 (63)
	5-10	25 (37)	25 (38)	24 (37)
Baseline hemoglobin level — g/dl Mean (SD)		9.1 (1.8)	9.2 (1.9)	9.0 (1.5)
No. of vaso-occlusive crises in the past 12 months N(%)		NR	NR	NR
Criz: crizanlizumab, g/dl: grams per deciliter, N: number, NR: not reported, SD: standard deviation				

Table D4. Key Efficacy Outcomes in SUSTAIN{Ataga, 2017, 1001;Liles, 2018, 1002; Kutlar, 2019, 1011; Ataga, 2019, 1012}

Study			Ataga 2017 + Kutlar 2019		
Interventions			High-Dose Criz	Low-Dose Criz	Placebo
N			67	66	65
Acute Pain Crisis	***ITT***				
	Median Rate/year (IQR)		1.63 (0.00-3.97)	2.01 (1.00-3.98)	2.98 (1.25-5.87)
	% Difference; P-Value		-45.3; P=0.01	-32.6; P=0.18	NR; NR
	No. of Patients with crisis rate of zero at end of trial		24	12	11
	PP				
	Median Rate/year (IQR)		1.04 (0.00-3.42)	2.00 (1.00-3.02)	2.18 (1.96-4.96)
	% Difference; P-Value		NR; P=0.01	NR; P-0.13	NR; P=0.02
	No. of Patients with crisis rate of zero at end of trial		15	7	5
Acute Chest Syndrome	Median Rate/year (IQR)		0 (0.00-0.00)	0 (0.00-0.00)	0 (0.00-0.00)
	% Difference; P-Value		0.0; p=0.78	0.0; P=0.87	--
Splenic Sequestration	Median Rate/year (IQR)		NR	NR	NR
	% Difference; P-Value		NR	NR	NR
Annual Rate of Uncomplicated sickle-cell related pain crisis	Median Rate/year (IQR)		1.08 (0.00-3.96)	2.00 (0.00-3.02)	2.91 (1.00-5.00)
	% Difference; P-Value		-62.9; P=0.02	-31.3; P=0.12	--
	Acute pain crisis events in the year prior to study				
	Median Rate/year	2-4	1.00 (0-11.8)	NR	1.97 (0-13.3)
		5-10	1.85 (0-24.3)	NR	4.84 (0-19.2)
	Genotype				
	Median Rate/year	HbSS	1.63 (0-24.3)	NR	3.00 (0-19.2)
		Non-HbSS	0.99 (0-15.2)	NR	2.00 (0-13.3)
	HU Use				
	Median Rate/year	Yes	1.74 (024.3)	NR	3.13 (0-13.5)
		No	0.98 (0-11.8)	NR	1.98 (0-19.2)
Patients with no acute pain crisis during treatment, n(%)	***ITT***				
	0		24 (35.8)	NR	11 (16.9)
	PP**				
	0		15 (37.5)	NR	5 (12.2)
	Acute pain crisis events in the year prior to the study				
	2-4		17/42 (40.5)	NR	10/41 (24.4)

	5-10	7/25 (28.0)	NR	1/24 (4.2)
	Genotype			
	HbSS	15/47 (31.9)	NR	8/47 (17.0)
	Non-HbSS	9/20 (45.0)	NR	3/18 (16.7)
	HU Use			
	Yes	14/42 (33.3)	NR	7/40 (17.5)
	Nonii	10/25 (40.0)	NR	4/25 (16.0)
	HU use / acute pain crisis events in the year prior to study			
	Yes/2-4	11/25 (44.0)	NR	6/24 (25.0)
	Yes/5-10	3/17 (17.6)	NR	1/16 (6.3)
	No/2-4	6/17 (35.3)	NR	4/17 (23.5)
	No/5-10	4/8 (50.0)	NR	0/8 (0.0)
Hepatic Sequestration	Median Rate/year (IQR)	NR	NR	NR
	% Difference; P-value	NR	NR	NR
Priapism	Median Rate/year (IQR)	NR	NR	NR
	% Difference; P-value	NR	NR	NR
Hospitalization	No Hospitalization	46%	NR	35%
	≥1 Hospitalization	54%	NR	65%
	Median time to first hospitalization (months)	6.3	NR	3.2
	HR [95%CI]	0.683 [0.437-1.066]	NR	0.683 [0.437-1.066]
	Median Rate/year (IQR)	4.00 (0.00-25.72)	6.87 (0.00-18.00)	6.87 (0.00-28.30)
	% Difference; P-Value	-41.8; P=0.45	0.00; P=0.84	--
Brief Pain Inventory	Mean Score Change	Small change*		
	Difference; p-value	No significant changes from baseline*		
Time to First Sickle-Cell Related Pain Crisis	***ITT***			
	Median time (IQR)	4.07 (1.31-NR)	2.20 (0.95-6.60)	1.38 (0.39-4.90)
	Hazard ratio (95% CI)	0.50 (0.33-0.74)	0.75 (0.52-1.10)	--
	P-Value	0.001	0.14	--
	PP			
	Median time (IQR)	6.55 (3.02-NR)	NR	1.58 (0.46-4.93)
	Hazard ratio (95% CI)	NR	NR	NR
	P-Value	0.001	NR	<0.001

	Acute pain crisis events in the year prior to study				
	2-4	Median time	4.76 (1.81-NR)	NR	1.61 (0.62-6.70)
		Hazard ratio (95% CI)	0.53 (0.31-0.90)	NR	0.53 (0.31-0.90)
	5-10	Median time	2.43 (1.25-7.75)	NR	1.03 (0.30-2.97)
		Hazard ratio (95% CI)	0.47 (0.25-0.89)	NR	0.47 (0.25-0.89)
	Genotype				
	HbSS	Median time	4.07 (1.31-NR)	NR	1.12 (0.33-4.17)
		Hazard ratio (95% CI)	0.50 (0.31-0.80)	NR	0.50 (0.31-0.80)
	Non-HbSS	Median time	6.90 (1.41-NR)	NR	3.09 (1.12-6.21)
		Hazard ratio (95% CI)	NR	NR	0.47 (0.21-1.05)
	HU Use				
	Yes	Median time	2.43 (1.15-NR)	NR	1.15 (0.33-4.90)
		Hazard ratio (95% CI)	0.58 (0.35-0.96)	NR	0.58 (0.35-0.96)
	No	Median time	5.68 (3.09-NR)	NR	2.86 (0.79-4.53)
		Hazard ratio (95% CI)	0.39 (0.20-0.76)	NR	0.39 (0.20-0.76)
Time to Second Sickle-Cell Related Pain Crisis	***ITT***				
	Median time (IQR)		10.32 (4.47-NR)	9.20 (3.94-12.16)	5.09 (2.96-11.01)
	Hazard ratio (95% CI)		0.53 (0.33-0.87)	0.69 (0.44-1.09)	--
	P-Value		0.02	0.1	--
	HU Use: No				
	Hazard ratio (95% CI)		0.40 (0.17-0.93)	NR	0.40 (0.17-0.93)
	Non-HbSS Genotype				
	Hazard ratio (95% CI)		0.30 (0.11-0.81)	NR	0.30 (0.11-0.81)

CI: confidence interval, Criz: crizanlizumab, HU: hydroxyurea, IQR: interquartile range, ITT: intent-to-treat, NR: not reported, PP: per-protocol
***language taken directly from trial**
****abstract only reports on patients with no acute pain crises during treatment**

Table D5. Key Safety Events in SUSTAIN{Ataga, 2017, 1001; Kutlar, 2019, 1011}

Study		Ataga 2017 + Kultar 2019		
Interventions		High-Dose Criz	Low-Dose Criz	Placebo
N		66	64	62
No. of patients with ≥1 Serious Adverse Events, n (%)		17 (26)	21 (33)	17 (27)
Treatment – Emergent Adverse Events, Number of events; n (%)	2-4 acute pain crises	313; 36 (87.8)	NR	217; 34 (87.2)
	5-10 acute pain crises	146; 21 (84.0)	NR	141; 21 (91.3)
	HbSS Genotype	312; 39 (84.8)	NR	255; 38 (86.4)
	Non-HbSS Genotype	147; 18 (90.0)	NR	103; 17 (94.4)
	HU Use: Yes	242; 35 (85.4)	NR	226; 35 (89.7)
	HU Use: No	217; 22 (88.0)	NR	132; 20 (87.0)
Adverse Events Leading to Discontinuation, Number of events; n (%)	2-4 acute pain crises	1; 1 (2.4)	NR	1; 1 (2.6)
	5-10 acute pain crises	1; 1 (4.0)	NR	6; 2 (8.7)
	HbSS Genotype	1; 1 (2.2)	NR	6; 2 (4.5)
	Non-HbSS Genotype	1; 1 (5.0)	NR	1; 1 (5.6)
	HU Use: Yes	0; 0 (0.0)	NR	7; 3 (7.7)
	HU Use: No	2; 2 (8.0)	NR	0; 0 (0.0)
Most Frequent Adverse Events, n (%)				
Pyrexia		2 (3)	0	1 (2)
Influenza		0	3 (5)	0
Pneumonia		3 (5)	2 (3)	3 (5)
Adverse Events, n (%)				
Headaches		11 (17)	14 (22)	10 (16)
Back Pain		10 (15)	13 (20)	7 (11)
Urinary Tract Infection		9 (14)	7 (11)	7 (11)
Nausea		12 (18)	11 (17)	7 (11)
Arthralgia		12 (18)	9 (14)	5 (8)
Pain in Extremity		11 (17)	8 (12)	10 (16)
Upper respiratory tract infection		7 (11)	7 (11)	6 (10)

Pyrexia	7 (11)	6 (9)	4 (6)
Diarrhea	7 (11)	5 (8)	2 (3)
Musculoskeletal Pain	8 (12)	4 (6)	6 (10)
Pruritus	5 (8)	7 (11)	3 (5)
Vomiting	5 (8)	7 (11)	3 (5)
Chest Pain	1 (2)	7 (11)	1 (2)

Criz: crizanlizumab, HU: hydroxyurea, N: number

D7. Study Quality of Voxelotor HOPE Trial

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
HOPE Vichinsky 2019	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Yes	Good

ITT: intent-to-treat

Table D8. Study Design of Voxelotor Trials{Vichinsky, 2019, 1003}

Study	Voxelotor (HOPE)
Design	Phase 3, double-blind, randomized, multi-center, placebo-controlled trial. Patients were randomized 1:1:1 to receive a once-daily high-dose (1500 mg) oral dose of voxelotor, low-dose (900 mg) of voxelotor, or placebo. Stratification factors included hydroxyurea use (yes or no), geographic region (North America, Europe, or other), and age (adolescent [12-17 years] or adults [18 to 65 years]).
Inclusion Criteria	• Ages 12-65 with confirmed sickle cell disease (homozygous hemoglobin S, sickle hemoglobin C disease, hemoglobin Sβ-thalassemia, or other genotypic variants of SCD) • Hemoglobin level between 5.5 and 10.5 g/dl • 1-10 vaso-occlusive crises in past 12 months • Participants receiving hydroxyurea at a stable dose (at least 3 months) were eligible
Exclusion Criteria	• Participants receiving regular red-cell transfusion therapy, had received transfusion in past 60 days, or had been hospitalized for vaso-occlusive crisis within 14 days before providing informed consent
N	274
Interventions	• Voxelotor 1500 mg (n=90) • Voxelotor 900 mg (n=92) • Placebo (n=92)
Follow-up	28-35 day Screening Period, up to 72 week Treatment Period and End-of-trial visit at 4 weeks after last dose.

Outcomes	• ***Primary Endpoint:*** % participants with hemoglobin response • ***Secondary Endpoints:*** ○ Change in hemoglobin from BL to wk 24 ○ Lab markers associated with hemolysis (indirect bilirubin level, absolute reticulocyte count, % reticulocytes, lactate dehydrogenase level) ○ Annualized incidence rate of vaso-occlusive crisis

Table D9. Key Baseline Characteristics of Voxelotor trials{Vichinsky, 2019, 1003}

Study		**Vichinsky 2019**	
Interventions		High-Dose VOX	Placebo
N		90	92
Age, Median (Range)		24	28
Female, n (%)		58 (64)	50 (54)
		59 (66)	63 (68)
Concomitant Hydroxyurea, n (%)	Yes	58 (64)	58 (63)
	No	32 (36)	34 (37)
HbSS Genotype, n (%)	HbSS	61 (68)	74 (80)
	HbSC	3 (3)	2 (2)
	HbSβ0	18 (20)	11 (12)
	HbSβ+	7 (8)	3 (3)
	Other	1 (1)	2 (2)
Baseline hemoglobin level — g/dl Median (range)		8.7 (5.9-10.8)	8.6 (6.1-10.5)
No. of vaso-occlusive crises in the past 12 months N(%)	0	NR	NR
	1	35 (39)	39 (42)
	2-10	55 (61)	53 (58)
Hospitalizations due to painful crisis in the past 12 months, Median (range)		NR	NR

VOX: voxelotor, N: number, %: percent, g/dL: grams per deceliter

Table D10. Key Efficacy Outcomes in Voxelotor trials{Vichinsky, 2019, 1003;Vichinsky, 2019, 1095}

Study		Vichinsky 2019	
Interventions		High-Dose VOX	Placebo
N		90	92
Acute Pain Crisis	Median Rate per-person-year (95%CI)	2.77 (2.15-3.57)	3.19 (2.50-4.07)
	% Difference P-Value	NR	NR
	No. of Patients with crisis rate of zero at end of trial	≥1: 59(67)	≥1: 63 (69)
28-day Observation Period for Patients who Discontinued VOX			
N		21	17
Acute pain crises reported		6	8
Number of patients reporting acute pain crises		5	5
Incidence Rate		4.63	7.01
Secondary and Tertiary Outcomes			
Acute Chest Syndrome	Median Rate/year (IQR)	NR	NR
	% Difference; P-Value	NR	NR
Splenic Sequestration	Median Rate/year (IQR)	NR	NR
	% Difference; P-Value	NR	NR
Annual Rate of Uncomplicated sickle-cell related pain crisis	Median Rate/year (IQR)	NR	NR
	% Difference; P-Value	NR	NR
Painful Sickle Cell Crisis (PSCC) %	0	NR	NR
	1	NR	NR
	2	NR	NR
	3	NR	NR
Hepatic Sequestration	Median Rate/year (IQR)	NR	NR
	% Difference; P-value	NR	NR
Priapism	Median Rate/year (IQR)	NR	NR
	% Difference; P-value	NR	NR
Hospitalization	Median Rate/year (IQR)	NR	NR
	% Difference ;P-Value	NR	NR
Brief Pain Inventory	Mean Score Change	NR	NR

	Difference ; p-value	NR	NR
Time to First Sickle-Cell Related Pain Crisis	Median time (IQR)	NR	NR
	Hazard ratio (95% CI)	NR	NR
	P-Value	NR	NR
Time to Second Sickle-Cell Related Pain Crisis	Median time (IQR)	NR	NR
	Hazard ratio (95% CI)	NR	NR
	P-Value	NR	NR
Hemoglobin Response, n (%)		46 (51)	6 (7)
Absolute change in Hemoglobin (g/dL)	No. of participants	88	91
	LS Mean (95% CI)	1.1 (0.9-1.4)	-0.1 (-0.3-0.2)
Indirect Bilirubin	No. of participants	85	85
	LS Mean (95% CI)	-29.1 (-35.9 to -22.2)	-3.2 (-10.1 to 3.8)
Percentage of Reticulocytes	No. of participants	88	91
	LS Mean (95% CI)	-19.9 (-29.9 to - 10.9)	4.5 (-4.5 to 13.6)
Absolute Reticulocyte Count	No. of participants	88	91
	LS Mean (95% CI)	-8.0 (-18.1 to2.1)	3.1 (-7.0 to 13.2)
Lactate Dehydrogenase	No. of participants	88	97
	LS Mean (95% CI)	-4.5 (-11.9 to 2.8)	3.4 (-4.0 to 10.9)

IQR: interquartile range, CI: confidence interval, LS: least squares, VOX: voxelotor

Table D11. Subgroup Analyses of HOPE Trial{Howard, 2019, 1093;Ware, 2019, 1094}

Study		Vichinsky 2019	
		High Dose VOX	Placebo
Mean Percent Change in Hemolysis Markers by change in Hb at 24 weeks - PP			
N	**74**	**76**	
Absolute Reticulocyte	Change in Hb >1g/ dL	-16.7	NR
	Change in Hb ≤1 g/ dL	1.5	NR
Percent of Reticulocytes	Change in Hb >1g/ dL	-35.2	NR
	Change in Hb ≤1 g/ dL	-3.6	NR
Indirect Bilirubin	Change in Hb >1g/ dL	-37.0	NR
	Change in Hb ≤1 g/ dL	-24.9	NR
LDH	Change in Hb >1g/ dL	-11.0	NR
	Change in Hb ≤1 g/ dL	-1.1	NR
Mean Change (95% CI) in laboratory parameters from Baseline to Week 24			
Hb g/dL (N=229)	Hydroxyurea Use - Yes	1.3 (1.0, 1.6)	0.0 (-0.2 , 0.2)
	Hydroxyurea Use - No	1.3 (0.8, 1.8)	0.0 (-0.2, 0.3)
HbF % (n=131)	Hydroxyurea Use - Yes	-1.8 (-3.1, -0.5)	-0.1 (-1.8, 1.5)
	Hydroxyurea Use - No	0.2 (-0.9, 1.3)	0.5 (0.0, 1.1)

Hb: hemogloblin, HbF: fetal hemoblogin, g/dL: grams per decliliter, VOX: voxelotor, PP: per protocol, LDH: lactate dehydrogenase

Table D12. Key Safety Events in Voxelotor trials{Vichinsky, 2019, 1003; Howard, 2019, 1009}

Study	Vichinsky 2019		Howard 2019
Interventions	High-Dose VOX	Placebo	VOX 900mg
N	90	92	7
Serious Adverse Events, n (%)	17 (19.3)	15 (16.5)	0 (0)
Treatment -Emergent Adverse Events, n (%)	83 (94.3)	81 (89.0)	0 (0)
Adverse Events Leading to Discontinuation, n (%)	8 (9.1)	4 (4.4)	0 (0)
Headaches, n(%)	23 (26)	20 (22)	2 (29)
Back Pain, N(%)	10 (11)	10 (11)	2 (29)
Urinary Tract Infection, N(%)	NR	NR	NR
Nausea, n(%)	15 (17)	9 (10)	NR
Deaths, n (%)	NR	NR	0 (0)
VOX: voxelotor, N: number			

Table D13. Study Quality of L-Glutamine{Niihara, 2018, 1006;Niihara, 2018, 1007;Niihara, 2014, 1007}

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
Niihara 2018	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
Niihara 2014	No	No	Yes	Yes	N/A	No	Yes	No	Poor

ITT: intent-to-treat

Table D14. Study Design of the L-Glutamine Trials{Niihara, 2018, 1006;Niihara, 2014, 1013}

Study	L-Glutamine (Endari)	Niihara 2014
Design	Phase III, year-long, randomized, placebo-controlled, double-blind, parallel-group trial. Participants were randomized 2:1 to receive L-glutamine or placebo with randomization stratified by region of participating site and status with respect to hydroxyurea use.	Phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Participants were randomized 1:1 to oral L-glutamine at 0.3 grams per kilogram or oral placebo twice daily for 48 weeks
Inclusion Criteria	• Sickle cell anemia (homozygous hemoglobin S [HbSS]), or sickle cell thalassemia (HbSβ^0-thalassemia) • At least 5 years of age • Had at least 2 pain crises (no upper limit) documented in the previous year Patients who were receiving treatment with hydroxyurea at a dose that had been stable or at least 3 months before screening and who intended to continue that treatment were eligible to participate.	• Sickle cell anemia or sickle β0-thalassemia as documented by hemoglobin electrophoresis • At least 5 years old • At least 2 episodes of painful crises within 12 months of the screening visit
Exclusion Criteria	• Hospitalized for a reason not related to sickle cell disease within 2 months before screening • Prothrombin-time international normalized ration higher than 2.0 • Serum albumin level ration higher than 3.0g • Clinically significant renal or liver disease • Had treatment with L-glutamine within 30 days before screening.	• Significant medical condition that required hospitalization within 2 months of the screening visit • Diabetes mellitus • Treated with an experimental drug within 30 days of screening visit
N	230	62
Interventions	• L-Glutamine (N=152) • Placebo (N=78)	• L-Glutamine (N=33) • Placebo (N=29)
Follow-up	48-week treatment period followed by a 3-week tapering period and an observation period of 2 weeks. Total trial duration of 53 weeks.	48-week treatment period with a 3-week tapering period. Final visit 2 weeks post final dose of study at week 53.

Outcomes	• ***Primary Endpoint:*** Number of pain crises through week 48
	• ***Secondary Endpoints:***
	  ○ Number of hospitalizations for SC-related pain
	  ○ Number of ED visits
	  ○ Changes in hemoglobin measures
		• ***Primary Endpoint:*** frequency of painful sickle cell crises
		• ***Secondary Endpoints:*** frequency of hospitalizatios for sickle cell pain, frequency of emergency room visits for sickle cell pain, number of days patients' usual daily activities were interrupted due to sickle cell pain, heigh and weight.

Table D15. Key Baseline Characteristics of L-Glutamine Trials{Niihara, 2014, 1013;Niihara, 2015, 1007;Niihara, 2018, 1006}

Study		Niihara 2018 NEMJ + Blood + 2015		Niihara 2014	
Interventions		L-Glutamine	Placebo	L-Glutamine	Placebo
N		152	78	33	29
Age, Median (Range)		19 (5 to 57)	17 (5 to 58)	29.0 (13-58)	26.0 (9-55)
Age Group (Years)	5-12	34 (22.4)	17 (21.8)	0.00	2 (6.9)
	13-18	41 (27)	26 (33.3)	3 (9.1)	1 (3.4)
	>18	77 (50.7)	35 (44.9)	20 (91)	26 (89.6)
Female, n (%)		79 (52)	45 (57.7)	22 (66.7)	10 (34.5)
Black, n (%)		144 (94.7)	73 (93.6)	32 (97.0)	28 (6.6)
Concomitant Hydroxyurea, n (%)	Yes	101 (66.4)	52 (66.7)	NR	NR
	No	NR	NR	NR	NR
HbSS Genotype, n (%)	HbSS	136 (89.5)	71 (91.0)	31 (93.9)	24 (82.8)
	HbSC	NR	NR	NR	NR
	HbSβ^0	14 (9.2)	7 (9.0)	2 (6.1)	5 (17.2)
	HbSβ^+	2 (1.3)	0 (0)		
	Other	NR	NR	NR	NR
Sickle-Cell Related Pain crises in past 12 months, no. (%)	0-1	1 (0.7)	1 (1.3)	NR	NR
	2-5	128 (84.2)	61 (78.2)	NR	NR
	6-9	15 (9.9)	14 (17.9)	NR	NR
	≥ 10	8 (5.3)	2 (2.6)	NR	NR

Baseline hemoglobin level — g/dl Median (range)	8.8 ± 1.4	8.7 ± 1.2	NR	NR
Hematocrit level at baseline – g/dl	27.7 ± 4.4	27.5 ± 3.6	NR	NR
No. of vaso-occlusive crises in the past 12 months N(%)	NR	NR	NR	NR

NR: not reported, g/dl: grams per deciliter, n: number

Table D16. Key Efficacy Outcomes in L-Glutamine Trials{Niihara, 2014, 1013;Niihara, 2015, 1007;Niihara, 2018, 1006;Niihara, 2018, 1007;Niihara, 2015, 1007}

Study		**Niihara 2018 NEJM + Niihara 2018 Blood + Niihara 2015**		**Niihara 2014**	
Interventions		L-Glutamine	Placebo	L-GLutamine	Placebo
N		152	78	33	29
Acute Pain Crisis	Median (range)	3 (0-15)	4 (0-15)	NR	NR
	% Difference P-Value	NR; P=0.005		NR	NR
Acute Chest Syndrome	No. of episodes n(%)				
	0	139 (91.4)	60 (76.9)	NR	NR
	≥ 1	13 (8.6)	18 (23.1)	NR	NR
	1	10 (6.6)	13 (16.7)	NR	NR
	2	3 (2.0)	4 (5.1)	NR	NR
	3	0 (0)	1 (1.3)	NR	NR
	% Difference; P-Value	NR; P=0.003		NR	NR
Splenic Sequestration	Median Rate/year (IQR)	NR	NR	NR	NR
	% Difference; P-Value	NR	NR	NR	NR
Annual Rate of Uncomplicated sickle-cell related pain crisis	Median Rate/year (IQR)	NR	NR	NR	NR
	% Difference; P-Value	NR	NR	NR	NR
Painful Sickle Cell Crisis (PSCC)	0	24%	10%	NR	NR
	1	6%	8%	NR	NR
	2	36	35%	NR	NR

	3	34%	47%	NR	NR
	Week 24				
	Mean number of Events (SD)	NR	NR	2.5 (2.55)	5.5 (8.46)
	P-Value	NR		0.060	
	Week 48				
	Mean number of events (SD)	NR	NR	4.5 (5.37)	10.8 (18.74)
	P-Value	NR		0.076	
Hepatic Sequestration	Median Rate/year (IQR)	NR	NR	NR	NR
	% Difference; P-value	NR	NR	NR	NR
Priapism	Median Rate/year (IQR)	NR	NR	NR	NR
	% Difference; P-value	NR	NR	NR	NR
No. of hospitalization for sickle cell-related pain	Median (range)	2 (0-14)	3 (0-13)	NR	NR
	% Difference ;P-Value	NR; P=0.005		NR	
	Week 24				
	Mean	NR	NR	0.8	1.3
	P-Value	NR		0.036	
	Week 48				
	Mean	NR	NR	1.5	2.3
	P-Value	NR		0.072	
No. of Emergency department visits for sickle cell related pain	Median (range)	1 (0-12)	1 (0-15)	NR	NR
	P-Value	0.09		NR	
	Week 24				
	Mean	NR	NR	3.7	9.4
	P-Value	NR		0.105	
	Week 48				
	Mean	NR	NR	1.9	4.7
	P-Value	NR		0.129	

Cumulative no. of days in hospital	Median (range)	6.5 (0-94)	11 (0-187)	NR	NR
	P-Value	0.02		NR	NR
Brief Pain Inventory	Mean Score Change	NR	NR	NR	NR
	Difference; p-value	NR	NR	NR	NR
Time to First Sickle-Cell Related Pain Crisis	Median time (IQR)	84 (NR)	54 (NR)	NR	NR
	Hazard ratio (95% CI)	0.69 (0.52-0.93)		NR	NR
	P-Value	0.02		NR	NR
Time to Second Sickle-Cell Related Pain Crisis	Median time (IQR)	212 (NR)	133 (NR)	NR	NR
	Hazard ratio (95% CI)	0.68 (0.49-0.96)		NR	NR
	P-Value	0.03		NR	NR
Mean Corpuscular Volume (MCY)					
Not receiving hydroxyurea	Mean (SD)	94.9 (10.2)		NR	NR
Receiving Hydroxyurea	Mean (SD)	104.0 (13.9)		NR	NR
NADH (mmol/ml RBC)	Mean ± SD (range)	NR	NR	NR	NR
	P-value	NR	NR	NR	NR
Total NAD (mmol/ml RBC)	Mean ± SD (range)	NR	NR	NR	NR
	P-value	NR	NR	NR	NR
Redox Potential (%)	Mean ± SD (range)	NR	NR	NR	NR
	P-value	NR	NR	NR	NR
Hemoglobin (g/dL)	Mean ± SD (range)	NR	NR	NR	NR
	P-value	NR	NR	NR	NR
Subjective Clinical Response					
Energy Level	Increased	NR	NR	NR	NR
	Decreased	NR	NR	NR	NR
	No Change	NR	NR	NR	NR
Activity Level	Increased	NR	NR	NR	NR
	Decreased	NR	NR	NR	NR
	No Change	NR	NR	NR	NR
Chronic Pain Level	Increased	NR	NR	NR	NR
	Decreased	NR	NR	NR	NR
	No Change	NR	NR	NR	NR

Narcotics Dosage	Increased	NR	NR	NR	NR
	Decreased	NR	NR	NR	NR
	No Change	NR	NR	NR	NR

Table D17. Key Safety Events in L-Glutamine Trials {Niihara, 2014, 1013;Niihara, 2018, 1006}

Study	Niihara 2018		Niihara 2014	
Interventions	L-Glutamine	Placebo	L-Glutamine	Placebo
N	152	78	37	33
Adverse Events (%)	98%	100%	94.6%	90.9%
Serious Adverse Events, n (%)	78.2%	87.1%	64.7%	63.6%
Sickle Cell Crisis (%)	NR	NR	59.5%	51.5%
Treatment - Emergent Adverse Events, n (%)	NR	NR	NR (8.1%)	NR (9.1%)
Adverse Events Leading to Discontinuation, n (%)	NR	NR	19 (51.4%)	21 (63.6%)
Cardiac Disorders				
Tachycardia	8 (5.3)	4 (5.1)	NR	NR
Gastrointestinal Disorders				
Constipation	38 (25.2)	19 (24.4)	NR	NR
Nausea	34 (22.5)	13 (16.7)	NR	NR
Vomiting	22 (14.6)	10 (12.8)	NR	NR
Abdominal pain upper	16 (10.6)	6 (7.7)	NR	NR
Diarrhea	12 (7.9)	5 (6.4)	NR	NR
Gastroenteritis	NR	NR	5%	15%
General Disorders and administration site conditions				
Chest Pain (noncardiac)	21 (13.9)	7 (9.0)	NR	NR
Fatigue	9 (6.0)	1 (1.3)	NR	NR
Infections and Infestations				
Urinary Tract Infection	10 (6.6)	3 (3.8)	NR	NR
Musculoskeletal and connective tissue disorders				
Pain in Extremity	24 (15.9)	6 (7.7)	NR	NR
Back Pain	20 (13.2)	5 (6.4)	NR	NR
Arthralgia	NR	NR	5%	21%

Nervous System Disorders				
Headache	32 (21.2)	14 (17.9)	NR	NR
Dizziness	8 (5.3)	4 (5.1)	NR	NR
Respiratory, Thoracic, and Mediastinal disorders				
Nasal Congestion	11 (7.3)	5 (6.4)	NR	NR
NR: not reported. **Niihara 1998 saw no adverse reactions.**				

Table D18. Unpublished L-Glutamine Studies

Unpublished L-Glutamine Studies{Food and Drug Administration. Center for Drug Evaluation and Research, 2019, 23}						
Title / Trial Sponsor	**Study Design**	**Study Arms**	**Patient Population**	**Primary Outcomes**	**Results**	**Completion Dates**
L-Glutamine						
L-Glutamine Therapy for Sickle Cell Anemia **NCT00586209** **Sponsor: Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center** **Collaborator: Emmaus Medical Inc.**	Prospective Phase II, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Assignment Enrollment: 15 4-week screening period 12-week treatment period 5 week tapering period	Intervention: Weight-based L-Glutamine with upper limit of daily dose at 30g/day (n=5) Comparator: Placebo (n=10)	Inclusion: 1. Subjects (≥18 years of age) with sickle cell anemia or sickle β0-thalassemia. 2. At least two episodes of painful crises within 12 months of screening Exclusion: 1. Significant medical condition requiring hospitalization within 2 months of screening 2. Diabetes mellitus with untreated	1. Number of occurrences of painful sickle cell crises	**Adverse Events n (%)** L-Glutamine: 4 (80) Placebo: 7 (70) **Serious Adverse Events n (%)** L-Glutamine: 2 (40) Placebo: 5 (50) **Diarrhea** L-Glutamine: 2 (40) Placebo: NR **Nausea / Vomiting** L-Glutamine: 2 (40) Placebo: NR **Sickle Cell Crisis**	November 2009

Unpublished L-Glutamine Studies{Food and Drug Administration. Center for Drug Evaluation and Research, 2019, 23}						
Title / Trial Sponsor	**Study Design**	**Study Arms**	**Patient Population**	**Primary Outcomes**	**Results**	**Completion Dates**
			fasting blood sugar >115 mg/dL		L-Glutamine: 1 (20) Placebo: NR **Hypertension** L-Glutamine: 1 (20) Placebo: NR	
Legacy Study 8775	Phase 2a, Randomized, Single-Center, Double-Blind, Placebo-Controlled Crossover Enrollment: 24 24-week treatment period followed by 5 week tapering period prior to crossover	Intervention: Oral L-Glutamine 30g/day (10 g, TID) Comparator: Placebo	Inclusion: 1. Subjects (≥18 years of age) with a diagnosis of sickle cell anemia 2. At least 3 episodes of painful crises during the 12 month period prior to randomization Exclusion: None Reported	1. Total NAD 2. NAD redox potential 3. RBC endothelial cell adhesiveness 4. Hematologic parameters 5. Frequency of painful crises 6. Number of hospitalization day 7. Number of painless days 8. Safety.	Of the 6 evaluable patients, there was a significant increase in number of pain days (p=0.00885). The improvement in number of painful crises was not statistically significant (p=0.28).	Unknown
NAD: nicotinamide adenine dinucleotide, NR: not reported, RBC: red blood cell, TID: three times a day						

Outcomes of Interest

Clinical Outcomes	
Acute	**Chronic**
Acute Pain Episode	Chronic Pain
Stroke/Cerebrovascular Accident	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

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-related costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	

	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al.

Description of evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.{Pickard, 2019, 5001}
2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).
3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.
4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.
5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.
6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

Table E2. Age-specific Annual Probability of Death

Age	Percent that die at each age	Probability of Death	Probability of Death (Annual)	Adjusted by Risk Factors
<1	1.5%	0.0150	0.0150	0.0013
1-4	2%	0.0203	0.0051	0.0004
5-9	1.5%	0.0155	0.0031	0.0003
10-14	1.5%	0.0158	0.0032	0.0003

15-19	4%	0.0428	0.0087	0.0007
20-24	8%	0.0894	0.0186	0.0016
25-34	20%	0.2454	0.0278	0.0023
35-44	27%	0.4390	0.0562	0.0047
45-54	20%	0.5797	0.0830	0.0070
55-64	11%	0.7586	0.1325	0.0111
65-74	2%	0.5714	0.0812	0.0068
75-84	1.5%	1.0000	0.9688	0.0812

Table E3. Undiscounted Results for the Base Case for Crizanlizumab versus Optimal Usual Care Alone

Treatment	Usual Care	Crizanlizumab	Difference	ICER	
Treatment Cost	-	$1,695,927	$1,695,927	-	
Other Costs	$1,633,664	$1,552,076	-$81,587	-	
Total Cost	$1,633,664	$3,248,003	$1,614,339	-	
Acute Pain Crises	63.23	42.67	-20.56	$78,530	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
Lys	21.08	26.01	4.93	$210,087	per LY gained
evLYG	10.60	14.54	3.94	$262,924.49	per evLY gained
QALYs	10.60	12.31	1.71	$604,601	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year

Table E4. Undiscounted Results for the Base Case for Voxelotor versus Optimal Usual Care Alone

Treatment	Usual Care	Voxelotor	Difference	ICER	
Treatment Cost	-	$1,859,194	$1,859,194	-	
Other Cost	$1,209,430	$1,826,809	$617,379	-	
Total Cost	$1,209,430	$3,686,003	$2,476,573	-	
Acute Pain Crises	63.23	64.90	1.67	$1,175,812	per acute pain crisis avoided
Hemoglobin (g/dL)	-0.10	1.10	1.20	$80,634	per g/dL per year
Lys	21.08	25.59	4.52	$279,848	per LY gained
evLYG	10.60	14.44	3.85	$328,816	per evLY gained
QALYs	10.60	12.54	1.94	$652,308	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year

Table E5. Undiscounted Results for the Base Case for L-glutamine versus Optimal Usual Care Alone

Treatment	Usual Care	L-glutamine	Difference	ICER	
Treatment Cost	-	$420,255	$420,255	-	
Other Costs	$1,144,760	$1,002,983	-$141,777	-	
Total Cost	$1,144,760	$1,423,237	$278,478	-	
Acute Pain Crises	63.23	59.09	-4.14	$96,119	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
LYs	21.08	21.65	0.57	$488,441	per LY gained
evLYG	10.60	11.02	0.42	$662,503	per evLY gained
QALYs	10.60	10.79	0.19	$1,446,810	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost-effectiveness ratio, LY: life year, QALY: quality-adjusted life year

Description of Competing Events Calculations

To simplify the model it was assumed that only one chronic condition and one acute condition could occur each cycle. This creates a situation where chronic conditions and acute conditions become competing events. Therefore, by decreasing one event in the model it allows other events to occur more frequently. To correct for the competing events, the model was calibrated to minimize the difference in the number of acute events and chronic conditions because of the reduction in acute pain crises in the treatment arm. Specifically, the steps were to:

1. Remove the risks of acute pain crisis from the model, i.e., make all risk factors of acute pain crisis equal to 1
2. Run the model with the treatment effect as reported in the appropriate trial
3. Calculate adjustment factors that minimize the difference in each acute and chronic condition other than acute pain crisis, since treatment effects should only affect acute pain crisis without the risk factors applied; there was a small effect due to competing events
4. Add the risks of acute pain crisis on the other acute and chronic conditions back into the model
5. Calculate results of the model.

This method can be validated by investigating how the model predicts acute and chronic conditions compared to known SCD populations, as was done in the validation section above.

Appendix F. Real World Evidence Final Protocol

Acronym/Title	ICER sickle cell disease (SCD) model inputs
Protocol version and date	V 1.0, 15 January 2020
Study type / Study phase	Observational study
Study Investigator	Brigham Women's Hospital Principle Investigator: Sebastian Schneeweiss, MD, ScD
Country(-ies) of study	United States
Protocol Author(s)	Collaboration between Aetion, Inc., Brigham Women's Hospital, and Institute for Clinical and Economic Review

The study will be conducted in compliance with the protocol

and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of contents

2. List of abbreviations

AEP Aetion Evidence Platform®

CCAE Commercial Claims and Encounters

CKD Chronic kidney disease

COB Coordination of Benefits

ER Emergency room

HbC hemoglobin C

HbSS homozygous sickle hemoglobin

ICER Institute of Clinical and Economic Review

IQR Interquartile range

MDCR MarketScan Medicare Supplemental and Coordination of Benefits Database

OLS Ordinary least squares

SCD Sickle cell disease

SD Standard deviation

3. Rationale and background

A series of analyses using the Aetion Evidence Platform® (AEP) were conducted within a Marketscan dataset to obtain evidence on the characteristics of commercially-insured patients with sickle cell disease (SCD), rates of treatment, rates acute and chronic outcomes, and the costs associated with these outcomes. Results from this analysis were used to inform the Institute for Clinical and Economic Review (ICER) cost-effectiveness model.

4. Research questions and objectives

The objectives of this study are:

To characterize patients with SCD. Specifically,

- To describe baseline patient characteristics including demographics
- To describe rates of acute and chronic clinical outcomes of interest
- To estimate the incidence of chronic outcomes of interest
- To describe rates of treatment, including bone marrow transplant, use of hydroxyurea, and chronic transfusion
- To estimate costs of acute and chronic events of interest

5. Research methods

5.1.1 Study population

The study population was derived from patients with SCD. Patients entered the cohort on their first diagnosis of SCD within all available data (2002 – 2017). The population was restricted to patients with three or more SCD diagnoses during available data (see appendix for further detail), implemented by requiring two additional diagnoses following cohort entry.

As noted below, subsets of this overall SCD population were evaluated for the cost analyses.

5.1.1.1 Cohort subset 1 *(analysis of acute event costs)*

For each acute event of interest, a cohort of patients with SCD and with the event between January 01, 2014 and December 01, 2017 was identified. Only these later years of data (2014 – 2017) were used to obtain more recent and relevant cost estimates. Patients entered the cohort on the acute event date. Only patients with an incident acute event were included; those patients with an event in the 180 days prior to the cohort entry date were excluded. Each patient was included only once, on the first qualifying event.

Patients were required to have at least 30 days of enrollment prior to cohort entry in order to obtain baseline cost estimates. The event-based cohorts were nested within the broader population of patients meeting the sickle cell disease definition.

5.1.1.2 Cohort subset 2 *(analysis of chronic event costs)*

For each chronic event of interest, patients were identified from within a parent population of patients with an SCD diagnosis between January 2014 and December 2016 and at least three diagnoses total during available follow-up. Subjects included patients who were newly diagnosed with the chronic condition and a risk-set sampled referent group, identified during January 01, 2014 and December 31, 2016.

Patients with chronic conditions were required to be newly-diagnosed with the chronic condition, having no diagnoses in the 180 days prior to the cohort entry date. While this focus on incident patients may have reduced the generalizability, it allowed for clearer temporality between chronic condition status and cost and more valid estimates.

For each patient with the chronic condition, up to three referent patients were risk-set sampled from a pool of potential patients who did not have the chronic condition on the exposed patient's cohort entry date and met the same enrollment, inclusion and exclusion criteria. Risk-set sampled referent patients were assigned the same cohort entry date as the patient with the chronic condition.

Patients were not allowed to be sampled for the referent group if they had the chronic condition on the potential cohort entry date or in the 180 days prior to the potential cohort entry date. In addition, patients were only eligible to be sampled as referent on days they had a prescription, outpatient visit or inpatient visit to ensure they were similar in terms of being engaged with the healthcare system.

5.2 Variables

Refer to **Annex 1: Variable definitions** for the definitions of patient characteristics including SCD, study treatment, and outcome events of interest.

5.2.1 Patient characteristics

The following patient characteristics were evaluated on each patient's cohort entry date:

- Age
- Gender
- Geographic region
- Age category (< 2, 2 – 4, 5 – 12, 13 – 18, 18+)
- Age category (<18, 18+)
- Medicare coverage
- The presence of specific SCD diagnosis codes were evaluated over all available data for each patient.
- Sickle cell – hemoglobin C (HbC)
- Sickle cell – homozygous sickle hemoglobin (HbSS)
- Sickle cell – thalassemia
- Sickle cell disease - other

5.2.2 Treatment

Treatments of interest were:

- Bone marrow transplant
- Use of hydroxyurea
- Chronic transfusion

The hydroxyurea analysis was restricted to patients with complete prescription information.

5.2.3 Outcomes definition

The following study outcomes are defined below.

5.2.3.1 Acute outcomes for rate estimates

Acute outcomes were:

- Renal infarction (any diagnosis) – inpatient
- Stroke (any diagnosis) – inpatient
- Myocardial infarction (any diagnosis) – inpatient
- Acute chest syndrome (any diagnosis) – emergency room (ER) or inpatient
- Acute pain episode (any diagnosis) – ER or inpatient
- Iron overload episode (chelation treatment preceded by a diagnosis)

5.2.3.2 Chronic outcomes *(first recorded following cohort entry)* for rate estimates

Chronic outcomes were:

- Pulmonary hypertension
- Heart failure
- Opioid dependence
- Nephropathy / chronic kidney disease (CKD)
- Fatigue
- Cognitive impairment

5.2.3.3 Acute outcomes for cost estimates

Costs were estimated for the following acute outcomes:

- Stroke (any diagnosis) – inpatient
- Myocardial infarction (any diagnosis) – inpatient

- Acute chest syndrome (any diagnosis) – ER or inpatient
- Acute pain episode (any diagnosis) – ER or inpatient
- Iron overload episode (chelation treatment preceded by a diagnosis)

Note: Cost analyses were planned for renal infarction, but were not possible due to the small number of patients with an event during the analysis period.

5.3 Data sources

All analyses were performed using de-identified administrative claims data without access to personal identifying information. Study findings contained aggregate data only that could not be used to identify individual patients.

5.3.1 IBM Truven MarketScan

Truven MarketScan Databases

The Truven MarketScan databases capture de-identified, longitudinal, individual-level administrative claims data from the United States. The data available for this study included the Commercial Claims and Encounters (CCAE) Database and Medicare Supplemental and Coordination of Benefits Database. The IBM MarketScan Commercial Claims and Encounters (CCAE) Database contains data from active employees, early retirees, COBRA continuees, and dependents insured by employer- sponsored plans (i.e., individuals not eligible for Medicare). The IBM MarketScan Medicare Supplemental and Coordination of Benefits (COB) Database (also known as MDCR) is created for Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans. This database contains predominantly fee-for-service plan data. Among the SCD population, 3% of patients had Medicare coverage.

The following tables of the MarketScan databases were available for analysis: Enrollment Detail, Inpatient Admissions, Inpatient Services, Outpatient Services, Outpatient Pharmaceutical Claims, and Long Term Care. These tables provide information on plan enrollment, healthcare utilization and expenditures, demographics, and integrated records for inpatient events, outpatient events, and pharmacy dispensings. Unless otherwise noted, drug event duration was calculated from the "Days Supply" field, and in cases where this field was 0, the duration was assumed to be 1 day.

Data were available from December 31, 2002 to December 31, 2017, and represent approximately 192 million patients.

5.3.2 General notes on administrative databases

Electronic outpatient pharmacy dispensing records are considered accurate because pharmacists fill prescriptions with little room for interpretation, and are reimbursed by insurers on the basis of detailed, complete, and accurate claims submitted electronically.[1,2] Pharmacy dispensing information is usually seen as the gold standard of drug exposure information compared to self-reported information[3] or prescribing records in outpatient medical records.[4] Drugs used during hospital stays are not recorded in this data source. Prescribing information based on physician notes may overestimate actual medication use because up to 50% of prescriptions are never filled at the pharmacy.[5]

5.4 Statistical analysis

5.4.1 Rate of acute outcomes

Rates of acute outcomes were evaluated over the time period beginning on the cohort entry date, and ending on the first of disenrollment or end of data. Death is not captured within Marketscan data, but will trigger disenrollment. The total number of events across the population were counted and divided by total follow-up time. Rates were presented as events per 1000 person-years. Total event counts across the population were also provided.

The iron overload episode analysis was restricted to patients with complete prescription information.

Counts of events during a 1-year period were also calculated. This analysis was restricted to the subset of the population with a full year of follow-up. Mean number of events per patient and standard deviation (SD) was reported for all acute events. In addition, frequencies of counts of acute pain episode during follow-up were reported.

5.4.2 Rates of chronic outcomes *(first recorded occurrence following cohort entry)*

Rates of chronic conditions were evaluated over the time period beginning on the cohort entry date, and ending on the first of disenrollment, end of data, or occurrence of outcome. The rate was calculated as the number of patients with an outcome divided by total follow-up time. Rates were presented as the value per 1000 person-years.

Note: This event rate should not be interpreted as a true incidence rate – refer to incidence analysis in Section 5.4.3.

5.4.3 Incidence of chronic outcome

In order to assess incidence of chronic conditions among patients who did not already have the chronic condition, an analysis was conducted restricted to patients with 180 days of baseline data who did not have the condition of interest recorded during that period. This analysis was conducted within a subset of SCD patients present in the data during 2013 – 2017, with cohort entry set to the first day when the

patient had 180 days of prior enrollment data. One limitation is the possibility that 180 days is not a sufficient look-back period for ascertaining the presence of chronic conditions, particularly if the patient had not actively sought care for the condition.

5.4.4 Rates of treatment *(following cohort entry)*

Rates of treatment were evaluated over the time period beginning on the cohort entry date, and ending on the first of disenrollment, end of data, or occurrence of treatment. The rate was calculated as the number of patients with an outcome divided by total follow-up time. Rates were presented as the value per 1000 person-years.

5.4.5 Costs of acute events

Cost analyses were based on paid amounts reported in the Marketscan data. For each acute outcome, incremental costs were estimated during the 14 day period beginning on the acute outcome date (day 0 – 13) and the 14 days following (day 14 – 27). For acute myocardial infarction and stroke, an average 30-day cost during the 28 to 365 days following the event was also provided. All costs were inflated to 2019 US dollars using the Medical Care Services Component of the Consumer Price Index.[6]

Incremental costs were calculated using a pre-post design among patients with the outcome of interest, with each patient serving as his or her own control.[7,8] For each patient, a 14-day and 30-day average baseline cost was estimated using all available data during up to 180 days preceding the acute outcome date. The total cost during the 14 days beginning on the acute event (day 0 – 13) was calculated for each patient. The incremental cost was estimated as the difference between the day 0 – 13 cost and the 14-day average baseline cost. Mean (sd) and median [IQR] incremental cost values were calculated across the population as an estimate of the cost likely attributed to the acute outcome. A similar procedure was used for the day 14 – 27 incremental cost calculation, restricted to patients who were still in the dataset during this period. For the calculation of 30-day costs during the 28 – 365 days following the acute event, incremental cost was calculated as 30*(total cost during day 28 to day 365 divided by follow-up days during day 28 to day 365) minus the 30-day baseline cost.

Because repeat events and other high cost acute events are modeled, including their costs within the estimated cost of an acute outcome would result in double-counting their costs. To avoid this, follow-up – and the accumulation of costs – was censored on the occurrence of MI, stroke, renal infarction or bone marrow transplant following the acute event date. Patients with these events during the 180 days preceding the acute event date were excluded from the analysis in order to obtain representative baseline cost data. Due to the higher prevalence of acute pain and acute chest syndrome, these events were not explicitly excluded; rather it was assumed that their costs during baseline and follow-up would net out across the population. Follow-up was additionally censored on the end of 365 days, end of data, or disenrollment.

To assess sensitivity of results to extreme cost values, an additional analysis was performed where incremental cost values were Winsorized,[9] using the 5th and 95th percentile of the cost distribution as cut points. These procedure involves replacing cost values below the 5th percentile with the 5th percentile value and values above the 95th percentile with the 95th percentile value. Thus, extreme values are pulled in, but the weight on the tails of the distribution is maintained.

5.4.6 Costs of chronic events

Costs of chronic conditions were estimated by comparing patients with the condition to matched patients without the condition. In order to obtain annual cost estimates, analyses were restricted to the subset of patients with complete 1-year follow-up. Cost analyses were based on paid amounts reported in the Marketscan data during the 1 year follow-up period. All costs were inflated to 2019 US dollars using the Medical Care Services Component of the Consumer Price Index.[6]

The effect of each chronic condition on cost was estimated by fitting an ordinary least squares (OLS) regression model predicting total 1-year cost as a function of the presence of the chronic condition, adjusting for patient characteristics at baseline. Baseline patients' characteristics include demographic factors measured on cohort entry date, health care resource utilization, costs, receipt of SCD treatments, and presence of other chronic conditions and acute outcomes during the 180 days prior to cohort entry.

The following patient characteristics were included in the fully-adjusted analysis:

- Age
- Age categories (<2, 2-4, 5-12, 13-18, 18+)
- Gender
- Region
- Presence of cognitive impairment
- Presence of nephropathy / CKD
- Presence of pulmonary hypertension
- Presence of opioid dependence
- Presence of heart failure
- Presence of fatigue

- Occurrence of iron overload episode
- Occurrence of acute chest syndrome (any dx) - ER or inpatient
- Occurrence of acute pain episode (any dx) - ER or inpatient
- Occurrence of stroke (any dx) - inpatient
- Treatment with chronic transfusion
- Treatment with hydroxyurea
- Number of different prescription filled, at generic entity level
- Total inpatient costs
- Total outpatient costs
- Total pharmacy costs
- Hospitalization
- Number of outpatient visit days
- Number of emergency department visit days
- Number of prescriptions filled

5.4.7 Subgroup analysis

5.4.7.1 Rates of acute and chronic outcomes, incidence of chronic outcomes, and rates of treatment stratified by age

For rates of acute and chronic outcomes of interest, incidence of chronic outcomes, and rates of treatment, results were reported for the overall population and stratified on age group at cohort entry. Age categories were 0 – 1, 2 – 4, 5 – 12, 13 – 18, and 18+. In addition, results were generated for the combined pediatric (age <18) group.

5.4.7.2 Cost of acute events analysis stratified by age

For the cost of acute events analysis, results were stratified on age < 18 vs 18+. Due to small numbers of patients < 18 with myocardial infarction (n = 1), stratified results were not provided for myocardial infarction.

5.4.8 Software

Results were generated using the Aetion Evidence Platform® version r3.18.20191126_1826-0-g7a6bbbef8-dirty. The AEP has been previously validated for a range of studies[10,11] and for predicting clinical trial findings.[12] A full listing of all component software versions can be found in **Annex 2: Software Components**.

6. References

Annex 1: Variable definitions

Variables	Algorithm	Source
Disease		
Sickle cell disease	Events occurring in any setting with one of the following diagnoses in any position ICD10 ● D57.0 - Hb-SS disease with crisis ● D57.00 - Hb-SS disease with crisis, unspecified ● D57.01 - Hb-SS disease with acute chest syndrome ● D57.02 - Hb-SS disease with splenic sequestration ● D57.1 - Sickle-cell disease without crisis ● D57.2 - Sickle-cell/Hb-C disease ● D57.20 - Sickle-cell/Hb-C disease without crisis ● D57.21 - Sickle-cell/Hb-C disease with crisis ● D57.211 - Sickle-cell/Hb-C disease with acute chest syndrome ● D57.212 - Sickle-cell/Hb-C disease with splenic sequestration ● D57.219 - Sickle-cell/Hb-C disease with crisis, unspecified ● D57.4 - Sickle-cell thalassemia ● D57.40 - Sickle-cell thalassemia without crisis	Reeves et al, 2014[xiii]

	• D57.41 - Sickle-cell thalassemia with crisis • D57.411 - Sickle-cell thalassemia with acute chest syndrome • D57.412 - Sickle-cell thalassemia with splenic sequestration • D57.419 - Sickle-cell thalassemia with crisis, unspecified ICD9 • 282.41 - SICKLE-CELL THALASSEMIA WITHOUT CRISIS • 282.42 - SICKLE-CELL THALASSEMIA WITH CRISIS • 282.6 - SICKLE-CELL DISEASE • 282.60 - SICKLE-CELL DISEASE UNSPECIFIED • 282.61 - HB-SS DISEASE WITHOUT CRISIS • 282.62 - HB-SS DISEASE WITH CRISIS • 282.63 - SICKLE-CELL/HB-C DISEASE WITHOUT CRISIS • 282.64 - SICKLE-CELL/HB C DISEASE WITH CRISIS • 282.68 - OTHER SICKLE-CELL DISEASE WITHOUT CRISIS • 282.69 - OTHER SICKLE-CELL DISEASE WITH CRISIS	
Treatments		

Hydroxyurea	The occurrence of **Prescription Claims** with the following attributes: **- NDC Generic Name** is any of: { "HYDROXYUREA" }	
Transfusion	● The occurrence of **Inpatient Service or outpatient event** with the following attributes: – **Procedure Code (Position 1), ICD-10** is any of: { "30230P1", "30240H1", "30240N1", "30243H1", "30230N1", "30233P1", "30230H1", "30243N1", "30243P1", "30233H1", "30233N1", "30240P1" } • 30230P1 - Transfusion of Nonautologous Frozen Red Cells into Peripheral Vein, Open Approach • 30240H1 - Transfusion of Nonautologous Whole Blood into Central Vein, Open Approach • 30240N1 - Transfusion of Nonautologous Red Blood Cells into Central Vein, Open Approach • 30243H1 - Transfusion of Nonautologous Whole Blood into Central Vein, Percutaneous Approach • 30230N1 - Transfusion of Nonautologous Red Blood Cells into Peripheral Vein, Open Approach	Code search (ICD10)

	• 30233P1 - Transfusion of Nonautologous Frozen Red Cells into Peripheral Vein, Percutaneous Approach • 30230H1 - Transfusion of Nonautologous Whole Blood into Peripheral Vein, Open Approach • 30243N1 - Transfusion of Nonautologous Red Blood Cells into Central Vein, Percutaneous Approach • 30243P1 - Transfusion of Nonautologous Frozen Red Cells into Central Vein, Percutaneous Approach • 30233H1 - Transfusion of Nonautologous Whole Blood into Peripheral Vein, Percutaneous Approach • 30233N1 - Transfusion of Nonautologous Red Blood Cells into Peripheral Vein, Percutaneous Approach • 30240P1 - Transfusion of Nonautologous Frozen Red Cells into Central Vein, Open Approach – **Procedure Code (Position 1), CPT and HCPC** is any of: { “36440”, “36450”, “S3906”, “P9010”, “S9538”, “36455”, “36430”, “P9038”, “P9011”, “P9022”,	

	"P9051", "P9056", "P9057", "P9021", "P9054", "P9058", "P9016" } • 36440 - Push transfusion, blood, 2 years or under / Push transfusion, blood, 2 years or younger • 36450 - Exchange transfusion, blood; newborn • S3906 - TRANSFUSION, DIRECT, BLOOD OR BLOOD COMPONENTS • P9010 - BLOOD (WHOLE), FOR TRANSFUSION, PER UNIT • S9538 - HOME TRANSFUSION OF BLOOD PRODUCT(S); ADMINISTRATIVE SERVICES, PROFESSIONAL PHARMACY SERVICES, CARE COORDINATION AND ALL NECESSARY SUPPLIES AND EQUIPMENT (BLOOD PRODUCTS, DRUGS, AND NURSING VISITS CODED SEPARATELY), PER DIEM / HOME TRANSFUSION OF BLOOD PRODUCT(S); ADMINISTRATIVE SERVICES, PROFESSIONAL PHARMACY SERVICES, CARE COORDINATION AND ALL NECESSARY SUPPLIES AND EQUIPMENT (BLOOD PRODUCTS, DRUGS, AND NURSING VISITS CODED SEPARATELY), PER DIEM	

	• 36455 - Exchange transfusion, blood; other than newborn • 36430 - Transfusion, blood or blood components • P9038 - RED BLOOD CELLS, IRRADIATED, EACH UNIT • P9011 - BLOOD (SPLIT UNIT), SPECIFY AMOUNT / BLOOD, SPLIT UNIT • P9022 - RED BLOOD CELLS, WASHED, EACH UNIT • P9051 - WHOLE BLOOD OR RED BLOOD CELLS, LEUKOCYTES REDUCED, CMV-NEGATIVE, EACH UNIT • P9056 - WHOLE BLOOD, LEUKOCYTES REDUCED, IRRADIATED, EACH UNIT • P9057 - RED BLOOD CELLS, FROZEN/DEGLYCEROLIZED/WASHED, LEUKOCYTES REDUCED, IRRADIATED, EACH UNIT • P9021 - RED BLOOD CELLS, EACH UNIT • P9054 - WHOLE BLOOD OR RED BLOOD CELLS, LEUKOCYTES REDUCED, FROZEN, DEGLYCEROL, WASHED, EACH UNIT • P9058 - RED BLOOD CELLS, LEUKOCYTES REDUCED, CMV-	

	NEGATIVE, IRRADIATED, EACH UNIT • P9016 - RED BLOOD CELLS, LEUKOCYTES REDUCED, EACH UNIT • **Procedure Code (Position 1), ICD-9** is any of: { "99.03", "99.04", "99.01" } – 99.03 - OTHER TRANSFUSION OF WHOLE BLOOD – 99.04 - TRANSFUSION OF PACKED CELLS – 99.01 - EXCHANGE TRANSFUSION	
Chronic transfusion	A sequence of 3+ transfusion events, with each spaced 2 – 6 weeks apart. The start of the first event was used as the episode start date	Based on a review of treatment patterns and clinical expert(s)[xiv,xv]
Bone marrow transplant	The occurrence of an **Inpatient Service** or **Outpatient** event with the following attributes: • **Procedure Code (Position 1), ICD-10** is any of: { "30230G2", "30230G3", "30230G4", "30233G2", "30233G3", "30233G4", "30240G2", "30240G3", "30240G4", "30243G2", "30243G3", "30243G4", "30250G1", "30253G1", "30260G1", "30263G1" } o 30230G2 - Transfusion of Allogeneic Related Bone Marrow into Peripheral Vein, Open Approach o 30230G3 - Transfusion of Allogeneic Unrelated Bone Marrow into Peripheral Vein, Open Approach	American Society for Blood and Marrow Transplantation[xvi]

	○ 30230G4 - Transfusion of Allogeneic Unspecified Bone Marrow into Peripheral Vein, Open Approach ○ 30233G2 - Transfusion of Allogeneic Related Bone Marrow into Peripheral Vein, Percutaneous Approach ○ 30233G3 - Transfusion of Allogeneic Unrelated Bone Marrow into Peripheral Vein, Percutaneous Approach ○ 30233G4 - Transfusion of Allogeneic Unspecified Bone Marrow into Peripheral Vein, Percutaneous Approach ○ 30240G2 - Transfusion of Allogeneic Related Bone Marrow into Central Vein, Open Approach ○ 30240G3 - Transfusion of Allogeneic Unrelated Bone Marrow into Central Vein, Open Approach ○ 30240G4 - Transfusion of Allogeneic Unspecified Bone Marrow into Central Vein, Open Approach ○ 30243G2 - Transfusion of Allogeneic Related Bone Marrow into Central Vein, Percutaneous Approach ○ 30243G3 - Transfusion of Allogeneic Unrelated Bone Marrow into Central Vein, Percutaneous Approach ○ 30243G4 - Transfusion of Allogeneic Unspecified Bone Marrow into Central Vein, Percutaneous Approach	

	○ 30250G1 - Transfusion of Nonautologous Bone Marrow into Peripheral Artery, Open Approach ○ 30253G1 - Transfusion of Nonautologous Bone Marrow into Peripheral Artery, Percutaneous Approach ○ 30260G1 - Transfusion of Nonautologous Bone Marrow into Central Artery, Open Approach ○ 30263G1 - Transfusion of Nonautologous Bone Marrow into Central Artery, Percutaneous Approach • **Procedure Code (Position 1), ICD-9** is any of: { "41.02", "41.03" } ○ 41.02 - ALLOGENEIC BONE MARROW TRANSPLANT WITH PURGING ○ 41.03 - ALLOGENEIC BONE MARROW TRANSPLANT WITHOUT PURGING • **Procedure Code (Position 1), CPT and HCPC** is any of: { "38240", "38243", "38242" } ○ 38240 - Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic / Bone marrow or blood-derived peripheral stem cell transplantation; allogenic / Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor ○ 38243 - Hematopoietic progenitor cell (HPC); HPC boost ○ 38242 - Allogeneic lymphocyte infusions / Bone marrow or blood-derived peripheral	

	stem cell transplantation; allogeneic donor lymphocyte infusions	
Ischemia-related outcomes: acute		
Acute pain episode	Events occurring in an inpatient or ER setting with any diagnosis of: ICD9: 282.42 - Sickle-cell thalassemia with crisis 282.62 - Hb-SS disease with crisis 282.64 - Sickle-cell/Hb-C disease with crisis 282.69 - Other sickle-cell disorders with crisis, unspecified ICD10: D57.00 - Hb-SS disease with crisis, unspecified D57.219- Sickle-cell/Hb-C disease with crisis, unspecified D57.419 - Sickle-cell thalassemia with crisis, unspecified D57.819 - Other sickle-cell disorders with crisis, unspecified	Shah et al, 2019[xvii] Bernard et al, 2008[xviii]
Acute chest syndrome	Events occurring in an inpatient or ER setting with any diagnosis of: ICD10:	Agarwal et al, 2018[xix] (ICD9)

	D57.211 - Sickle-cell /Hb-C disease with acute chest syndrome D57.01 - Hb-SS disease with acute chest syndrome D57.411 - Sickle-cell thalassemia with acute chest syndrome D57.811 - Other sickle-cell disorders with acute chest syndrome ICD9: 517.3 - Acute chest syndrome	Code search (ICD10)
Myocardial infarction	Events occurring in an inpatient setting with any diagnosis of: ICD9: 410.x0 - Acute myocardial infarction, episode of care unspecified ICD9: 410.x1 - Acute myocardial infarction, initial episode of care ICD10: I21.x - Acute myocardial infarction I22.x - Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	Kiyota Y et al, 2004[xx] Code search (ICD10)
Renal infarction	Events occurring in an inpatient setting with any diagnosis of: ICD10: N28.0 - Ischemia and infarction of kidney ICD9: 593.81 - vascular disorders of the kidney	Code search (ICD10)

Stroke (ischemic or hemorrhagic)	Events occurring in an inpatient setting with any diagnosis of: ICD9: 430.x - Subarachnoid hemorrhage 431.x - Intracerebral hemorrhage 433.x1 - Occlusion and stenosis of precerebral arteries, with infarct 434.x1 - Occlusion of cerebral arteries,with infarct 436.x - Acute, but ill-defined, cerebrovascular disease ICD10: I60.x - Nontraumatic subarachnoid hemorrhage I61.x - Nontraumatic intracerebral hemorrhage 162.x - Other and unspecified nontraumatic intracranial hemorrhage I63.xx - Cerebral infarction	Kumamaru et al, 2004 (ICD9)[xxi] Code search (ICD10)
Ischemia-related outcomes: chronic		
Opioid tolerance / dependence	Events occurring in an any setting with any diagnosis of: ICD-9: 304.00 - 304.03 - Opioid dependence	Agarwal et al, 2018 (ICD9)[xxii] Code search (ICD10)

	304.70–73 - Opioid dependence with other drug dependence ICD-10: F11.2x - Opioid dependence	
Pulmonary hypertension	Events occurring in an any setting with any diagnosis of: ICD10: I27.0x - primary pulmonary hypertension I27.2x - secondary pulmonary hypertension I27.81 - Cor pulmonale (chronic) (due to pulmonary hypertension) I27.9 - Pulmonary heart disease, unspecified (resulting from pulmonary hypertension) ICD9: 416.0 - primary pulmonary hypertension 416.8 - Other chronic pulmonary heart diseases (including secondary pulmonary hypertension) 416.9 - Chronic pulmonary heart disease, unspecified (heart disease resulting from pulmonary hypertension)	Agarwal et al, 2018 (ICD9)[xxii] Code search (ICD10)
Heart failure	Events occurring in an any setting with any diagnosis of: ICD9:	Brophy et al, 2004 (ICD9)[xxiii]

	428.xx - heart failure ICD10: I50 - heart failure	Code search (ICD10)
Nephropathy, chronic kidney disease	Events occurring in an any setting with any diagnosis of: ICD9: 585.x - chronic kidney disease 586, 593.9 - unspecified kidney failure 580.x - acute glomerulonephritis 582.x - chronic glomerulonephritis (nephritic syndrome) 250.4x, 249.4x - diabetes with renal manifestations 583.x -nephritis and nephropathy not specified as acute or chronic 581.x - nephrotic syndrome ICD10: N18.x - chronic kidney disease N19 - unspecified kidney failure N00.x - acute glomerulonephritis N03.x -chronic glomerulonephritis (nephritic syndrome)	Young et al, 2008 (ICD9)[xxiv] Glasheen et al, 2017 (ICD10)[xxv]

	N05.x - nephritis and nephropathy not specified as acute or chronic E08.2x - Diabetes mellitus due to underlying condition with kidney complications E09.2x - Drug or chemical induced diabetes mellitus with kidney complications E10.2x - Type 1 diabetes mellitus with kidney complications E11.2x - Type 2 diabetes mellitus with kidney complications E13.2 - Other specified diabetes mellitus with kidney complications N04.x - nephrotic syndrome	
Neurocognitive impairment	Events occurring in an any setting with any diagnosis of: ICD9 • 331.83 - MILD COGNITIVE IMPAIRMENT SO STATED • 780.93 - MEMORY LOSS • 438.0 - COGNITIVE DEFICITS • 294.9 - UNSPECIFIED PERSISTENT MENTAL DISORDERS DUE TO CONDITIONS CLASSIFIED ELSEWHERE • 799.5 - SIGNS AND SYMPTOMS INVOLVING COGNITION	Amra S et al, 2017[xxvi] and code search (ICD10)

	• 799.51 - ATTENTION OR CONCENTRATION DEFICIT • 799.52 - COGNITIVE COMMUNICATION DEFICIT • 799.53 - VISUOSPATIAL DEFICIT • 799.54 - PSYCHOMOTOR DEFICIT • 799.55 - FRONTAL LOBE AND EXECUTIVE FUNCTION DEFICIT • 799.59 - OTHER SIGNS AND SYMPTOMS INVOLVING COGNITION • 290 - DEMENTIAS • 290.0 - SENILE DEMENTIA UNCOMPLICATED • 290.1x - PRESENILE DEMENTIA • 290.2x - SENILE DEMENTIA WITH DELUSIONAL OR DEPRESSIVE FEATURES • 290.3 - SENILE DEMENTIA WITH DELIRIUM • 290.4x - VASCULAR DEMENTIA • 291.2 - ALCOHOL-INDUCED PERSISTING DEMENTIA • 292.82 - DRUG-INDUCED PERSISTING DEMENTIA • 294.1x - DEMENTIA IN CONDITIONS CLASSIFIED ELSEWHERE • 294.2x - DEMENTIA UNSPECIFIED • 331.1 - FRONTOTEMPORAL DEMENTIA	

	• 331.19 - OTHER FRONTOTEMPORAL DEMENTIA • 331.82 - DEMENTIA WITH LEWY BODIES ICD10 • I69.11 - Cognitive deficits following nontraumatic intracerebral hemorrhage • I69.01 - Cognitive deficits following nontraumatic subarachnoid hemorrhage • I69.91 - Cognitive deficits following unspecified cerebrovascular disease • I69.21 - Cognitive deficits following other nontraumatic intracranial hemorrhage • I69.31 - Cognitive deficits following cerebral infarction • I69.81 - Cognitive deficits following other cerebrovascular disease • G31.83 - Dementia with Lewy bodies • G31.84 - Mild cognitive impairment, so stated • R41 - Other symptoms and signs involving cognitive functions and awareness • R41.0 - Disorientation, unspecified • R41.1 - Anterograde amnesia • R41.2 - Retrograde amnesia • R41.3 - Other amnesia	

	• R41.4 - Neurologic neglect syndrome • R41.8 - Other symptoms and signs involving cognitive functions and awareness • R41.81 - Age-related cognitive decline • R41.82 - Altered mental status, unspecified • R41.83 - Borderline intellectual functioning • R41.84 - Other specified cognitive deficit • R41.840 - Attention and concentration deficit • R41.841 - Cognitive communication deficit • R41.842 - Visuospatial deficit • R41.843 - Psychomotor deficit • R41.844 - Frontal lobe and executive function deficit • R41.89 - Other symptoms and signs involving cognitive functions and awareness • R41.9 - Unspecified symptoms and signs involving cognitive functions and awareness • F01 - Vascular dementia • F01.5 - Vascular dementia • F01.50 - Vascular dementia without behavioral disturbance • F01.51 - Vascular dementia with behavioral disturbance • F02 - Dementia in other diseases classified elsewhere	

	• F02.8 - Dementia in other diseases classified elsewhere • F02.80 - Dementia in other diseases classified elsewhere without behavioral disturbance • F02.81 - Dementia in other diseases classified elsewhere with behavioral disturbance • F03 - Unspecified dementia • F03.9 - Unspecified dementia • F03.90 - Unspecified dementia without behavioral disturbance • F03.91 - Unspecified dementia with behavioral disturbance	
Anemia-related outcomes: acute		
Acute pain syndrome	(see above)	
Acute chest syndrome	(see above)	
Iron overload episode	Defined as chelation, with an iron overload diagnosis during the past 60 days. Chelation drug prescriptions within 180 days of one another were considered part of the same episode.	Clinical expert(s) and assumptions
Iron Overload Due to pRBCs	Events in any setting with a primary diagnosis of: Hemochromatosis due to repeat transfusions	Code search (ICD10)

	ICD10 E83.111 ICD9 275.02	
Use of chelation drugs	Use of iron chelation drug - “DEFEROXAMINE MESYLATE”, “DEFERASIROX”, “DEFERIPRONE”	
Stroke	(see above)	
Anemia-related outcomes: chronic		
Opioid tolerance / dependence	(see above)	
Pulmonary hypertension	(see above)	
Heart failure	(see above)	
Nephropathy, chronic kidney disease	(see above)	
Neurocognitive impairment	(see above)	

Fatigue	ICD10 • G93.3 - Postviral fatigue syndrome • R53.0 - Neoplastic (malignant) related fatigue • R53.1 - Weakness • R53.81 - Other malaise • R53.82 - Chronic fatigue, unspecified • R53.83 - Other fatigue ICD9 • 780.7 - MALAISE AND FATIGUE • 780.71 - CHRONIC FATIGUE SYNDROME • 780.79 - OTHER MALAISE AND FATIGUE	U.S. Agency for Healthcare Research and Quality. Clinical Classifications Software (CCS), 2018.[xxvii]

Annex 2: Software Components

Package	Version
R	3.4.2
Formula	1.2.2
Hmisc	4.0.3
RColorBrewer	1.1.2
Rcpp	0.12.13
RcppArmadillo	0.8.100.1.0

- SparseM
- 1.77
- TH.data
- 1.0.8
- acepack
- 1.4.1
- aetionstats
- 2.0
- colorspace
- 1.3.2
- dichromat
- 2.0.0
- digest
- 0.6.12
- epitools
- 0.5.10
- forecast
- 8.2
- fracdiff
- 1.4.2
- ggplot2
- 2.2.1
- gridExtra
- 2.3
- gtable
- 0.2.0
- jsonlite
- 1.5
- labeling
- 0.3
- latticeExtra
- 0.6.28
- magrittr
- 1.5
- metafor
- 2.0.0
- multcomp
- 1.4.8
- munsell
- 0.4.3
- mvtnorm
- 1.0.6
- plyr
- 1.8.4
- polspline
- 1.1.12

- proto
- 0.3-10
- quadprog
- 1.5.5
- quantreg
- 5.34
- reshape
- 0.8.7
- reshape2
- 1.4.2
- rms
- 5.1.1
- sandwich
- 2.4.0
- scales
- 0.5.0
- stringi
- 1.1.6
- stringr
- 1.2.0
- timeDate
- 3042.101
- tseries
- 0.10.42
- zoo
- 1.8.0

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